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CURCUMIN POTENTIATES THERAPEUTIC EFFICACY OF VOGLIBOSE

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ABSTRACT

Introduction: Herbal antidiabetic preparations are often used as an add-on therapy in diabetes and such herbal preparations often contain curcumin. Hence, in the present investigation the combine effects of curcumin and voglibose in normal as well as diabetic rats was studied. **Methods:** Streptozotocin (60 mg/kg i.p.) diabetic rats was treated for 14 days with curcumin (30 mg/kg p.o) and voglibose (0.06 mg/kg p.o). After treatments, the blood glucose level was assessed. Data was analyzed using one-way analysis of variance (ANOVA) followed by post hoc Scheffe's test. **Results:** Treatment of diabetic rats with curcumin or voglibose alone decreased the blood glucose level. The combination of voglibose with curcumin further decreased blood glucose levels in diabetic rats, indicating synergestic effect. **Conclusion:** The results highlights that curcumin and voglibose given alone showed effect against STZ induced Hyperglycemia but the combination of curcumin with voglibose showed better and synergistic effect. Therefore, it might be a promising strategy for combating diabetic complications.

KEYWORDS: Hyperglycemia; Curcumin; Voglibose; Streptozotocin; Antidiabetic activity.

1. INTRODUCTION

In today's society, diabetes is a serious metabolic disease. Its frequency has risen considerably in recent years, causing the World Health Organization to classify it as a major public health crisis.[1] The International Diabetes Federation's specialists estimate that 193 million people worldwide have undiagnosed diabetes and are at risk of developing chronic complications. According to estimations, there will be 629 million persons with diabetes worldwide in 2045.[2] It is a chronic metabolic condition characterised by a loss of glucose

homeostasis as well as changes in lipid and protein metabolism due to abnormalities in insulin secretion, action, or both. Insulin is a protein (hormone) produced by beta cells in the pancreas in response to a variety of stimuli, including glucose, sulphonylureas, and arginine, but glucose is the most important factor.[3]

Analyzing blood sugar levels can be used to diagnose diabetes. On fasting, blood sugar level is 80 mg/dl, and in the postprandial stage, it can reach 160 mg/dl. Finger prick blood sugar test, fasting blood sugar test and glucose tolerance diagnostic test are some of the laboratory tests used to diagnose diabetes.[4]

Impaired insulin secretion, tissue insulin resistance, or a combination of the two are thought to be the most popular factors that contribute to the pathogenic mechanisms of T2DM, a disease spectrum that starts with tissue insulin resistance and progresses to a state marked by complete loss of pancreatic beta cell secretory activity.[5] The fundamental mechanism underlying hyperglycemia involves over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissue.[6]

Streptozotocin (STZ) is a synthetic nitrosoureido glucopyranose derivative isolated from Streptomyces achromogenes fermentations that is utilised as an antitumor antibiotic and is chemically linked to other nitrosureas used in cancer therapy.[7] It produces β-cell toxicity, which leads to insulin insufficiency, and is easily carried into pancreatic β-cells by GLUT-2. The β-cell O-GlcNAcase enzyme, which is in charge of removing O-GlcNAcase from protein, is specifically inhibited by STZ. This leads in β-cell death and irreversible O-glycosylation of intracellular proteins.[8]

When taken alongside standard medications, a combination of herbal pharmaceuticals (or isolated phytochemicals) has been demonstrated to be effective in the treatment of some disorders.[9] Among all of the available medical systems in the world, Indian traditional medicine is one of the most comprehensive.[10]

Turmeric contains curcumin, a yellow pigment derived from *Curcuma longa* that has anticarcinogenic and anti-inflammatory characteristics, including an inhibitory action on TNF-a. Curcumin has also been found to inhibit NO synthesis and scavenge nitrite and peroxynitrite radicals released by macrophages, which helps to lower blood glucose levels and improve the antioxidant capacity of pancreatic β-cells.[11] The anti-inflammatory,

antioxidant, antiviral, antifibrotic, anticoagulant, and glucose-regulating properties of curcumin are its distinguishing features.[12]

In the treatment of diabetes, alpha-glucosidase inhibitors and fast-acting, short-duration insulin secretagogues are widely utilized. In the final step of carbohydrate digestion, voglibose, alpha -glucosidase inhibitor, reduces the breakdown of disaccharides into monosaccharides by acting competitively on the activities of disaccharidase (alpha -glucosidase). This decreases glucose breakdown and absorption, preventing postprandial hyperglycemia.[13]

As a result, examining these interactions is crucial for illness treatment that is both safe and effective. Despite the fact that Curcumin nanoparticles have been shown to have anti-diabetic properties, the interaction between Curcumin with Voglibose has yet to be studied.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

Streptozotocin sterile powder 1gm was purchased from Teva Parenteral Medicines Inc. Irvine.

Curcumin was purchased from Yarrow chem Products Ghatkopar (west) Mumbai, India.

Voglibose was purchased from Discovery Mankind Pharma Ltd. New Delhi.

2.2 Maintenance of animals

Albino rats of Wistar strain weighing 180-200g were used for the studies after obtaining the permission from institutional animal ethical committee. The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light/dark cycle; at an ambient temperature of 25 ± 5 °C; 35-60% of relative humidity). The animals were fed with standard rat pellet diet and water *ad libitum*.

2.3 Oral glucose tolerance test

For Oral Glucose Tolerance Test, rats was divided into four groups (n = 6). Medications were given orally to overnight fasted animals.

After half an hour of test medication administration, a glucose solution (2.5g/kg body weight) was given orally in a volume of 1 ml, and blood glucose levels were monitored at 0, 30, 60, 90, and 120 minutes using a Glucopoint glucometer.

2.4 Hypoglycaemic study

For hypoglycaemic study, rats were divided into four groups (n = 6) and were administered vehicle (1ml), curcumin(30mg), voglibose (0.06mg), curcumin(30mg) and voglibose(0.06mg) respectively. The blood glucose levels were estimated on days 0, 7 and 14.

2.5 Induction of Hyperglycemia

Diabetes was induced using streptozotocin (STZ). The animals fasted overnight and diabetes was induced by way of a single intra peritoneal injection of a freshly prepared solution of STZ (60 mg/kg b.w.) in a 0.1 M citrate buffer (pH 4.5). On the third day of STZ-injection, the animals with fasting glycaemia higher than 200 mg/dL and with signs of polyuria and polydipisia were considered to be diabetic and included in the study.

2.6 Experimental design

The diabetic animals, divided into four groups (n = 6) were administered vehicle, curcumin (30 mg/kg), voglibose (0.06 mg/kg), curcumin (30mg) and voglibose (0.06 mg/kg), respectively, for 14 days. The fasting blood glucose levels were estimated on days 0, 7 and 14.

At the end of the treatments, the blood samples were collected for the analysis of blood glucose level. The experimental procedures were approved by the Institutional Animal Ethics Committee.

2.7 Statistical analysis

Using the 7.5 version of SPSS computer programme, data were statistically examined using one way ANOVA, followed by a post hoc Scheffe's test. When the p-value was less than 0.05, the results were considered significant.

3. RESULTS

3.1 Effect of curcumin, voglibose and its combination in oral glucose tolerance test

The curcumin, voglibose and its combination showed a significant reduction in blood glucose levels from 30 min onwards in oral glucose tolerance test as compared to normal group. The results are represented in table 1.

Table 1: Effect of curcumin, voglibose and its combination in oral glucose tolerance test.

Group	Treatment	Blood-Glucose Level (mg/dl)				
		0min	30min	60min	90min	120min
I	Normal Control (Glucose 2.5g/kg)	90.6±9.2	106.7±10.6	157.4±15.7	166.7±16.6	250.1±10.10
II	Curcumin (30mg/kg p.o) + Glucose (2.5g/kg)	83.8±8.3	110.5±11.20	99.8±9.9	94.2±9.4	91.1±9.2
III	Voglibose (0.06mg/kg p.o) + Glucose (2.5g/kg)	82.4±8.4	95.4±9.5	81.2±8.1	80.8±7.9	79.1±7.6
IV	Curcumin (30mg/kg p.o) + voglibose (0.06mg/kg p.o) + Glucose (2.5g/kg)	81.7±7.9	91.7±9.1	89.5±8.7	82.8±8.1	76.7±7.6

Each value represent mean ± S.E.M., *n*=6

3.2 Effect of curcumin, voglibose and its combination in normal animals

In normal animals, curcumin did not significantly reduced blood glucose level on 0^{th}, 7^{th} and 14^{th} day as compared to normal control group. Voglibose significantly reduced blood glucose level on 0^{th}, 7^{th} and 14^{th} day as compared to normal control group. Combination of curcumin and voglibose significantly reduced blood glucose level on 0^{th}, 7^{th} and 14^{th} day as compared to normal control group. The results are represented in table 2.

Table 2: Effect of curcumin, voglibose and its combination in normal animals.

Group	Treatment	Blood-Glucose Level (mg/dl)		
		Day 0	Day 7	Day 14
I	Normal Control	75.4±7.8	75.8±7.8	76.4±7.4
II	Curcumin (30mg/kg p.o)	74.5±7.9	74.6±7.6	73.7±7.3
III	Voglibose (0.06mg/kg p.o)	72.8±7.1	61.9±6.6	61.1±6.2
IV	Curcumin (30mg/kg p.o) + Voglibose (0.06mg/kg p.o)	70.5±6.9	57.9±5.8	53.8±5.3

Each value represent mean ± S.E.M., *n*=6

3.3 Effect of curcumin, voglibose and its combination in diabetic animals

In diabetic animals, curcumin did not significantly reduced blood glucose level on 0^{th}, 7^{th} and 14^{th} day as compared to normal control group. Voglibose significantly reduced blood glucose

level on 0th, 7th and 14th day as compared to normal control group. Combination of curcumin and voglibose significantly reduced blood glucose level on 0th, 7th and 14th day as compared to normal control group. The results are represented in table 3.

Table 3: Effect of curcumin, voglibose and its combination in diabetic animals.

Group	Treatment	Blood-Glucose Level (mg/dl)		
		Day 0	Day 7	Day 14
I	Diabetic Control STZ (60mg/kg i.p)	381.2±38.1	398.1±39.7	391.7±38.1
II	Curcumin (30mg/kg p.o)	370.5±37.9	360.1±5.1	359.5±5.7
III	Voglibose (0.06mg/kg p.o)	356.1±36.3	149.6±15.1	140.9±14.10
IV	Curcumin (30mg/kg p.o) + Voglibose (0.06mg/kg p.o)	331.2±33.3	116.8±9.66	110.2±12.44

Each value represent mean ± S.E.M., *n*=6

4. DISCUSSION

A series of metabolic illnesses known as diabetes mellitus are characterised by chronic hyperglycemia carried on by deficiencies in insulin secretion, insulin action, or both. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins. These metabolic abnormalities are introduced on by insufficient insulin levels to start producing an adequate response and insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, liver, at the level of insulin receptors, signal transduction system, and effector enzymes or genes. The kind and length of diabetes affect the severity of symptoms. Some people with diabetes have no symptoms, especially those who have type 2 diabetes in its early stages. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome.[14]

Most diabetic complications are caused by persistent hyperglycemia, a typical symptom of diabetes. Treatment should seek to lower blood glucose levels to near-normal levels in all individuals. Oral hypoglycemic medications are currently available for Hyperglycemia treatment. The majority of medications have failed due to ineffectiveness or side effects. There is no cure for diabetes. This problem has highlighted the need for more better, safer, and less expensive diabetes management techniques. Alternative therapies must be discovered in order to solve these challenges and give better therapeutic management. An excellent method to treat hyperglycemia and other DM problems is to combine the actual antidiabetic medications with phytochemicals.[15]

Streptozotocin is a deoxy-s [(methyl-nitrosoamino) carbonyl)-amino]-D gluco pyranose molecule that causes Hyperglycemia in most laboratory animals. Streptozotocin and other beta cell toxins in high dosages cause insulin insufficiency and Hyperglycemia. Although streptozotocin is favoured because of its more selective beta cell cytotoxicity, its sensitivity varies by species, strain, sex, and nutritional condition, and there are batch variances in activity.[16]

In the search for alternatives to current medication for diabetes mellitus, curcumin has gained attention in the last decade for its antidiabetic properties.[17] Curcumin also reported to have beneficial effects on various diseases, like multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis, and Alzheimer's disease.[18] In addition, it could delay development of T2DM, improve β-cell functions, prevent β-cell death, and reduce insulin resistance in animals.[19]

Voglibose is alpha -glucosidase inhibitor that also stimulates GLP-1 secretion.[20] Inhibition of enzymes in the digestive organs, such as alpha-glucosidase, can be used to prolong glucose absorption as a treatment for diabetes. Alpha-Glucosidase (α-d-glucoside glucohydrolase) is an exo-type carbohydrase that catalyses the liberation of α-glucose from the non-reducing end of the substrate in microbes, plants, and animal tissues. The blocking of this enzyme decreases the rise in blood sugar after a carbohydrate meal.[21] It slows and reduces the absorption of monosaccharides by preventing the intestinal breakdown of complex carbohydrates into simple sugars.[22]

In our Investigation, the oral glucose tolerance test studies revealed that curcumin, voglibose and combination of curcumin and voglibose has the capacity to lower blood glucose.

Hypoglycemic studies experiments conducted for our investigation showed that curcumin, voglibose, and combinations of curcumin and voglibose had the ability to reduced blood glucose.

In our present antidiabetic study, group II animals treated by curcumin did not significantly reduced blood glucose level. Group III animals treated by voglibose could significantly reduced blood glucose level as compared to toxicant group. Group IV animals treated by its combination could significantly reduced blood glucose level as compared to toxicant group.

5. CONCLUSION

Results obtained from the present study proved that curcumin when given alone did not show effect against STZ induced Hyperglycemia in rats and voglibose when given alone could significantly reduced blood glucose level but more prominent effect was observed when combination of curcumin and voglibose was given. Hence combination of these drugs showed synergestic effect.

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