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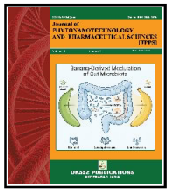

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Improved glycemic control and pancreatic antioxidant protection with biochanin-A and metformin in experimental diabetes

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Abstract

Diabetes mellitus is a metabolic disorder where hyperglycaemia and insulin dysfunction promote tissue injury, with oxidative stress contributing to pancreatic β-cell damage. Given the antihyperglycaemic and antioxidant activities of biochanin-A (BCA) and metformin's clinical utility, this study evaluated their combination in streptozotocin (STZ)-induced diabetic rats. Adult Sprague Dawley rats (150-200 g) were made diabetic using STZ (65 mg/kg, i.p.) in citrate buffer (pH 4.5); rats with fasting glucose >250 mg/dl were included. Rats were allocated to five groups (n=5/group): normal control, diabetic control, metformin (250 mg/kg, p.o.), BCA (40 mg/kg, p.o.), and metformin + BCA (250 + 40 mg/kg, p.o.), treated for 15 days. Outcomes included body weight, fasting glucose, food/water intake, oral glucose tolerance test (2.5 g/kg dextrose with AUC), insulin tolerance test, pancreatic oxidative biomarkers (SOD, catalase, GSH, TBARS). Diabetic controls showed hyperglycaemia, weight loss, reduced SOD, catalase, GSH, elevated MDA, and islet damage with β-cell loss. All treatments significantly reduced glucose and improved oxidative indices versus diabetic controls (p<0.0001), but metformin + BCA produced greater glycaemic reduction than monotherapies, better weight preservation, improved glucose handling, and superior restoration of antioxidant markers. The BCA-metformin combination enhanced antidiabetic efficacy and pancreatic antioxidant protection, suggesting potential for improving glycaemic control and reducing oxidative stress complications.

1. Introduction

Diabetes mellitus (DM) is likely one of the oldest metabolic disorders known to humans, with its first mention appearing in an Egyptian manuscript around 3000 years ago. By 2030, it is anticipated to rank as the 7th leading cause of death. Type 2 DM was initially identified as part of the metabolic syndrome in 1988. This widespread disease impacts approximately 17 million individuals globally. Diabetes mellitus and its associated complications pose a significant public health challenge for contemporary societies. It is widely acknowledged that DM exists in four primary forms: type 1, type 2, gestational diabetes, and diabetes arising from other specific causes (CDC, 2015). Insulin-dependent diabetes mellitus (IDDM), also referred to as type 1 diabetes mellitus, is less common, affecting 5-10% of patients who cannot produce insulin due to the destruction of pancreatic â-cells (Hashim *et al.,* 2024; Hashim *et al.,* 2023). Type 1 diabetes mellitus (T1DM) is believed to originate from an immune-mediated disorder that selectively targets and destroys pancreatic β-cells following inflammatory infiltration of the islets of Langerhans, a pathological process known as insulitis. Insulitis is an inflammatory condition of the pancreatic islets, crucial components of the pancreas responsible for regulating blood glucose levels. Most diabetes patients have type 2 or non-insulin-dependent diabetes mellitus (NIDDM). NIDDM patients can initially produce insulin but have a deficient cellular response. In both types, reduced glucose uptake into muscle and fat tissue leads to chronic extracellular hyperglycemia, causing tissue damage and pathophysiological complications. Type 2 DM, previously called non-insulin-dependent DM, is the most prevalent form of DM, characterised by high blood sugar, insulin resistance, and relative insulin deficiency. Type 2 DM results from the interplay of genetic, environmental, and behavioural risk factors (Shoaib *et al.,* 2020).

Often called “free radical scavengers,” antioxidants are chemicals that can help stop or lessen the harm that free radicals do to cells. These unstable molecules, known as free radicals, are produced by the body as byproducts of many metabolic processes. Oxidative stress is the result of an imbalance between the body’s antioxidant defences and the generation of free radicals. This oxidative stress can cause lipid peroxidation, DNA damage, and cellular damage, all of which can contribute to a number of illnesses, including diabetes and neurological diseases (Singh *et al.,* 2024).

Biochanin-A (BCA) is an isoflavone present in red clover, soy, alfalfa sprouts, peanuts, and chickpeas. Its flavonoid structure is likely responsible for its antioxidant and anti-inflammatory properties. It exhibits a range of pharmacological effects, including neuroprotective, antiallergic, antihyperglycemic, and hepatoprotective actions. Additionally, it offers cardioprotective benefits, acts as a peroxisome proliferator-activated receptor (PPARs) agonist, and has vasorelaxant, neuroprotective, antiparasitic, antiproliferative, and antifibrotic

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activities. Biochanin A has also been shown to activate sirtuin1 (silent mating type information regulation 2 homolog) (SIRT1). Various studies have demonstrated that biochanin A can effectively reduce hyperglycemia in type 1 diabetic rats. Recently, it has been reported that biochanin A enhances lipid metabolism and insulin sensitivity in diet-induced obesity and is also noted for its sirtuin1 (silent mating type information regulation 2 homolog) (SIRT1) activation effect at the cellular level (Oza *et al.,* 2018).

Metformin, an oral medication belonging to the biguanide class of antihyperglycemic agents, is the most commonly prescribed drug for lowering blood sugar in individuals with type 2 diabetes mellitus (T2DM). In addition to its widespread use in T2DM, metformin has shown benefits for patients with type 1 diabetes mellitus (T1DM) by enhancing insulin sensitivity. Recent research has highlighted the diverse benefits of metformin, including cardiovascular protection, anticancer properties, and anti-inflammatory effects. Among these, the anti-inflammatory properties of metformin have garnered significant attention due to their promising clinical potential. It has been reported that metformin can activate the AMPK/PI3K/Akt signalling pathway in human vascular smooth muscle cells, thereby exerting anti-inflammatory effects by inhibiting NF-κB and subsequently reducing the production of proinflammatory cytokines. Furthermore, recent clinical studies have indicated that metformin treatment in patients with impaired glucose tolerance (IGT) aids in down-regulating various proinflammatory cytokines released from inflammatory cells (Goldberg *et al.,* 2022).

Streptozotocin (STZ), also known as (2-deoxy-2 (3-(methyl-3-nitrosoureido)-D glucopyranose), is an antimicrobial compound frequently employed to create a T1DM model (insulin-dependent diabetes mellitus, IDDM). Additionally, it serves as a chemotherapeutic alkylating agent that selectively targets pancreatic â-cells through the GLUT2 glucose transporter, leading to â-cell necrosis and subsequently hindering insulin secretion, a process known as insulitis. Therefore, managing the inflammatory response presents a viable therapeutic strategy for impacting the disease (Shoaib *et al.,* 2020).

This work aimed to assess the combined impact of biochanin-A and metformin on diabetic rats induced with STZ. Currently, there is no scientific evidence available regarding the joint effect of biochanin-A and metformin, which could potentially offer synergistic effects and additional advantages in diabetes treatment.

2. Materials and Methods

2.1 Drugs and chemicals

All the chemicals and pharmaceuticals utilised are of analytical grade and were sourced from certified companies, including Sigma, Merck, Changshu Yangyuan Chemical in China, and Fisher Scientific Ltd in Mumbai, India, among others.

2.2 Animals

Adult male Sprague Dawley rat body weight (150-200 g) were procured from Central Drug Research Institute (CDRI), Lucknow and housed in the Animal House Facility, Faculty of Pharmacy, Integral University, Lucknow. Polypropylene cages were used to keep the animals (5 in each cage). The laboratory was maintained at 12 h light and 12 h dark cycle, and all the animals had free access to a standard pellet diet and drinking water *ad libitum*. The animal house temperature was maintained at 23 ± 2°C and relative humidity was also maintained at (50 ± 15 %). Seven days were given to the animals for acclimatisation. Ethical clearance was obtained from the Institutional Animal Ethical Committee (IAEC) (Approval No: IU/IAEC/20/21), Integral University, Lucknow.

2.3 Experimental design

All Sprague Dawley rats were divided into 5 groups (5 animals in each), and initial body weight of all groups of animals were recorded.

Diabetes induction: Rats were housed without food, although they were given access to water the night before. After a 15-min pause, streptozotocin (STZ) was combined with an ice-cold citrate buffer (pH 4.5, 0.1 M) and injected intraperitoneally at a dose of 65 mg/kg body weight within 5 min. 72 h after the injection, blood glucose levels were measured. Diabetic rats were given water and 5% glucose 24 h after the STZ injection to prevent hypoglycemia-related mortality. After 72 h, blood samples were taken from the tail vein and examined using an Accucheck glucometer. Research studies on diabetes involved animals that had plasma glucose levels more than 250 mg/dl.

The treatment schedule and period for each group of animals were 15 days (given in Table 1). At the end of the study, the final body weight and glucose tolerance test of all animals were recorded. After that, the animal was anaesthetised with thiopentone sodium, and blood samples were collected through retro orbital puncture for the estimation of blood sugar and other biochemical tests.

Table 1: Treatment schedule

Groups (N= 5)	Treatment	Dosage, Route of administration and duration
NC	Vehicle (1% CMC)	10 ml/kg, p.o. once a day for 15 days.
DC	Streptozotocin	65 mg/kg, i.p. Single dose.
MET	Diabetic rat + Metformin	250 mg/kg, p.o. once a day for 15 days.
DC + BCA	Diabetic rat +Biochanin-A (BCA)	40 mg/kg, p.o. once a day for 15 days.
MET + BCA	Diabetic rat + Metformin + Biochanin-A	250 mg/kg + 40 mg/kg, p.o. once a day for 15 days.

(N = Number of rats, NC = Normal control, DC = Diabetic control, STD = Standard, i.p. = intraperitoneal, STZ = Streptozotocin, p.o. = per oral).

2.4 Evaluated parameters

2.4.1 Blood glucose estimation

The level of fasting blood glucose was measured by Accu-check active kit following the manufacturer's instructions.

2.4.2 Body weight changes

To determine the variations in body weight among all the experimental animals, their initial and final weights were recorded using a weighing scale. The difference in body weight was obtained by deducting the initial weight of each animal from its final weight.

2.4.3 Oral glucose tolerance test

OGTT was performed to measure the glucose tolerance. After an overnight fasting, dextrose solution (40% wt/vol.) was administered intragastrically into rats at a dose of 2.5 g/kg body weight and blood sugar was checked at 0, 30, 60 and 120 min time points. Glucose levels were considered at specific intervals (Matthews *et al.,* 1990). Glucose tolerance (OGTT) was measured by calculating the area under the curve (AUC) for glucose by the trapezoidal method (Subramanian *et al.,* 2008). AUC = (basal glycaemia + glycaemia 0.5 h) × 0.25 + (glycaemia 0.5 h + glycaemia 1 h) × 0.25 + (glycaemia 1 h + glycaemia 2 h) × 0.5.

2.4.4 Insulin tolerance test

The insulin tolerance test (ITT) evaluates insulin sensitivity by monitoring endogenous glucose disappearance over time in response to an injection of human insulin. To avoid hypoglycemia induced by the insulin injection, the test is conducted in a fasted rat between 8 and 10 h.

2.5 Assessment of oxidative biomarkers in pancreas

Antioxidant levels, including glutathione, catalase, superoxide dismutase, and thiobarbituric acid reactive substances, were assessed in pancreatic tissue (Jollow *et al.,* 1974; Marklund and Marklund, 1974; Ohkawa *et al.,* 1979; Claiborne, 1985).

2.6 Statistical analysis

The data is presented as the mean ± SEM for each group of four animals. Statistical analysis was conducted using one-way ANOVA, followed by Dunnett's test to compare all groups against the control (Graph Pad Instat, USA).

3. Results

3.1 Effect of metformin and biochanin-A on the blood glucose level

In the diabetic control group (DC), the glucose level significantly increased ($p<0.0001$) when compared with the normal control group (NC). The glucose level was significantly decreased ($p<0.0001$) with all the treated groups (*i.e.,* Diabetic rat + Metformin (250 mg), Diabetic rat + Biochanin-A (40 mg), Diabetic rat + Metformin + Biochanin-A) when compared with diabetic control (DC), however the % reduction in combination treated group was better as compared to metformin and biochanin-A treated groups (Table 2).

3.2 Effect of metformin and biochanin-A on body weight change

The % body weight was decreased in diabetic control rats (DC) and diabetic rats treated with metformin when compared with the normal control group (NC). While in the Diabetic rat + Biochanin-A (40 mg) and Diabetic rat + Metformin + Biochanin-A) treated group, it was increased when compared to metformin (250 mg) alone (Table 3).

Table 2: Effect of metformin and biochanin-A on the blood glucose level

Treatment	Blood glucose concentration (mg/dl)		% Change in blood glucose level
	Initial blood glucose level	Final blood glucose level	
NC	105.87 ± 1.647	113 ± 2.387	-
DC	310.96 ± 4.523	342.67 ± 3.205***	-
Diabetic rat + Metformin	289.92 ± 4.414	165.45 ± 2.102###	43%
Diabetic rat + Biochanin-A	288.2 ± 3.081	185.07 ± 1.677###	36%
Diabetic rat + Biochanin-A + Metformin	313.52 ± 2.81	166.42 ± 1.657###	47%

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA), and individual comparison was done by Dunnett's t-test. ***$p<0.0001$ = Significant, when compared with NC. ###$p<0.0001$=Significant when compared with DC.

Table 3: Effect of metformin and biochanin-A on the body weight change

Treatment	Body weight change (g)		% change in body weight	
	0 Day	15 Day	Increase	Decrease
NC	155.35 ± 4.54	179.10 ± 3.13	15%	-
DC	150.80 ± 2.56	138.28 ± 3.23***	-	83%
Diabetic rat + Metformin	162.00 ± 4.36	153.36 ± 3.19##	-	53%
Diabetic rat + Biochanin-A	150.6 ± 5.83	155.44 ± 3.53#	32%	-
Diabetic rat + Biochanin-A + Metformin	143.36 ± 6.46	160.84 ± 3.59##	12%	-

All values were expressed as mean ± SEM. Significant difference between various groups (ANOVA), and individual comparison was done by Dunnett's t-test. ***$p<0.0001$ = Significant, when compared with NC. ###$p<0.0001$=Significant when compared with DC.

3.3 Effect of metformin and biochanin-A on the oral glucose tolerance (OGT)

In the diabetic control group (DC), the blood glucose level was gradually increased up to 1.5 h when compared with the normal control group (NC). The blood glucose level was decreased and maintained up to 1 h in all the treated groups (*i.e.,* Diabetic rat + Metformin (250 mg), Diabetic rat + Biochanin-A (40 mg), Diabetic rat + Metformin + Biochanin-A) when compared with diabetic control (DC). However, it was maintained in the combination group of metformin (250 mg) with Biochanin-A (40 mg) treated group when compared with standard metformin (250 mg) (Figure 1).

3.4 Effect of metformin and biochanin-A on insulin tolerance (IT)

After performing the insulin tolerance test **(**ITT**),** it was observed that in the case of the diabetic control group (DC), the blood glucose was decreased when compared with normal control group (NC). Whereas in all treatment groups (*i.e.,* Diabetic rat + Metformin (250 mg), Diabetic rat + Biochanin-A (40 mg), Diabetic rat + Metformin + Biochanin-A), the blood glucose was gradually decreased up to one hour when compared with Diabetic control (DC). Moreover, the blood glucose level was maintained up to 1.5 h in the combination group of metformin (250 mg) with Biochanin- A (40 mg) treated, when compared with metformin (250 mg) (Figure 2).

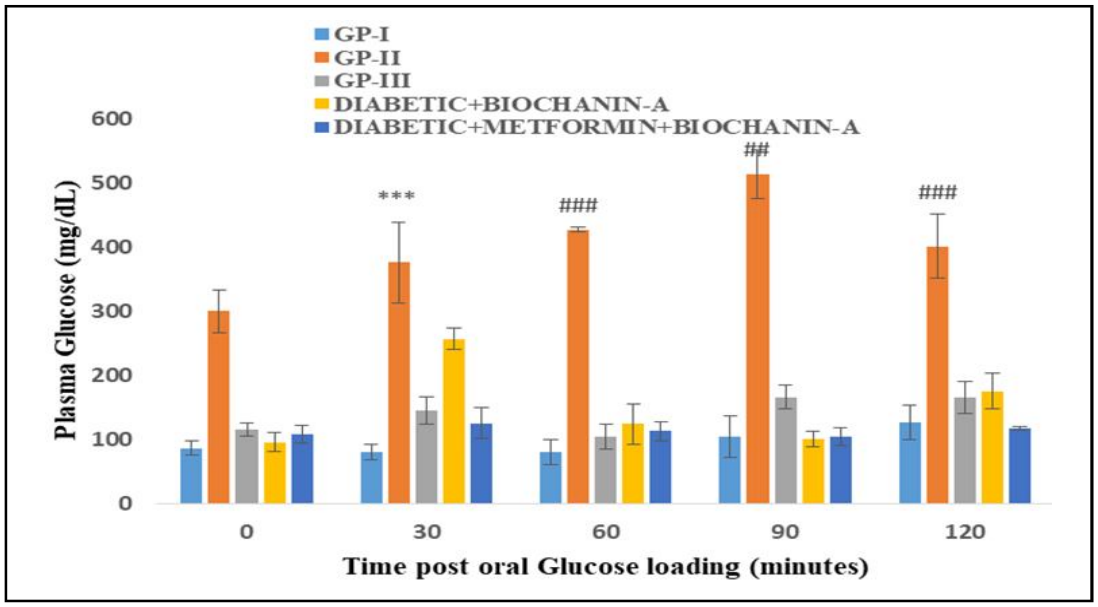

Figure 1: Effect of metformin and biochanin-A on the OGT.
All values were expressed as mean ± SEM. $^{***}p<0.0001$=Significant, when compared with NC, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.01$=Significant when compared with DC.

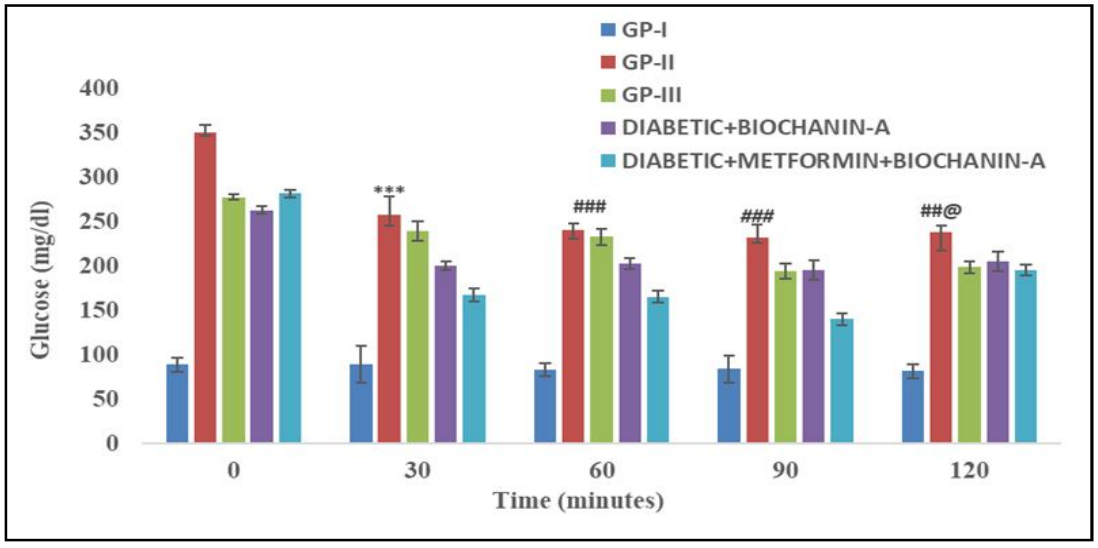

Figure 2: Effect of metformin and biochanin-A on insulin tolerance.
All values were expressed as mean ± SEM. $^{***}p<0.0001$=Significant, when compared with NC, $^{\#\#\#}p<0.01$=Significant when compared with DC.

3.5 Effect of metformin and biochanin-A on SOD, MDA, GSH and catalase level in pancreas tissue

In the diabetic control group (DC), the SOD, GSH and catalase levels significantly decreased ($p<0.0001$) while MDA level significantly increased when compared with the normal control group (NC). The SOD, GSH and catalase level was significantly increased ($p<0.0001$) while MDA level significantly decreased with all the treated groups (*i.e.,* Diabetic rat + Metformin (250 mg), Diabetic rat + Biochanin-A (40 mg), Diabetic rat + Metformin + Biochanin-A) when compared with diabetic control (DC), however better modulation was observed in combination of Metformin (250 mg) with Biochanin- A (40 mg) treated group when compared with Metformin (250 mg) alone (Table 4).

Table 4: Effect of metformin and biochanin-A on SOD, MDA, GSH and catalase levels

Treatment	SOD level (µg /mg of protein)	MDA level (nmol /mg of protein)	GSH level (µg/ mg of protein)	Catalase level (µg/ mg of protein)
NC	62.53 ± 0.65	0.84 ± 0.02	64.447 ± 1.52	7.855 ± 0.33
DC	32.787 ± 0.59***	1.32 ± 0.03***	19.9 ± 0.40**	3.11 ± 0.37***
STD (Diabetic rat + Metformin)	44.19 ± 2.14$^{\#\#\#}$	0.99 ± 0.04$^{\#\#\#}$	34.1 ± 0.52$^{\#}$	4.64 ± 0.28$^{\#\#\#}$
Diabetic rat + Biochanin-A (BCA)	43.25 ± 1.29$^{\#\#\#}$	1.13 ± 0.08$^{\#}$	44.31 ± 0.93$^{\#}$	5.15 ± 0.40$^{\#\#}$
Diabetic rat + Metformin + Biochanin - A	46.49 ±1.59$^{\#\#\#}$	0.90 ± 0.01$^{\#\#\#}$	48.16 ± 1.70$^{\#\#}$	6.45 ± 0.26$^{\#\#\#}$

All values were expressed as mean ± SEM. $^{***}p<0.0001$=Significant, when compared with NC, $^{\#}p<0.05$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$=Significant when compared with DC.

4. Discussion

As a metabolic disease, diabetes mellitus (DM) is mainly defined by persistently high blood sugar levels. It is classified into two primary forms, I and II, and is said to be one of the most common diseases in the world, impacting significant populations worldwide. Diabetes can lead to complications such as renal failure, heart attack or stroke, lower limb amputation, and blindness (Anwar *et al.,* 2024). Rats with streptozotocin-induced diabetes showed a decrease in body weight. Dehydration and the breakdown of proteins and fats in tissues as a result of insufficient insulin may be the cause of this weight loss in diabetic rats. Furthermore, the reduced weight gain seen in diabetic rats may possibly be due to enhanced catabolic processes that cause muscular atrophy. In the past, a single large dosage of streptozotocin (STZ), a highly selective drug toxic to pancreatic islet β-cells, was used to cause total β-cell death and diabetes within 48 h.

The most popular first hypoglycemic drug for treating diabetes mellitus is metformin. Its possible anti-inflammatory qualities are gaining attention in addition to its capacity to reduce glucose levels. Because it considerably lowers plasma fasting insulin levels and efficiently lowers blood glucose levels without producing major hypoglycemia, it is thought to be the most commonly given medicine for treating type 2 diabetes. Metformin is a common insulin sensitizer used to treat type 2 diabetes. Metformin can reduce fat mass and stop the growth of malignant cells in addition to reducing blood glucose. The reduction of gluconeogenesis, which lowers hepatic glucose synthesis, and the activation of peripheral glucose consumption in the muscle, gut, and liver are responsible for its glucose-lowering impact (Vieira *et al.,* 2022).

Phosphodiesterase (PDE)4 is the specific target of biochanin-A, which inhibits it and raises cAMP levels. The clearance of calcium from the intracellular space and its uptake into the sarcoplasmic reticulum (SR) are improved by this activation of cAMP-dependent protein kinase (PKA). Biochanin-A therapy lowers plasma glucose levels and raises insulin levels in diabetic rats. This is probably because existing ß-cells secrete more insulin, which increases tissue utilization of glucose. In contrast to administering metformin alone, we observed that the combination of metformin and Biochanin-A dramatically improved weight gain, stabilized blood glucose levels, and increased insulin production from existing β-cells in diabetic rats (Chaichamnong *et al.,* 2025; Adnan *et al.,* 2025).

Catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) are important endogenous antioxidant enzymes and compounds. By transforming $O_2^{\bullet}$ into H_2O_2, a more stable reactive oxygen species, SOD serves a critical function in keeping cellular $O_2^{\bullet}$ levels within physiological bounds. In the meantime, CAT converts H_2O_2 into H_2O and O_2. Depending on the quantity of its substrate, H_2O_2, catalase displays two different kinds of enzymatic activity. It functions as a catalyst at high H_2O_2 concentrations and as a peroxidant at lower amounts. Using glutathione (GSH) as a hydrogen donor, GPx converts H_2O_2 to O_2 and H_2O, which is further oxidized to glutathione disulfide (GSSG). Thus, the primary mechanism of the cell involves using superoxide dismutase, catalase, and glutathione peroxidase to prevent superoxide anion or hydrogen peroxide from engaging in reactions that produce more reactive oxidants, such as hydroxyl radicals.

Research has indicated that metformin and biochanin-A possess antioxidant capabilities by elevating the levels of enzymatic antioxidants such as SOD, catalase, and GSH, while reducing MDA levels in pancreatic tissue. In this investigation, the combined treatment of metformin with biochanin-A led to an increase in GSH, catalase, and SOD levels and a decrease in MDA levels in diabetic rats, compared to the effects of metformin alone.

5. Conclusion

Our findings provided substantial evidence supporting the antidiabetic effectiveness of combining metformin with biochanin-A, as it helps reduce oxidative stress in pancreatic tissue. The research concluded that the combination of metformin and biochanin-A offers superior antidiabetic and antioxidant benefits compared to using metformin alone. Such combinations appear to be a promising therapy for maintaining glycemic control and may potentially decrease or postpone the onset of diabetic complications. Nevertheless, further studies are needed to confirm this potential.

Availability of data and material

All data are provided within the manuscript.

Authorship contribution statement

Rukhsar Anwar: Contributed to conceptualization, methodology design, data curation, and writing the original draft of the manuscript. **Badruddeen**: Contributed to conceptualization and critical review of the manuscript. **Anas Islam**: Contributed to data collection. **Juber Akhtar:** Contributed to supervision and visualization of data presentation. **Mohammad Irfan Khan and Nitin Ranjan Gupta:** Contributed to project administration, validation, and final manuscript approval. **Mohammad Ahmad:** Contributed to literature review, data organization, and editing of the final draft.

Consent for publication

All authors gave their full consent for publication and submission to this journal.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Ethics approval

The study was approved by the Institutional Animal Ethical Committee (IAEC), Integral University, Lucknow (Approval No: IU/IAEC/20/21).

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