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Baicalin: A potential therapeutic agent for diabetes and renal protection

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ABSTRACT

Background: Diabetes is a complex metabolic disease manifested by raised glucose levels in the blood and impaired insulin function leading to various organ complications, including diabetic nephropathy. Baicalin, a flavonoid derived from Scutellaria baicalensis Georgi, has garnered substantial attention for its diverse beneficial effects, including anti-inflammatory, anti-allergic, anti- apoptotic properties, etc. Intriguingly, in vivo studies in rats have further unveiled baicalin's potential to directly modulate pancreatic beta cells, suggesting a promising role as an anti-diabetic agent.

Objective: The purpose of this study is to comprehensively explore the anti-diabetic effect of baicalin, focusing on key parameters such as plasma insulin levels, glucose levels, hemoglobin, and glycated hemoglobin levels in streptozotocin-

induced diabetic rats. Additionally, we sought to explore Baicalin's ability to provide renal protection by evaluating serum renal markers.

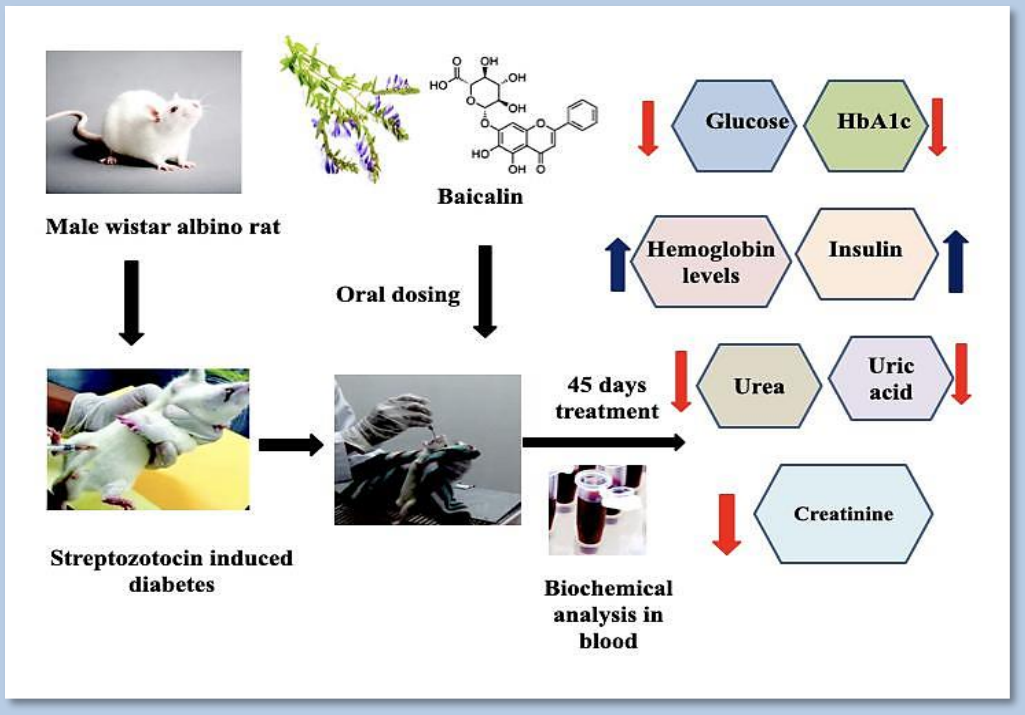
Methodology: This study involved a total of 30 Wistar albino male rats. Diabetes was created in rats by a single intraperitoneal streptozotocin injection (40 mg/kg). After 72 hours, the rats with diabetes were segregated into four treatment groups (Group II to Group V) comprising 6 animals each. Group I consist of six normal control rats (without diabetes). The groups received different treatment protocols, including normal saline, DMSO, Baicalin (50 mg/kg/day), and glibenclamide (6 mg/kg/day) for 45 days. Throughout the study, meticulous observations were made regarding the animals' general appearance, body weight, behavior, and their fasting glucose levels in venous blood.

Results: Oral dosing with Baicalin at the rate of 50 mg/kg body weight revealed notable enhancements in insulin secretion and hemoglobin levels, alongside notable reductions in blood levels of glucose and glycated hemoglobin compared to the glibenclamide-treated type 2 diabetic rats. Additionally, Baicalin displayed a protective action on renal tissue, as shown by reduced serum creatinine, uric acid, and urea levels.

Conclusion: Our investigation unveils Baicalin's potential as a promising anti-diabetic agent with the added benefit of renal tissue protection. The observed improvements in various physiological parameters warrant further exploration of Baicalin's therapeutic mechanisms and clinical applications, presenting it as a compelling candidate for diabetes management and diabetic nephropathy prevention.

IAEC Approval No: AVMC/IAEC/2019/07/25/08

Keywords: **B**aicalin, Blood glucose, Diabetes, Male wistar rats, Streptozotocin



INTRODUCTION

Diabetes, a multifaceted metabolic disorder arising from dysregulation of insulin production and activity, poses a significant global health challenge. In type 1 diabetes there is autoimmune destruction of the pancreatic beta cells, while in type 2 diabetes there is peripheral insulin resistance and dysfunction of pancreatic beta cells [1]. These disturbances lead to impaired peripheral glucose absorption, elevated blood glucose levels, and compromised energy metabolism [2]. Over the past 30 years, the prevalence of diabetes has risen considerably, making it a leading cause of mortality and morbidity, with India ranking second in diabetes prevalence globally [3-5].

The prevalence of diabetes poses a substantial risk for micro and macrovascular complications, including nephropathy. Approximately one in three adults with diabetes end up with kidney disease, making diabetes the principal reason of kidney failure in the United States [6]. In diabetes, the kidneys face increased demands to clear excess glucose from the bloodstream, leading to inflammation and scarring of the nephrons, ultimately culminating in nephropathy. Additionally, hypertension, a frequent complication of diabetes, plays a pivotal role in developing diabetic nephropathy. The persistent elevation of glucose levels in blood, a hallmark symptom of diabetes, triggers the generation of reactive oxygen species (ROS) through glycosylation and glucose oxidation. This oxidative stress induces chronic and transient cellular alterations, contributing to cell death and organ damage [7].

Research shows that plants offer potential solutions with their anti-diabetic and antioxidant properties, which can mitigate diabetes-related symptoms and oxidative stress [8]. Consequently, the Interest in plant-based bioactive antioxidant therapies is growing, presenting promising avenues to combat progressive complications associated with diabetes. Various natural bioactive compounds in food sources deliver health benefits, encompassing antioxidants, anti-inflammatory effects, anti-fungal properties, and various preventive effects [9].

One such bioactive flavonoid called Baicalin (BA) or 7-glucuronic acid, 5, 6-dihydroxyflavone (see Figure 1), derived from *Scutellaria baicalensis* Georgi, holds prominence in Traditional Chinese medicine [10]. Baicalin exhibits diverse beneficial effects, including anti-inflammatory, anti-allergic, and apoptosis-inducing characteristics [10]. It has been reported to exert hepatoprotective effects against liver damage induced by lipopolysaccharide/D-galactosamine [11]. Moreover, studies have shown its renal protective properties in ameliorating oxidative stress and inflammation [12]. Furthermore, in diabetes management, a recent study revealed that oral administration of baicalin reduces hyperglycemia-induced mitochondrial damage in pancreatic beta cells of diabetic rats, highlighting its potential as an anti-diabetic agent [13]. Additionally, baicalin, the active metabolite of baicalein, effectively addresses complications related to diabetes, cardiovascular diseases, cancer, inflammatory disorders, oxidative stress, and bacterial infections [14].

Baicalin's antioxidant effects are primarily attributed to its ability to scavenge reactive oxygen species (ROS) and inhibit lipid peroxidation. The hydroxyl groups at positions 5 and 6 on the flavone backbone act as potent scavengers of free radicals, neutralizing ROS and preventing oxidative damage to cells and tissues [15]. Additionally, the glucuronic acid moiety at position 7 enhances the water solubility of Baicalin, facilitating its distribution and bioavailability in various organs [16].

Regarding its anti-inflammatory properties, Baicalin modulates key inflammatory pathways by inhibiting the activation of nuclear factor-kappa B (NF-κB) and other pro-inflammatory transcription factors [17]. It also suppresses the production of inflammatory cytokines,

such as interleukins and tumor necrosis factor-alpha (TNF-α), thus attenuating the inflammatory response [44]. ., Baicalin's anti-inflammatory effects are crucial in mitigating diabetes-related complications, where chronic inflammation plays a pivotal role in the development of nephropathy and other diabetic complications [1844].

Baicalin's biological activity, including anti-inflammatory activity, antitumour activity, and antiviral activity, is primarily linked to its immune response regulation by modulating Toll-like receptors (TLRs) [19]. Recent reports suggest that baicalin may be an effective treatment for renal interstitial fibrosis (RIF), potentially due to its potential inhibition of TGFβ-Smad mediated signaling pathway [20]. Hu et al. [21] proposed that the therapeutic effects of baicalin is related to many number of pathways of anti-oxidant, anti-inflammatory and anti-apoptotic activities through regulation of TNF-α, IL, MAPK, JAK/STAT, NF-kB, PI3K/Akt and P2 X 3.

Baicalin's antidiabetic effects are multi-faceted and involve various mechanisms targeting both insulin production and glucose regulation. Studies have shown that baicalin enhances insulin secretion from pancreatic beta cells, thereby improving glucose homeostasis. It achieves this by promoting the phosphorylation of protein kinase B (Akt) and increasing the expression of glucose transporter 2 (GLUT2) and glucokinase, which are crucial for glucose uptake and metabolism in beta cells [22]. Furthermore, baicalin exhibits insulin-sensitizing properties in peripheral tissues, enhancing insulin signaling and glucose uptake in skeletal muscle and adipose tissue. It activates the AMP-activated protein kinase (AMPK) pathway, leading to improved insulin sensitivity and reduced insulin resistance [23].

Additionally, baicalin exerts protective effects on pancreatic beta cells by reducing oxidative stress and apoptosis, preserving beta cell function, and delaying the progression of diabetes [24]. These combined mechanisms contribute to its potential as an antidiabetic agent, making it a promising candidate for managing diabetes and its associated complications. ZzhaoLiu et al. [25] reported that the LD50 of 80% ethanol extracts of *Scutellaria baicalensis* was 39.60 g/kg in mice. Yi et al. [26] reported that ethanol extracts of *Scutellaria baicalensis* produced some reversible inflammatory changes in rat liver at the dose of 2500 mg/kg per day.

Unravelling the enigmatic mechanisms of its action requires ongoing scientific exploration and collaborative efforts [14]. We continued to explore more by designing the present study to evaluate its potential therapeutic role as an anti-diabetic agent and in ameliorating STZ-induced and oxidative stress-mediated kidney complications in Wistar albino rats.

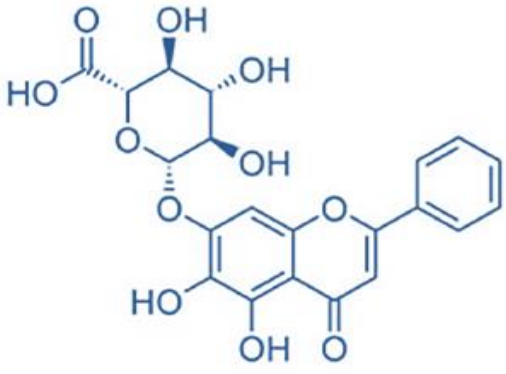


Figure 1. Chemical structure of baicalin

Figure 1 displays the chemical structure of Baicalin (BA), a flavonoid substance isolated from Scutellaria baicalensis Georgi. BA consists of a flavone backbone with hydroxyl groups at positions 5 and 6, and a glucuronic acid moiety attached at position 7. This distinctive structure with hydroxyl groups at positions 5, 6, and a glucuronic acid moiety at position 7 contributes to BA's antioxidant and anti-inflammatory properties, making it a potential candidate for therapeutic applications.

METHODOLOGY

Experimental animals: In this experiment, healthy Wistar albino male rats weighing between 180 and 200 g were utilized as subjects. The animals were maintained in polypropylene cages and provided with ad libitum access to clean reverse osmosis filtered drinking water and standard maintenance pellet feed (VRK nutritional solutions, Pune, India). The experimental rooms were maintained at a controlled temperature range of 22 °C to 26 °C with relative humidity ranging from 45% to 60% following a 12:12 hour light:dark cycle. Measures were taken to maintain a noise level within 80 decibels and a light intensity below 250 lux, ensuring a suitable environment for the animals. The study was conducted at a registered animal facility (996/PO/Re/S/06/CPCSEA) and approval was gained from the Institutional Animal Ethics Committee (IAEC no - AVMC/IAEC/2019/07/25/08) at Aarupadai Veedu Medical College and Hospital, Puducherry, India. Throughout the entire experimental period, the subjects were maintained in accordance with standard guidelines for animal care and welfare.

Drugs preparation: Glibenclamide (≥99%, HPLC), STZ (≥98%, HPLC), and baicalin (95% purity) were procured from Sigma-Aldrich and saved at 4°C till use. The other chemicals utilized in this experiment were of high analytical grade and were procured from Merck and Himedia, India. Glibenclamide (6 mg/kg/day) and baicalin (50 mg/kg/day) were prepared fresh by dissolving in dimethyl sulfoxide (DMSO) (> 99.9 % purity) before oral administration to the rats.

Diabetes induction: To induce diabetes, the rats were given one dose of intraperitoneal injection with a fresh STZ solution (40 mg/kg body weight) in 0.1 M citrate buffer (pH 4.5). After three days following STZ treatment, the rats with fasting blood glucose levels exceeding 230 mg/dL were categorized as diabetic animals. Subsequently, these diabetic animals were subjected to further research.

Experimental study design: The experimental study involved a sample of 30 male rats (6 animals each in five groups) calculated using G power version 3.1 with an effect size of 1, a significance level set at 5% and a power of 90%. The rats were assigned randomly to 5 groups (6 rats in each group) using an online graphpad random number generator.

- Group I comprised normal (non-diabetic) control rats (NC).
- Group II comprised diabetic control rats (DC).
- Group III comprised diabetic rats that were administered DMSO (vehicle control) for 45 days (D+DMSO).
- Group IV comprised diabetic rats that were administered baicalin (50 mg/kg body weight daily) for 45 days (D+BA).
- Group V comprised diabetic rats that received oral administration of glibenclamide (6 mg/kg body weight daily) for 45 days (D+GC)

Baicalin and glibenclamide were orally administered to the diabetic albino Wistar rats in Groups IV and V, respectively. In contrast, the normal and diabetic control groups were fed normal saline alone. Water intake was measured (ml) by calculating the difference between the

initial water level and the final water level remaining in the feeding bottles at determined time intervals. Urine output was measured at determined time intervals by housing the animals in metabolic cages. At the end of the experiment, the animals were left for overnight fasting, weighed, and euthanized via cervical dislocation. Glucose levels were measured from blood samples obtained from the tail vein of all rats on days 0, 22, and 45 using the Trinder technique [27]. Serum samples were collected from each rat by centrifuging the blood at 4000 rpm at 25ºC for 4 minutes, followed by storage at -20ºC for subsequent biochemical parameter examination.

Biochemical parameter analysis: On the 45th day of the experiment, cervical dislocation was performed, and heart blood samples were collected for biochemical assessment. Plasma insulin, hemoglobin, and glycated hemoglobin levels were estimated and quantified using ELISA kits (Boehringer Mannheim Kit, Age Diagnostic Pvt Ltd, Indiana polis) [28]. Uric acid levels were measured using the Automated SPAN Diagnostic Reagent, from India). Urea and creatinine levels were measured using the diacetylmonoxime technique [29-31].

Data interpretation: The data were interpreted by determining the mean and standard deviation in each group of six rats. The collected data were analyzed using one-way ANOVA and Duncan's multiple range test, using SPSS version 15 software (SPSS, Chicago). P-value of less than 0.05 was considered as statistically significant result.

RESULTS

Impact of baicalin treatment on behavior and appearance in diabetic rats: The influence of baicalin treatment on the overall appearance and behavior of the experimental animals was investigated. The Wistar rats were administered baicalin at the dose of 50 mg/kg body weight, and its safety was evaluated. Before the onset of diabetes, no significant changes were observed among the animals. However, in group IV, where STZ-induced diabetic rats were subjected to six weeks of baicalin therapy, a noticeable increase in water intake was observed on comparison to the diabetic rats in the control group. Despite this rise in water intake, the baicalin-treated group exhibited lower water consumption than the diabetic control group throughout the treatment period. Moreover, the diabetic rats that received baicalin treatment showed increased thirst (polydipsia) and reduced urinary excretion, but no clinical symptoms or mortality were observed. The findings from this investigation suggest that baicalin administration in diabetic rats led to alterations in thirst and urinary habits without any adverse clinical effects. Table 1a & 1b summarizes the results obtained from baicalin administration and its impact on the overall appearance and behavior of the experimental animals in group IV. These findings add to the growing body of evidence supporting the potential therapeutic value of baicalin in diabetes research. Further studies are necessary to unravel the underlying mechanisms and explore its potential as a therapeutic agent in managing diabetes and its associated problems.

Body weight comparison and effects of baicalin and glibenclamide in diabetic rats: Our investigation observed a considerable change in body weight between diabetic and normal control rats, with diabetic rats exhibiting lower body weight. However, administering baicalin (at the dose of 50 mg/kg body weight) and glibenclamide to diabetic rats, diabetic control rats, and normal rats did not result in statistically significant changes in body weight among the groups. The lack of noticeable alterations in the body weight of the experimental animals is illustrated in Figure 2. These findings indicate that baicalin treatment does not significantly affect the body weight of diabetic rats. While these results provide valuable insights into the specific

aspect of body weight, our investigation focused on other key factors related to diabetes management. To explore the broader impact of baicalin on diabetes management, we conducted further studies. In the subsequent sections, we present the results of our experiments, focusing on blood glucose levels, insulin levels, hemoglobin, glycated hemoglobin, uric acid, urea, and creatinine. This will provide a deeper understanding of baicalin's impact on diabetic rats and its therapeutic implications for diabetes management.

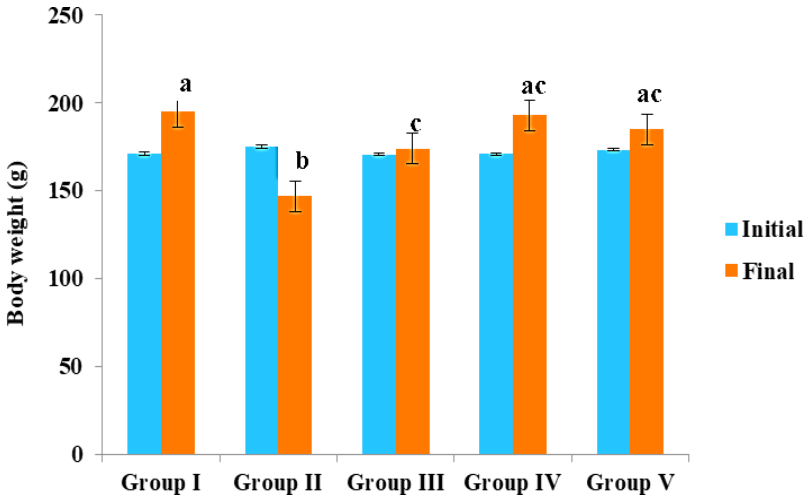


Figure 2. Effects of baicalin and glibenclamide on body mass in diabetic rats

Figure 2 illustrates a comprehensive body mass comparison among distinct experimental groups in this study. The assigned labels are as follows: Group I is normal control rats, Group II is diabetic control rats, Group III is diabetic rats treated with DMSO, Group IV is diabetic rats treated with Baicalin (50 mg/kg body weight), and Group V is diabetic rats treated with Glibenclamide (6 mg/kg body weight). The presented data for each group depict the rats' mean body mass ± standard deviation (SD) within the corresponding group. The superscripts (a, b, and c) mentioned in the figure represent statistically significant differences ($P<0.05$) between the experimental groups in each specific experiment. These significant differences highlight the remarkable effects of the diverse treatments and interventions on the body mass of diabetic rats on comparison to the control group.

Table 1a. The general observations in group IV experimental animals

Group	6-hr group					12-hr group					24-hr group					48-hr group					72-hr group				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Condition of coat	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Discharge from eyes, nose, mouth and anus	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Chromodacryorrhea	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A

Group	6-hr group					12-hr group					24-hr group					48-hr group					72-hr group				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Subcutaneous lumps or swellings	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Abnormal body posture	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Breathing abnormalities	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Wetness/soiling of perineum	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Fecal matter	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mortality	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A

S – Smooth and Shining; A – Absent; N – Normal

Table 1b. The behavioral observations in group IV experimental animals

Group	6-hr group					12-hr group					24-hr group					48-hr group					72-hr group				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
General behavior	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Feed intake	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Water intake	N	PD	N	PD	N	N	PD	N	PD	N	N	PD	N	PD	N	N	PD	N	PD	N	N	PD	N	PD	N
Nervous signs	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Urination	N	PU	N	PU	N	N	PU	N	PU	N	N	PU	N	PU	N	N	PU	N	PU	N	N	PU	N	PU	N
Tremors/corner sitting	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A

N – Normal; PD – Polydipsia (increased thirst); A – Absent; PU – Polyuria (frequent urination)

Effect of baicalin on levels of blood glucose in diabetic rats: Glucose levels in plasma were meticulously measured in both standard and experimental rats at specific time points: the 0th, 22nd, and 45th days after treatment initiation. During the third and fourth weeks of observation, a significant difference was observed between the baicalin-treated diabetic rats and the normal saline control group. The baicalin-treated diabetic rats exhibited significant less blood glucose levels ($p<0.05$) than the control group. The data is presented in Table 2, which comprehensively compares blood glucose levels between the standard and experimental animal groups. The substantial reduction in blood glucose levels in baicalin-treated diabetic rats indicates the potential of baicalin as a therapeutic agent for regulating blood glucose levels in diabetic conditions. Further investigations were conducted in the diabetic rats to determine the impact of baicalin treatment on insulin, hemoglobin, and glycated hemoglobin levels, supporting the observed blood glucose reduction. These findings highlight baicalin's promising role as a potential therapeutic intervention for managing diabetes.

Table 2. Levels of blood glucose in diabetic rats administered with baicalin and glibenclamide.

Study groups	Day 0	Day 22	Day 45
Control	82.23±6.05	85.28±6.90	88.91± 6.17[a]
Diabetic control	243.81 ± 17.88	258.13 ± 27.58	282.95±15.19[b]
Diabetic + DMSO	249.40 ± 13.44	210.40 ± 21.14	180.60± 14.5[c]
Diabetic + Baicalin (50mg/kg body weight)	242.50 ± 21.35	180.46 ± 18.65	122.70±14.51[d]
Diabetic +Glibenclamide (6mg/kg body weight)	256.67 ± 17.87	172.38 ± 21.70	107.67±11.47[ad]

Table 2 data demonstrates the changes in the levels of blood glucose over time in the various experimental groups. Notably, treatment with baicalin and glibenclamide significantly reduced the levels of blood glucose compared to the diabetic control group, indicating their potential as therapeutic agents for regulating glucose levels in diabetic rats. The observed differences in blood glucose levels among the experimental groups are statistically significant ($p<0.05$), as denoted by the superscripts (a, b, c, d, and ad).

Impact of baicalin on the levels of blood glucose, insulin, hemoglobin, and glycated hemoglobin in diabetic rats: This investigation was aimed to determine the impact of baicalin treatment on the levels of blood glucose, insulin, hemoglobin, and glycated hemoglobin in STZ-induced diabetic rats. In the treated groups, oral dosing with baicalin and glibenclamide caused a significant increase in plasma insulin and hemoglobin levels ($p < 0.05$). Additionally, glycated hemoglobin levels decreased in the treated groups following baicalin and glibenclamide treatment. Table 3 presents a comparative analysis of insulin and glycated hemoglobin levels in healthy and experimental rats. The administration of baicalin orally at a dose of 50 mg/kg body weight effectively influenced these crucial blood parameters. Moreover, compared to glibenclamide, baicalin treatment led to reduced blood levels of hemoglobin, insulin, and glycated hemoglobin. These findings highlight the significant impact of baicalin on blood insulin, glycated hemoglobin and hemoglobin levels in diabetic rats, suggesting its potential as a therapeutic agent for managing diabetes. Further analyses were conducted to explore the underlying mechanisms of baicalin's effects on blood markers, including uric acid, urea, and creatinine, providing valuable insights into baicalin's therapeutic role in diabetes management.

Table 3. Effects of baicalin and glibenclamide treatment on the levels of blood hemoglobin, glycated hemoglobin, and plasma insulin in diabetic rats

Groups	Insulin (µIU/ml)	Hemoglobin (g/dl)	HbAlc (%)
Control	16.23±1.41[a]	13.08±1.78[a]	0.83 ±0.31[a]
Diabetic control	6.61±0.62[b]	6.01±0.64[b]	1.07±0.55[b]
Diabetic+ DMSO	8.80 ±0.56[c]	7.60 ±0.22[c]	0.90 ±0.06[c]
Diabetic + Baicalin (50mg/kg body weight)	13.18±1.23[d]	11.37±0.76[d]	0.74±0.03[d]
Diabetic + Glibenclamide (6mg/kg body weight)	14.07 ±1.46[a]	12.81±0.88[ad]	0.57±0.02[a]

Table 3 compares experimental groups' insulin, hemoglobin, and glycated hemoglobin levels. Baicalin treatment (50 mg/kg) and glibenclamide treatment (6 mg/kg) increased insulin and hemoglobin levels and decreased glycated hemoglobin levels in comparison to the diabetic control group. The control group had increased insulin and hemoglobin levels but decreased glycated hemoglobin levels. Significant differences ($P < 0.05$) between the experimental groups were observed during statistical analysis. The data shows the mean ± standard deviation for 6 rats, and different superscripts (a, b, c, d, and ad) differentiate the experiment results.

Renoprotective effects of baicalin on diabetic nephropathy: evaluation of the levels of urea, uric acid, and creatinine in experimental rats: The investigation demonstrated elevated urea, creatinine, and uric acid levels in diabetic rats, as depicted in Figure 3. However, BA (Baicalin) and glibenclamide treatment significantly reduced these renal functional markers. The reductions in the level of uric acid, creatinine, and urea in the BA and glibenclamide-treated rats were statistically significant ($P < 0.05$). Notably, the most effective dose of BA was determined as 50 mg/kg. These results underscore the potential renoprotective effects of BA in managing diabetic nephropathy. The substantial and statistically significant decrease in the levels of uric acid, creatinine, and urea highlights the therapeutic promise of BA. Figure 3 visually validates the elevated levels of these markers in diabetic rats, reinforcing the presence of renal dysfunction in diabetes. Further investigations are warranted to elucidate the precise mechanisms of BA's renoprotective effects and its potential implications in clinical settings.

Figures 3 (a), (b), and (c) illustrate the effects of BA (Baicalin) on rat renal marker levels in control and experimental groups with STZ-induced changes. The standard deviation is calculated for each rat. The different alphabets (a, b, c, etc.) represent significant differences at $p < 0.05$ in each trial, showing the impact of BA treatment on renal marker levels in diabetic animals. The findings suggest that BA may hold promise as a potential therapeutic agent for managing diabetic nephropathy.

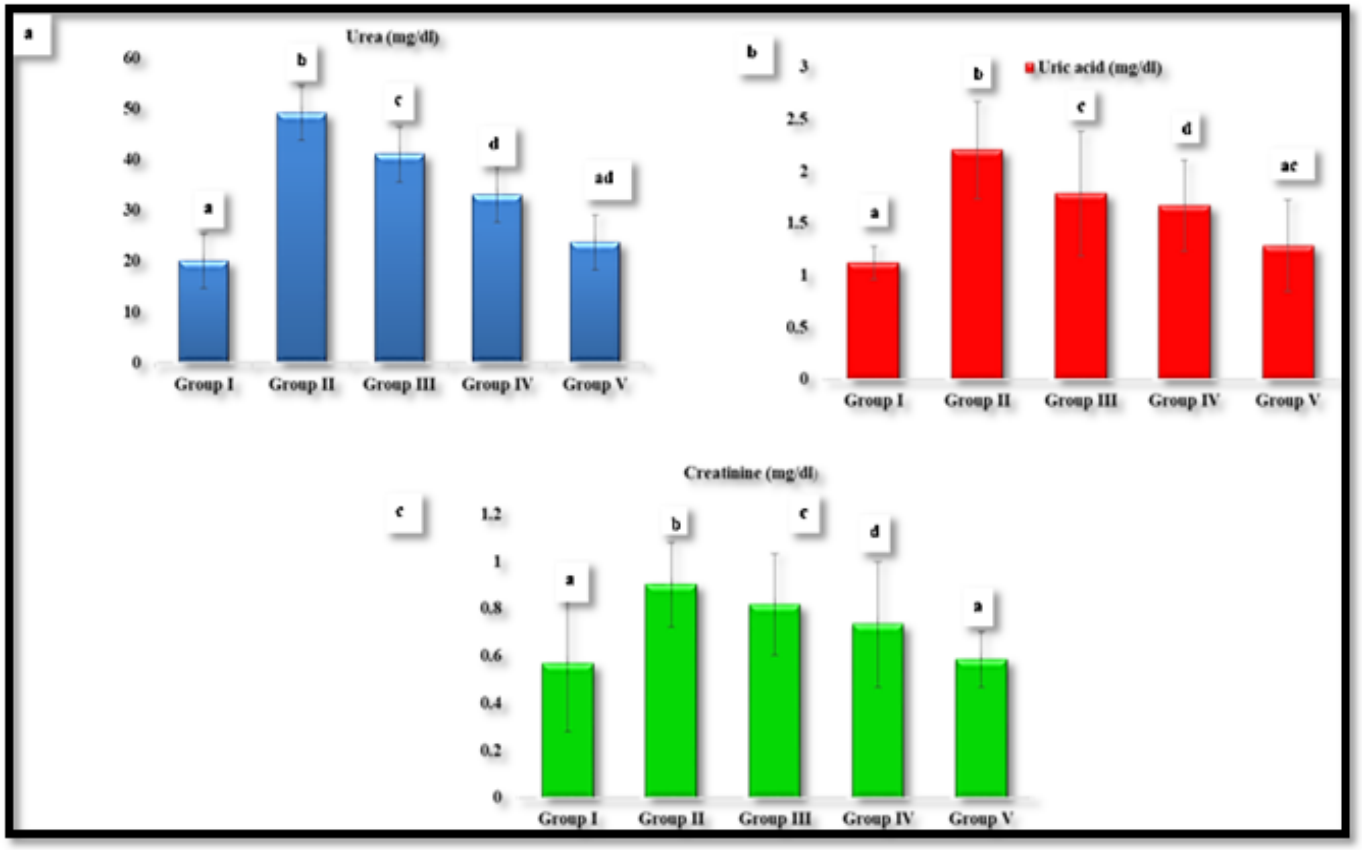


Figure 3 (a, b, c). Effect of baicalin on renal markers in diabetic rats

DISCUSSION

Diabetes mellitus is a prevailing global health issue, affecting millions of people. As the population grows, urbanization increases, and sedentary lifestyles become more common, diabetes is becoming more prevalent. Consequently, research on natural compounds with significant hypoglycemic properties is gaining momentum, given the absence of a permanent solution to diabetes and potential adverse effects of existing anti-diabetic drugs [32]. Among the natural compounds, Baicalin has garnered significant attention for its anti-diabetic properties.

Studies on streptozotocin-induced diabetic rats have shown that Baicalin improves glucose tolerance, reduces hyperglycemia, and protects against islet cell damage [14]. Additionally, a glucuronide derivative of Baicalin has demonstrated anti-diabetic and anti-complication effects [33]. This study was aimed to detect the protective role of Baicalin, a glycoside phytochemical compound, in streptozotocin-induced diabetic rats, using glibenclamide, a standard antidiabetic drug, as a reference for comparison.

Streptozotocin (STZ) is commonly used in experimental animal models to induce diabetes mellitus [34]. STZ treatment leads to the destruction of pancreatic cells, resulting in diabetes [35]. Following STZ administration, the rats exhibited significantly elevated blood glucose levels and symptoms akin to type 2 diabetes, consistent with other studies on STZ-induced experimental diabetes [36-38]. These findings indicate that the rats experienced oxidative stress, a known contributor to diabetic complications.

The protective role of Baicalin on STZ-induced diabetic rats was assessed through a 45-day

experimental study. The results revealed that Baicalin administration improved glucose tolerance and reduced hyperglycemia in diabetic rats, suggesting its potential as an anti-diabetic agent. Moreover, Baicalin showed protective effects against islet cell damage, further supporting its role in diabetes management [14]. Oxidative stress is a key factor contributing to diabetic complications. In this study, the observed symptoms in the diabetic rats, such as increased blood glucose levels, are indicative of oxidative stress [35]. Baicalin's ability to mitigate oxidative stress may underlie its anti-diabetic properties, although further research is required to decode the exact molecular mechanisms involved.

The present study's findings align with previous research on the anti-diabetic effects of Baicalin. A glucuronide derivative of Baicalein has also demonstrated promising anti-diabetic and anti-complication effects [33], indicating the potential of Baicalin and its derivatives in managing diabetes-related complications. The comparison with glibenclamide, a standard anti-diabetic drug, provided valuable insights into Baicalin's efficacy as a potential alternative therapy. Considering the potential adverse effects associated with conventional anti-diabetic drugs [32], Baicalin may offer a safer and more natural option for diabetes management.

As diabetes continues to be a prevalent health concern worldwide, researching natural compounds like Baicalin for diabetes management holds significant promise. These studies have the potential to drive the development of innovative and safer treatments for diabetes, ultimately benefiting millions of individuals worldwide affected by this chronic condition [32]. Translating these promising preclinical findings into human clinical trials will be a critical step in validating Baicalin's efficacy and safety as an anti-diabetic therapy [14]. The knowledge gained from such trials could pave the way for the incorporation of Baicalin-based therapies into mainstream diabetes management strategies, ultimately increasing the quality of life for individuals living with diabetes [14].

In this study, STZ was chosen as the agent to induce diabetes due to its cytotoxic effect on pancreatic cells [39]. STZ's ability to produce excessive reactive oxygen species (ROS), carbonium ions (CH3+), and alkali leads to the selective destruction of pancreatic cells without causing harm to other cell types [39]. The injection of streptozotocin at a dose of 40 mg/kg resulted in partial death of pancreatic cells, replicating the characteristics of type 2 diabetes [40]. The animals treated with STZ exhibited diabetic conditions characterized by raised levels of blood glucose resulting from abnormal lipid, protein, and carbohydrate metabolism due to insufficient pancreatic insulin secretion.

In addition to the findings from our study, several other studies have investigated the hypoglycemic efficacy of baicalin in diabetic animals. Ma et al. [41] reported a significant decrease in blood glucose levels and raised plasma insulin levels in diabetic rats supplemented with baicalin. Similarly, Zhang et al. [42] observed improved insulin sensitivity and glucose tolerance with baicalin treatment in diabetic animals. These consistent results across multiple studies provide robust evidence supporting the significant anti-diabetic efficacy of baicalin.

Baicalin's ability to lower blood glucose levels and enhance insulin secretion positions it as a promising candidate for developing therapeutic agents in diabetes management. Combining our study's results with evidence from previous research highlights the potential value of baicalin in diabetes treatment strategies. Furthermore, in STZ-induced diabetic animals, weight loss is common due to insulin deficiency [43-45]. However, our study found that rats treated with baicalin and glibenclamide experienced significant weight gain,

indicating improved insulin function [43-45]. This observation is consistent with recent studies - Gushiken et al. [43] reported weight gain with an herbal extract that improved insulin sensitivity. Yang et al. [44] found weight gain with a novel compound that enhanced glucose utilization, and Zhang et al. [45] reported weight gain, improved insulin sensitivity, and reduced hepatic gluconeogenesis through dietary interventions in diabetic rats. Additionally, studies by Ansari et al. [46] and Chen et al. [47] have explored the potential of other natural compounds in diabetes treatment, providing further support for the exploration of various natural agents in managing diabetes.

Our study suggests that baicalin may positively impact metabolic regulation and insulin function, leading to weight gain in diabetic animals. Additionally, our investigation explored glycated hemoglobin levels as an indicator of glucose-lowering drug efficacy and long-term blood sugar management [48]. Baicalin and glibenclamide administration significantly decreased glycated hemoglobin levels, resulting from reduced blood glucose levels and increased insulin production. Hyperglycemia-associated non-enzymatic glycation results in the production of advanced glycation end products, contributing to complications in type 2 diabetes [49].

Integrating our results with previous research indicates baicalin's potential as an effective anti-diabetic agent, aligning with mechanisms identified in other studies [50-52]. These findings reinforce the notion that baicalin improves insulin sensitivity, promotes insulin secretion, and reduces blood glucose levels in diabetic animals.

Nephropathy, a common complication of diabetes, is often attributed to diabetes-induced oxidative stress, which is believed to be the main causative factor for kidney damage [39]. In our study, we investigated the potential of baicalin, obtained from a traditional Chinese medicinal plant used to treat diabetic nephropathy, in mitigating kidney damage in diabetic rats. The kidneys have a vital role in maintaining the body's chemical balance by eliminating metabolic wastes and ions from the blood [40]. In diabetic nephropathy, the increased concentrations of substances such as urea, uric acid, and creatinine in the blood highlight the severity of kidney damage [49]. Our current investigation focused on evaluating whether treatment with baicalin could reduce these metabolite levels and thereby protect the renal tissue of diabetic rats.

Previous studies have reported that baicalin improves renal function in diabetic patients [42]. Consistent with these findings, our study demonstrated that baicalin treatment reduced the levels of urea, uric acid, and creatinine in diabetic rats [42]. This finding indicates that baicalin may have a protective action on the kidneys and could be beneficial in managing diabetic nephropathy. Moreover, recent studies have shown that baicalin can enhance insulin sensitivity by upregulating IRS-1 and GLUT4 expression [39]. This suggests that baicalin may directly affect the kidneys and influence overall glucose metabolism and insulin sensitivity. Our research aligns with these observations, further supporting the potential benefits of baicalin in managing diabetic nephropathy [39].

In addition to insulin sensitivity, baicalin has been reported to improve glucose tolerance and insulin sensitivity through AMPK activation [41]. This pathway may contribute to its renoprotective effects, as demonstrated in our study, where baicalin-treated diabetic rats showed improvements in kidney function [41]. Furthermore, baicalin has been shown to mitigate hyperglycemia-induced oxidative stress [48]. Considering

the link between oxidative stress and kidney damage in diabetes, this antioxidative property of baicalin is relevant to our investigation. Reducing oxidative damage in diabetic nephropathy could be a crucial mechanism by which baicalin protects the kidneys [48]. Our study provides evidence supporting the potential therapeutic value of baicalin in managing diabetic nephropathy [39, 41-42, 48]. The improvements in renal function, insulin sensitivity, and antioxidative effects suggest that baicalin may be a valuable adjunctive therapy for diabetic nephropathy management.

CONCLUSION

In conclusion, our study highlights the significant therapeutic potential of baicalin for diabetes treatment. The oral administration of baicalin at 50 mg/kg body weight demonstrated substantial improvements in insulin secretion, hemoglobin levels, and glycemic control compared to glibenclamide in type 2 diabetic rats, emphasizing its efficacy as an antidiabetic agent. Furthermore, baicalin exhibited renoprotective effects, suggesting its promise in reducing diabetic nephropathy, a severe complication associated with diabetes. These observed benefits make baicalin a promising candidate for diabetes management and renal protection.

To further enhance the clinical applicability of baicalin, it is essential to explore potential synergistic effects when combined with other antidiabetic agents or compounds. Investigating combination therapies could open new avenues for more effective and comprehensive diabetes management strategies. In addition, we believe that including both the sexes in the experiment could have provided gender differences to the effect of baicalin, if any. Also, we believe that histopathological analysis of major organs (which would be commonly affected by diabetes) could provide more elaborate data on the effect of baicalin in treating diabetes. These limitations should be addressed in future studies. Exploring baicalin's effects on other diabetes-related complications and utilizing different animal models can provide valuable insights into its broader therapeutic implications. In summary, baicalin holds excellent promise as a valuable addition to current diabetes management strategies, with the potential to benefit millions worldwide living with this chronic condition. Continued research and validation of its therapeutic effects will be essential in harnessing the full potential of baicalin for diabetes treatment and renal protection.

List of Abbreviations: DM - Diabetes Mellitus; BA-Baicalin; STZ- Steptozotocin; DMSO - Dimethyl sulfoxide; GC- Glibenclamide

Competing Interest: No conflict of interest associated with this work.

Author Contributions: The authors of this study hereby affirm that they are responsible for the content presented herein. Prithiviraj Nagarajan conceived the research theme, designed the experiments, generated and analyzed data, and prepared the initial manuscript. Pavithra Muthiah and Leena Rajathy Port Louis conducted the animal experiments, collected samples, and assisted in data acquisition. Ravikumar Sambandam obtained funding and research/ethics committee approvals and contributed to the manuscript editing. All authors have thoroughly reviewed and approved the final version of the manuscript intended for publication.

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Ethical Approval: The study was conducted following the guidelines of a registered animal facility (996/PO/Re/S/06/CPCSEA) and received approval from the Institutional Animal Ethics Committee (approval no: AVMC/IAEC/2019/07/25/08) of Aarupadai Veedu Medical College and Hospital, Puducherry, India.

Availability of Data and Materials: For any inquiries regarding the datasets used or analyzed during this study, please contact the corresponding author, who will provide the information upon request.

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