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Antidiabetic Activity Of Bioflavonoid Curcumin On Alloxan Induced Diabetic Rats

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Abstract

Aim: *The aim of the present study was the evaluation of antidiabetic effect by curcuin in alloxan-induced diabetes rats.*

Methods: *A single dosage of 120 mg/kg of alloxan was injected to induce diabetes, which was validated 72 hours later. Curcumin (40 and 80 mg/kg; oral) was given every day for three weeks. When compared to control animals, the group of animals given alloxan experienced a marked rise in hyperglycemia.*

Results: *The protective impact of curcumin was enhanced at both the lower and higher doses ($p < 0.05$; $p < 0.01$), and both doses (40 and 80 mg/kg) reduced the increases of blood glucose in diabetic rats. However, animals given alloxan experienced elevated hyperglycemia.*

Conclusion: *We found that the antioxidative/chelatory qualities of the flavonoids may be linked to their protective impact in experimental diabetes mellitus. It might possibly contribute to flavonoids' hypoglycemic action.*

Key words: *Curcumin, alloxan-induced diabetes, hypoglycemic effect, oxidative stress, antioxidant and flavonoids*

INTRODUCTION

One of the pathophysiology of diabetes mellitus is oxidative stress and antioxidant imbalances. Glucose oxidation, non-enzymatic protein glycation, and the oxidative breakdown of glycated proteins all contribute to the disproportionate formation of free radicals in diabetes (Maritim et al. 2003; Mehta et al. 2006). Increased lipid peroxidation, insulin resistance, and damage to cellular organelles and enzymes might result from abnormally high amounts of free radicals and the concurrent deterioration of antioxidant defense mechanisms (Bartošíková et al. 2003). These oxidative stress-related effects could encourage the emergence of diabetes mellitus complications. New information on the involvement of oxidative stress in diabetes has been revealed by experimental and clinical research, which also suggests a novel and distinct strategy for a potential "causal" antioxidant therapy of the flavonoids. The largest and most significant classes of polyphenolic chemicals found in plants are flavonoids. They are generally found in a variety of commonly consumed plant-based foods and beverages, including fruits, vegetables, wine, tea, and chocolate. Since the study of (Bentsáth et al. 1936), who suggested that flavonols were a crucial dietary component supporting the preservation of capillary permeability, interest in the biological activity of food-borne polyphenolics has grown. The increased interest in dietary antioxidants and metabolically active phytochemicals over the past ten years has drawn attention to other possibly advantageous effects of flavonoids, even if this theory was eventually dropped (Doubek et al. 2005). Many of the aforementioned bodily functions are attributed to flavonoids strong antioxidant activity, which may be their most significant role, by scavenging or quenching free radicals, chelating metal ions, or blocking the enzymatic systems that produce free radicals, flavonoids can exhibit their antioxidant properties. As was previously established, free radicals have a role in diabetes mellitus in both human and experimental settings. Alloxan administration is known to produce severe necrosis of pancreatic B-cells (Lankin et al. 2004; Heikkila et al. 1976). It has been proposed that alloxan causes the creation of H2O2 and certain free radicals, such as O2 and H_2O_2, which first harm and then cause the cells to die. As a result, the model mentioned above was thought to be sufficient for studying diseases like diabetes mellitus. It is now generally acknowledged that dietary polyphenolics may be crucial in defending the body against long-term conditions like diabetes mellitus, cancer, and cardiovascular disorders (Knekt et al. 2002).This study sought to determine how the flavonoid curcumin affected diabetes mellitus brought on by alloxan.

MATERIALS AND METHODS

Chemical agents

Alloxan (A) as well as curcumin were purchased from Sigma Chemical Company (St.Louis, MO).

Animals

Male wistar rats weighing 150–200 g that were acquired from our animal facility were used in the tests. Every facet of animal care adhered to the technical specifications and moral standards authorized by the Institutional Animal Ethics Committee. In an environmentally controlled animal facility (22 ± 1 °C, 60 ± 5% humidity, 12 h light: 12 h dark cycle), each animal was kept in a glass-bottomed metabolic cage with free access to a normal commercial feed and unlimited water. Every day in the morning, the weight growth, food and drink consumption, and urine output were recorded.

Induction and treatment of diabetes:

A single dosage of alloxan (120 mg/kg i.p.) was administered to rats at least 16 hours after they had fasted to induce diabetes mellitus. Blood glucose levels were measured 48 hours after the alloxan injection, and increasing blood glucose levels > 200 mg/dl verified the onset of diabetes mellitus. For this study, all of the diabetic rats were chosen, split up into groups, and given Curcumin 40 mg/kg (p.o.) (CUR40), Curcumin 80 mg/kg (p.o.) (CUR80), and Metformin 60 mg/kg (p.o.) for 21 days.

Experimental design

The rats were divided into 7 groups (n =6) and treated as follows:
Group I: normal control (Sod. Carboxymethyl cellulose-1% (CMC), orally).
Group II: diabetic control (Alloxan)
Group III: diabetics + Curcumin 40mg/kg (p.o) (CUR40)
Group IV: diabetics + Curcumin 80mg/kg (p.o) (CUR80)
Group V: diabetics + Metformin (60mg/kg)
Curcumin plus Metformin 60mg/kg combination treated groups are IIIa & IVa. Which were received Curcumin 40mg (CUR40) /kg (p.o) & Curcumin 80mgkg (CUR80).

Biochemical Evaluation

On day 0, day 7, day 14, and day 21 following treatment, blood samples were extracted from the eye's retroorbital region in each of the seven groups of rats. The blood samples were centrifuged at 1000 rpm for 15 minutes to separate the serum, and the levels of blood glucose (Trinder P. 1969), serum antioxidant (Blios MS. 1958), and superoxide dismutase (SOD) (Misra. HP. 1977) were estimated.

Statistical Analysis

The data has a mean ± standard deviation. One-way analysis of variance (ANOVA) was used for statistical comparisons, and p-values less than 0.05 were deemed significant.

RESULTS

Figure 1 Table 1 described the effects of curcumin on blood glucose levels after 0 days, 7 days, 14 days, and 21 days in control, diabetic, and flavonoid-treated rats treated with 40 mg/kg, 80 mg/kg, and a combination of metformin and curcumin. Table 2 &3 showed the SOD and TAS levels 21 days after the flavonoid therapy. The combination of metformin and flavonoid Curcumin significantly controlled the blood glucose levels ($p<0.001$). However, the animals that were given alloxan continuously showed signs of hyperglycemia. In diabetic rats, concurrent administration of curcumin alone and curcumin with metformin dramatically decreased blood glucose levels ($p < 0.001$). SOD and TAS levels were considerably raised by the flavonoid doses of curcumin 40 and curcumin 80, depending on the timing and dosage. The blood glucose levels in diabetic rats were considerably lower.

Table 1: Blood glucose levels of the control, diabetic, Curcumin 40mg treated and Curcumin 40mg with Metformin combination treated groups.

Groups/days	0 day	7 days	14 days	21 days
Control	78.4±5.4	88.1±6.4	91.4±7.1	92.7±6.8
Alloxan(A)	91.7±5.6	221.7±14.5	278.4±16.4	351.4±19.7
A+Curcumin40mg(CUR)	105±4.5	134.2±11.2**	114±9.7***	98.4±8.7***
A+Metformin(M)	87.6±6.1	106.4±8.7**	101.3±8.4***	76.4±7.8***
A+CUR+M	93.4±4.1	87.9±6.7**	79.5±5.6***	68.9±6.4***

Values were Mean±SD; n=6. ** p<0.01, *** p<0.001 Vs treated groups, diabetic group

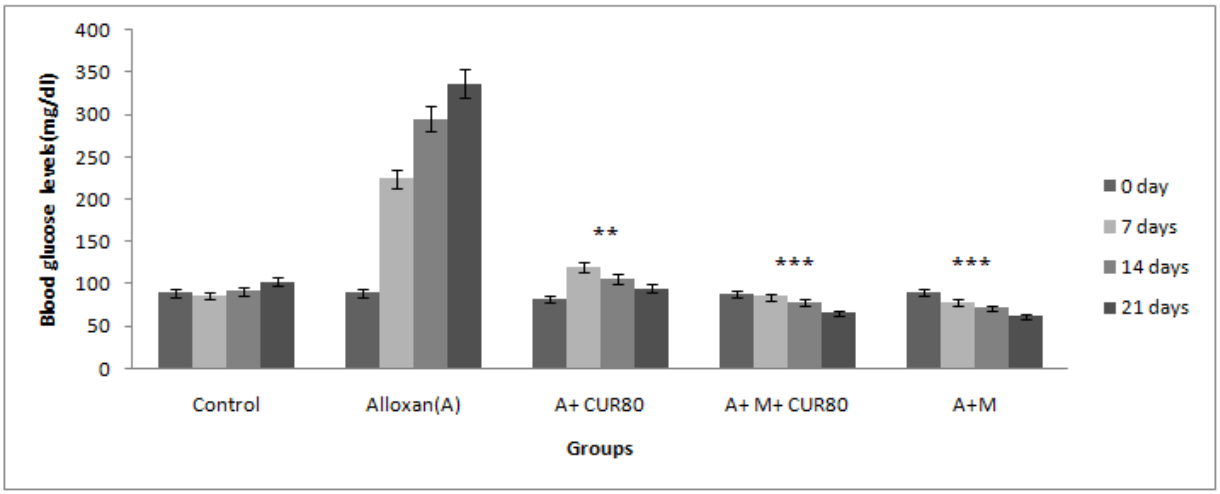

Figure 1: Blood glucose levels of the control, diabetic, CUR80, CUR80 with Metformin combination treated groups. (Values were Mean±SD: n=6. ** p<0.01 *** p<0.001 Vs treated groups, diabetic group).

Table 2: Effect of CUR 40mg, CUR 80mg and Metformin (60mg/kg) combinations for 21 days treated rats on serum SOD activity in control and diabetic rats. (Values are Mean ± SD, n = 6)

Groups/Parametes	**Superoxide dismutase levels =SOD (IU)**
Control	37.21±8.23
Alloxan(A)	11.3±2.82
A+ CUR40	15.2±1.4*
A+Metformin 60mg/kg(M)	19.5±4.2*
A+CUR40+M	24.3±0.6*
A+ CUR80	31.3±6.2**
A+CUR80+M	34.4±4.2***

(Data were significant values *p<0.05, ** p<0.01, *** p<0.001, vs control, diabetic and treated rats).

Table 3: Effect of CUR 40mg, CUR 80mg and Metformin (60mg/kg) combinations for 21 days treated rats on TAS activity in control and diabetic rats. (Values are Mean ± SD, n = 6)

Groups/Parametes	Total antioxidant status (nM of ascorbic acid)
Control	28.28 ± 9.51
Alloxan(A)	5.2±1.11
A+ CUR40	6.8±1.8*
A+Metformin 60mg/kg(M)	9.2±1.5*
A+CUR40+M	12.5±1.3*
A+ CUR80	18.4±1.2**
A+CUR80+M	23.3±2.1***

(Data were significant values *p<0.05, ** p<0.01, *** p<0.001, vs control, diabetic and treated rats).

DISCUSSION

In both animal models and clinical settings, the potential causes of oxidative stress in the pathophysiology of diabetes and its consequences have been thoroughly investigated for many years. In many animal models of diabetes, some research has discovered elevated lipid peroxides or ROS and oxidative stress (or both) (Hfaiedh N et al., 2013). the special ability of alloxan to kill pancreatic beta cells only.

Numerous scientists have suggested that free radicals contribute to the cell damage caused by alloxan. The alloxan radical converts the chemical diabetogen alloxan into dialuric acid when glutathione is present. Beta-cells in the islets of Langerhans are destroyed by reactive oxygen species produced during this redox cycling process. Furthermore, it has been proposed that alloxan toxicity may be related to transitional metals such iron, zinc, and copper (Onunogbo CC et.al., 2012). The current study shows that curcumin stopped rats' plasma glucose levels from rising as a result of alloxan. This is in line with earlier research on the effects of curcumin on streptozotocin-induced diabetes mellitus in rats and curcumin's ability to prevent diabetes mellitus (Kuroda M. et al., 2005). They discovered that in rats treated with alloxan, curcumin also returns glycaemia to normal. However, the impact of curcumin on this particular form of experimental diabetic mellitus is not mentioned in the literature. Our findings demonstrated that curcumin had a noticeably greater protective impact. It is well established that flavonoids have a close structure-activity relationship in their antioxidant actions (Kuroda M. et al., 2005). Our results demonstrated that a daily treatment with curcumin at doses of 40 mg/kg b.w. and/or 80 mg/kg b.w. alone and with metformin prevented a steep onset of hyperglycemia after alloxan administration and maintained blood glucose values closely above healthy controls for the duration of observation, which is thought to be a structural requirement for effective radical scavenging by flavonoids. (Mira L et al., 2022)

Curcumin's effects are noticeable and seem to be better at both lower and larger dosages. According to our findings, this is the most crucial factor in shielding living cells from oxidative damage. However, flavonoids have a detrimental influence on hyperglycemia. in diabetic rats treated with curcumin. According to research, certain flavonoids or plant extracts high in flavonoids may have strong antioxidant and anti-diabetic effects (Raju TN et al., 2006). Despite this, our findings demonstrated that oral curcumin administration improved the diabetic state by lowering hyperglycemia. It is clear that lowering hyperglycemia is the most crucial step in preventing diabetes mellitus. Numerous researchers have shown that animals' proteins have less non-enzymatic glycation (Kuroda M. et al., 2005). Research on flavonoids is being conducted to better understand how they work.

CONCLUSION

In conclusion, this study implies that curcumin administration may be able to stop rats from developing diabetes mellitus after being exposed to alloxan. We postulated that the antiradical and chelatory qualities of

the flavonoids utilized might be the cause of this effect. However, the hypoglycemic action of these flavonoids may also be due to suppression of renal glucose reabsorption.

Ethical Approval

All procedures followed accordance with the animal ethical Committee approval of viswabharati education society (006/1963/PO/Re/S/17/CPCSEA).

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Conflict of interest

Authors have declared that no conflict of interests.

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