# Original Article

# Complementary action of ginger as bioenhancers in the treatment of diabetes

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## ABSTRACT

**Aim and objective:** To evaluate the role of *Zingiber officinale* extract along with glibenclamide on lipid profile in alloxan & streptozotocin induced diabetes mellitus in rats. **Method and Materials:** The diabetes in rats was induced by the administration of intraperitoneal injection of alloxan (100mg/kg) and streptozotocin (65 mg/kg). After 2 days of injection, the hyperglycaemic rats (glucose level > 200 mg/dl) were separated and divided into five groups consisting of six rats in each group. The oral treatment was started from the same day for next three weeks. On 21st day the blood was collected for biochemical estimations by retro orbital puncture. The serum was obtained by centrifuging the blood samples at 3000 rpm for 10 m and used for estimation of SGPT, SGOT, SOD and CAT. **Results:** Diabetic rats treated with glibenclamide and glibenclamide along with ginger extract showed significant ($p<0.001$) reduction in the elevated levels of total cholesterol, triglycerides and LDL cholesterol in comparison to diabetic control group. The effect was less significant in rats treated with only ginger extract ($p<0.01$). Also, the HDL level was significantly ($p<0.001$) increased in glibenclamide and glibenclamide along with ginger treated group. Serum biomarkers such as SGPT and SGOT level were significantly elevated in diabetic control group. The animals treated with glibenclamide and glibenclamide in combination with ginger extract, the elevated SGPT and SGOT levels were normalised significantly ($p < 0.001$, $p < 0.01$ respectively) as compared to the diabetic control. From antioxidant studies, it was found that alloxan and streptozotocin induced diabetic control animals showed a significant decrease in the levels of SOD and CAT as compared to normal control. The animals treated with glibenclamide and glibenclamide + ginger extract combination showed significant increase in CAT and SOD ($p<0.01$ and $p<0.001$ respectively) as compared to diabetic control. **Conclusions:** The findings of the study suggest that, ginger shows complementary action with glibenclamide in the treatment of diabetes. So it can be considered as a safe supplementary in management of diabetes mellitus. Further studies has to conducted, to check whether dosage of glibenclamide can be reduced when it is given along with ginger.

***Key words:*** Diabetes, Bioenhancer, Ginger, Serum glutamic-oxaloacetic transaminase, Separation of Duty, Common Admission Test.

The major chronic complications associated with diabetes include retinopathy, neuropathy, nephropathy, atherosclerotic coronary artery disease and peripheral atherosclerotic vascular disease. Besides hyperglycemia, several other factors like hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis [1]. Diabetes has been known to medical sciences longer than any other hereditary metabolic diseases. Nevertheless, the existing methods of treatment for this age old illness are not completely satisfactory owing to low efficacy, associated adverse effects and compliance issues. Among the therapies non pharmacologic therapy (e.g. diet, exercise and weight loss) remains to be critical component in diabetes treatment. Dietary management includes the use of traditional medicines mainly derived from plants.

Several herbal preparations are used to treat diabetes, but their reported hypoglycemic effects are complex or even paradoxical in some cases. Several mechanisms have been proposed for the hypoglycemic effect of phytochemical, such as inhibition of carbohydrate metabolizing enzymes, manipulation of glucose transporters, □-cell regeneration and enhancing insulin releasing activity. *Eugenia jambolana* inhibits □-amylase, □-glucosidase, sucrase and increase glucose uptake by cells. Also increase insulin secretion and inhibit insulinase activity. *Momordica charantia* inhibits glucose-6-phosphatase, fructose-1, 6- biphosphatase and stimulates of hepatic glucose-6-phosphate dehydrogenase activities [2].

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The development of new therapies that are able to improve glycemia management and even to cure diabetes is of great interest. Use of plants for human health care is as ancient as human beings themselves India has one of the oldest, richest and diverse cultural traditions associated with the use of the plants and herbs for human, livestock and plant health [3]. Due to change in the lifestyle, the number of people in the world with diabetes has increased dramatically over recent years. The world is facing an explosive increase in the incidence of diabetes mellitus. According to the World Health Organization (WHO) estimates, the number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025, with one-third of affected individuals living in India and China alone [4].

Herbs are staging a comeback and herbal 'renaissance' is happening all over the globe. The herbal products today symbolize safety in contrast to the synthetics that are regarded as unsafe to human. World Health Organization has recognized the potential of traditional and folk medicines in the management and self-reliance of health care system and currently it is encouraging and promoting the traditional systems in "National Health Care Programmes" of various countries. The World Health Organization has estimated that 80% of the world's population use botanical medicine for their primary healthcare needs. Herbal bioenhancers without possessing their own inherent pharmacological activity of their own but when coadministered with other drugs, enhances their bioavailability and hence efficacy.

The interest for bioenhancers arises because of chemotherapeutic agents which are poorly bioavailable, administered for prolong periods, toxic and expensive. One of the unique ways to achieve reduction in drug dosage and therefore drug toxicity & cost is to increase drug bioavailability. The present pharmaceutical research is more concerned with different aspects of exploring new chemical molecules having new modes of action. New drug development technologies were developed from the economics of treatment. There is a revolutionary shift in the way medicines are administered due to recent developments for enhancing the bioavailability. The present global focus is on methods aimed at reducing drug treatment period leading to decrease in drug treatment cost. The reduction in cost of therapy will make more affordable for financially challenged wide sections of society [5].

## MATERIALS & METHODS

**Experimental Animals:** Wistar rats (180 to 200 g) of either sex were used for this study. They were maintained under standard conditions (temperature 22±2ºC, relative humidity 60±5% and 12 h light/dark cycle).The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They had free access to standard pellet diet and water ad libitum. All the animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the "National Academy of Sciences" and published by the "National Institute of Health". All the procedures were performed in accordance with Institutional Animal ethics committee constituted as per the direction of the committee for the purpose of control and supervision of experiments on animals (CPCSEA), under ministry of animal welfare division, Government of India, New Delhi, India.

**Chemicals:** All the chemicals and reagents used were of analytical grade and were purchased from Yarrow Chem, Loba Chem, Himedia and Agappe diagnostics.

## METHODOLOGY

**Preparation of aqueous extract of *gingiber officinale* rhizomes:** Aqueous ginger extract was prepared from locally available ginger rhizomes. Ginger rhizomes (500g) were peeled on crushed ice and were cut into small pieces and homogenized in750 ml cold, 0.9% NaCl solution and 250 mL ice cold water to make the volume up to 1000 ml. The homogenization was carried out in a blender for 12 m. The homogenized mixture was filtered three times through cheese cloth. The filtrate was centrifuged at 2000 rpm for 10 m and the clear supernatant fraction was separated and volume made up to 1000 ml with normal saline. The concentration of this ginger preparation was considered to have 500 mg / ml on the basis of the weight of the starting material. The extract was stored in sample tubes at -4°C until fed to animals [6].

**Routes of drug admistration:** The vehicle, standard drug and test drugs were administered orally with the help of an oral feeding needle.

**Pharmacological Screening**

**Alloxan induced anti-diabetic activity:** Fasting blood glucose was determined after depriving food for 16 h with free access to drinking water. Hyperglycemia was induced by single i.p injection of 100 mg/kg of alloxan monohydrate in normal saline. After 2 days of alloxan injection, the hyperglycemic rats (glucose level > 200 mg/dl) were separated and divided into five groups consisting of six rats in each group. The oral treatment was started from the same day except diabetic control groups for three weeks. The animals had free access to feed with water *ad libitum*.

**Experimental design:** Animals were randomly divided into 5 groups of 6 each. The different groups were assigned as follows: **Group I** - Vehicle control (normal saline), **Group II** - Diabetic control (alloxan100mg/Kg), **Group III** - Diabetic rats + ginger extract (500mg/kg), **Group IV** - Diabetic rats + glibenclamide (5mg/Kg), **Group V** - Diabetic rats + glibenclamide (5 mg/Kg) + ginger extract (500mg/Kg)

**Streptozotocin induced anti-diabetic activity:** Fasting blood glucose was determined after depriving food for 16 h with free access to drinking water. Hyperglycemia was induced by single i.p injection of 65 mg/kg of STZ in citrate buffer, freshly prepared and injected immediately to prevent degradation. After 2 days of streptozotocin injection, the hyperglycemic rats (glucose level > 200 mg/dl) were separated and divided into five groups consisting of six rats in each group. The oral treatment was started from the same day except diabetic control groups for three weeks. The animals had free access to feed with water *ad libitum*.

**Experimental design:** Animals were randomly divided into 5 groups of 6 each. The different groups were assigned as follows: **Group I:** Vehicle control (normal saline), **Group II:** Diabetic control (streptozotocin 65mg/Kg), **Group III:** Diabetic rats + ginger extract (500mg/kg), **Group IV:** Diabetic rats + glibenclamide (5mg/Kg), **Group V:** Diabetic rats + glibenclamide (5 mg/Kg) + ginger extract (500mg/Kg).

**Collection of blood and serum samples:** The above treatment was carried out in each group of animals for 21days. On 21st day the blood was collected for biochemical estimations by retro orbital puncture. The serum was obtained by centrifuging the blood samples at 3000 rpm for 10 m and they were used for estimation of SGPT, SGOT by using a corresponding kit from Agappe Diagnostics Pvt. Ltd. The intensity of the colored complex formed after treating with these reagents was estimated in semi-auto analyzer.

**The parameters studied were as follows:**

- Biochemical parameters such as

a. Serum lipid profile
b. Serum glutamic pyruvate transamase (SGPT)
c. Serum glutamic oxaloacetate transamase (SGOT)

- Endogenous antioxidant parameters include

a. Superoxide dismutase (SOD)
b. Catalase (CAT)

**Antioxidant Parameters**

**Tissue Preparation**

- Animals were sacrificed by cervical dislocation.
- The whole liver was perfused in situ with ice-cold saline, dissected out, blotted dry and immediately weighed.
- A liver homogenate was prepared with ice-cold saline-EDTA.
- The homogenate was centrifuged at 10,000 rpm for 10 m and the pellet discarded. The supernatant was again centrifuged at 20,000 rpm for 1 hour.

**Statistical analysis:** Results of biochemical estimation were reported as mean ± S.E.M. The total variation present in a data was analyzed by one way analysis of variance (ANOVA).

## RESULTS

Diabetic rats treated with glibenclamide and glibenclamide along with ginger extract showed significant reduction in the elevated levels of total cholesterol, triglycerides and LDL cholesterol in comparison to diabetic control group. The effect was less significant in rats treated with only ginger extract. Also, the HDL level was significantly increased in glibenclamide and glibenclamide along with ginger treated group as summarized in **(Table 1 & Table 2).**

**Serum biomarkers:** After 21days of experiment, serum biomarkers such as SGPT and SGOT level were significantly elevated in diabetic control group. In animals treated with glibenclamide and glibenclamide in combination with ginger extract, SGPT and SGOT levels were decreased significantly as compared to the diabetic control as shown in **(Table 3).**

**Antioxidant parameters:** From antioxidant studies, it was found that both alloxan and STZ induced diabetic control animals showed a significant decrease in the levels of SOD and CAT as compared to normal control. Animals treated with glibenclamide and glibenclamide + ginger extract combination showed significant increase in CAT and SOD as compared to diabetic control as shown in **(Table 4).**

**Table 1: Effect of ginger, glibenclamide and their combination on serum lipid profile in alloxan induced diabetic rats**

| Group | Cholesterol (mg/dl) | Triglyceride (mg/dl) | HDL (mg/dl) | LDL (mg/dl) |
|---|---|---|---|---|
| **Normal control** | 62.12±0.84 | 62.02±1.25 | 47.32±1.30 | 42.20±0.14 |
| **Diabetic control** | 6.13±1.57 | 89.45±0.35 | 20.18±0.34 | 97.24±0.37 |
| **Ginger Extract (500 mg/kg)** | 82.15±0.34* | 83.3±0.17* | 27.56±0.56* | 71.35±0.25* |
| **Glibenclamide (5 mg/Kg)** | 60.34±0.47** | 74.19±0.78** | 33.24±0.25** | 66.16±1.65** |
| **Glibenclamide (5 mg/Kg) + Ginger extract (500 mg/ Kg)** | 56.28±0.67** | 64.33±1.26** | 39.33±0.58** | 57.46±1.07** |

Values are expressed as Mean± S.E.M (n=6). One way ANOVA followed by Dunette's test. *p<0.01, **p<0.001 when compared with diabetic control group.

**Table 2: Effect of ginger, glibenclamide and their combination on serum lipid profile in streptozotocin induced diabetic rats**

| Group | Cholesterol | Triglycerides | HDL | LDL |
|---|---|---|---|---|
| **Normal control** | 66.23±2.15 | 60.58±0.05 | 48.51±1.54 | 43.19±3.21 |
| **Diabetic control** | 151.5±0.12 | 110.26±1.69 | 16.86±8.12 | 104.31±1.58 |
| **Ginger Extract (500 mg/kg)** | 118.3±0.25* | 98.0±6.18* | 31.57±3.51* | 87.68±1.95* |
| **Glibenclamide (5 mg/Kg)** | 105.61±6.12** | 82.84±2.89** | 36.85±0.24** | 75.21±2.68** |
| **Glibenclamide (5 mg/Kg) + Ginger extract (500mg/ Kg)** | 89.88±1.59** | 64.42±3.25** | 42.19±4.25** | 61.32±2.18** |

Values are expressed as Mean ± S.E.M (n=6). One way ANOVA followed by Dunette's test. *p<0.01, **p<0.001 when compared diabetic control group.

**Table 3: Effect of ginger, glibenclamide and their combination on serum SGPT and SGOT in alloxan and streptozotocin induced diabetic rats**

| Group | Alloxan | | STZ | |
|---|---|---|---|---|
| | SGPT | SGOT | SGPT | SGOT |
| **Normal control** | 56.43±1.28 | 64.52±1.45 | 58.61±2.65 | 62.63±3.75 |
| **Diabetic control** | 142.51±1.95 | 150.38±1.65 | 139.48±2.38 | 148.72±1.05 |
| **Ginger Extract (500 mg/kg)** | 116.21±3.24 * | 123.51±2.43 * | 113.45±2.09 * | 121.34±1.34 * |
| **Glibenclamide (5 mg/Kg)** | 102.81±2.65 ** | 98.91±2.85 ** | 92.80±2.11 ** | 84.64±1.69 ** |
| **Glibenclamide (5 mg/Kg) + Ginger extract (500 mg/ Kg)** | 89.38±1.65 ** | 87.45±2.25 ** | 79.52±3.54 ** | 76.57±1.95 ** |

Values are expressed as Mean ± S.E.M (n=6). One way ANOVA followed by Dunette's test. *p<0.01, **p<0.001 when compared diabetic control group

**Table 4: Effect of ginger, glibenclamide and their combination on serum SOD and CAT in alloxan and streptozotocin induced diabetic rats**

| Group | Alloxan | | STZ | |
|---|---|---|---|---|
| | SOD | CAT | SOD | CAT |
| **Normal control** | 12.65±1.18 | 8.25±1.65 | 11.36±3.25 | 6.45±2.57 |
| **Diabetic control** | 4.56±1.75 | 4.14±2.65 | 3.28±1.78 | 2.35±1.15 |
| **Ginger Extract (500 mg/kg)** | 6.16±1.34* | 4.76±2.12* | 5.56±1.76* | 3.25±1.43* |
| **Glibenclamide (5 mg/Kg)** | 7.55±2.76** | 5.92±1.85** | 8.46±1.32** | 4.05±2.96** |
| **Glibenclamide (5 mg/Kg) + Ginger extract (500 mg/ Kg)** | 8.21±2.65** | 6.85±1.25** | 9.52±2.54** | 4.46±2.75** |

Values are expressed as Mean ± SEM (n=6). One way ANOVA followed by Dunette's test. *p<0.01, **p<0.001 when compared diabetic control group

## DISCUSSION

The present study was undertaken to evaluate the antidiabetic activity of a standard synthetic antidiabetic drug glibenclamide in combination with an herbal bioenhancer drug ginger in diabetic rats. Diabetes is a global disease with a huge adverse impact on health and mortality, particularly from cardiovascular disorders. It occurs at any time of life from infancy to old age. Type-2 diabetes is primarily a lifestyle disorder, which accounts for around 90% of diabetes cases and increasing at an astonishing rate, particularly in developing countries like India [7].

Diabetes Mellitus is a group of disorders characterized by increased blood sugar, polyhydria, polyuria and weight loss. It is treated either by allopathic or with traditional system of medicines which utilizes herbs for cure. Two national surveys examined the prevalence and pattern of use of complementary and alternative medicine (CAM) among individuals with diabetes. One study by medical expenditure panel survey data in 2016 reported that individuals with diabetes were 1.6 times more likely to use CAM than persons without diabetes. Data from a national representative survey conducted from 2017 to 2022 reported that 35% of respondents with diabetes used CAM to treat their condition [8].

Herbs are often administered in combination with therapeutic drugs, raising the potential of herb–drug interactions. There is very little information published on herb–drug interactions while the use of herbs is progressively growing across the world. Certain herbal supplements can cause potentially dangerous side effects when taken with prescription drugs and the number of cases reported for the emerging herb–drug interactions are already on the rise [9]. In the present study, diabetes was induced using alloxan and streptozotocin (STZ). Alloxan is a cyclic urea derivative, is reported as a potent diabetogenic agent and has widely been used for the induction of experimental diabetes in animal species by damaging the insulin secreting pancreatic β-cells, resulting in a decrease in endogenous insulin release. Alloxan

produces oxygen radicals which causes pancreatic injury and could be responsible for increased blood glucose seen in the animals [10]. Over production (excessive hepatic glycogenolysis and gluconeogenesis) and decrease utilization of glucose by the tissues are the fundamental basis of hyperglycemia in diabetes mellitus. Streptozotocin is a broad spectrum antibiotic, induces diabetes in a wide variety of animal species by damaging the insulin-secreting cells of the pancreas [11].

Streptozotocin (STZ) induced diabetes is a valuable model for induction of diabetes mellitus. Diabetes mellitus induced by STZ may be due to pancreatic β-cells destruction resulting in a decrease in endogenous insulin release. IDDM can be induced by injecting STZ to adult rats whereas NIDDM is induced by administration of STZ to neonatal rats [12]. In this study the animals survived without insulin treatment and showed improvement by glibenclamide which act by stimulating residual beta cells of the pancreas indicate incomplete destruction of pancreatic beta cells of the diabetic rats in the present study. The model can therefore be considered as type II diabetic model showing symptoms like hyperglycemia, glycosuria, polyuria, loss of body weight in spite of polyphagia [13].

Non Insulin Dependent Diabetes Mellitus (NIDDM) also called as type 2 diabetes is a complex metabolic disorder that involves abnormalities in both insulin secretion and action at peripheral tissues. It is a more prevalent form of diabetes and responsible for 90% of the disease. In NIDDM, the kinetics of insulin release in response to meal or glucose is altered. So, postprandial blood glucose remains high and leads to glucose intolerance. Postprandial hyperglycemia plays an important role in the development of diabetic complications. Poor glycogen content in insulin dependent tissues such as liver, skeletal muscle and adipose tissues were observed in NIDDM due to insulin resistance. In NIDDM, partial or total deficiency of insulin causes derangement in carbohydrate metabolism [14].

Most employed oral hypoglycemic agents are sulfonylureas and biguanides. These drugs, however, have disadvantages such as primary and secondary failure of efficacy as well as the potential for induction of severe hypoglycemia. There is a need, therefore, for new candidate molecules that may effectively reduce insulin resistance or potentiate insulin action in genetically diabetic or obese individuals. New drugs that reverse insulin resistance without stimulating insulin release from β -cells also fulfill a major medical need in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). The search for such drugs with a potential to reduce long-term complications of NIDDM is, therefore, of current interest [15].

Glibenclamide is a second generation sulphonylurea derivative, oral hypoglycemic agent and found to be effective in diabetic rats that retain functioning of islet β-cells. Hence the principle mechanism of action is to stimulate the production and secretion of insulin by the β-cells of pancreas. This drug may lower down the output of glucose from the liver by insulin independent mechanism [16].

Ginger is the rhizome of the plant *Zingiber officinale* which is a proven herbal bioenhancer. Aqueous extract of ginger of concentration 500mg/ml was prepared and used for the study. In the present study, the blood lipid levels in both alloxan and STZ treated rats were significantly increased as compared to normal rats. Whereas the group treated with standard drug glibenclamide and those treated with glibenclamide + ginger extract combination showed significant reduction in lipid profile. The results indicate that the combination of glibenclamide and ginger extract could lead to increase in the effect of glibenclamide that may be helpful to reduce the dose of glibenclamide. Also, to minimize the adverse effects. Insulin deficiency leads to various metabolic aberrations in the rats; the rise in LDL level is accompanied by increase in SGPT and SGOT level. In this present study, glibenclamide and glibenclamide + ginger extract combination treated animals serum showed significant reduction in SGPT and SGOT level [17].

Oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed in diabetes by glucose oxidation, protein glycation and the subsequent degradation of glycated proteins. High levels of free radicals and the simultaneously declined antioxidant enzyme levels lead to cell damage, inactivation of enzymes and lipid peroxidation. Superoxide dismutase and catalase play an important role in the detoxification of super oxide anion and $H_2O_2$ respectively. In present study, Catalase and SOD which are most important antioxidant enzymes were found to be decreased in diabetic control group. Treatment with glibenclamide and glibenclamide + ginger extract combination restores the level of both enzymes [18].

## CONCLUSIONS

Intraperitoneal administration of alloxan and streptozotocin produced elevated levels of lipid triglycerides, LDL-cholesterol, hyperglycemia, loss of body weight, increase in serum biomarkers such as SGPT and SGOT (liver damage), increased oxidative stress due to decrease in antioxidants such as SOD and CAT. The animal groups treated with glibenclamide and glibenclamide in combination with ginger extract showed antidiabetic effect by restoring the above markers. The antidiabetic effects are better in animals treated with combination of glibenclamide and ginger extract in comparison to glibenclamide alone. The findings of the study suggest that, ginger shows complementary action with glibenclamide in the treatment of diabetes. So it can be considered as a safe supplementary in management of diabetes

mellitus. Further studies has to conducted, to check whether dosage of glibenclamide can be reduced when it is given along with ginger.

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