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ROLE OF GINGER AS BIOENHANCERS IN THE TREATMENT OF DIABETES

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Abstract:

Aim and objective: *The current study was undertaken to assess the complementary action of ginger as bioenhancer in the treatment of diabetes along with glibenclamide.*

Method and Materials: *The diabetes in rats was induced by administration of single intraperitoneal injection of streptozotocin at 65 mg/kg body weight. After 2 days of streptozotocin injection, the hyperglycaemic rats (glucose level > 200 mg/dl) were separated and divided into four groups consisting of six rats in each group. The oral treatment was started from the same day except diabetic control groups for nest three weeks. Body weight of animals in all groups were recorded at 0, 7th, 15th and 21st day Blood samples were withdrawn under mild anaesthesia from tail tip of the overnight fasted animals on 1st, 7th, 14th, and 21st day. Change in body weights of rats were measured every week. 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: *Treatment with glibenclamide and glibenclamide in combination with ginger extract significantly normalized the elevated blood glucose level (P<0.01).. There was a significant reduction of body weights in diabetic control animals. Glibenclamide and glibenclamide in combination with Ginger extract treated groups showed normalisation of reduced body weight as compared to diabetic control group (P<0.01). 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 STZ 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: *Intraperitoneal administration of STZ produced cardinal symptoms such as 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.*

Key words: *Diabetes, bioenhancer, ginger, SGOT, SGOT, SOD, CAT*

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INTRODUCTION:

India is the diabetic capital of the world, predicted to have 57.2 million diabetic populations by the year 2025. Diabetes mellitus is a disease in which homeostasis of carbohydrate, protein and lipid metabolism is improperly regulated by hormone insulin resulting in elevation of fasting and postprandial blood glucose levels. 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. Despite the great strides that have been made in the understanding and management of this disease, the graph of diabetes-related mortality is rising unabated. Although a number of synthetic drugs are available in the market, diabetes and its related complications still remain uncontrolled.[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]

Diabetes is a major public health problem. 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. A vast ethno botanical knowledge exists in India from ancient times. The need for conservation of medicinal plants and traditional knowledge, particularly in developing countries like India, taking into account the socio cultural and economic conditions is urgent.[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 AND 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 Administration:
The vehicle, standard drug and test drugs were administered orally with the help of an oral feeding needle.

Pharmacological Screening:
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 four 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.*[7]

Experimental Design:
Animals were randomly divided into 4 groups of 6 each. The different groups were assigned as follows.
Group I: Vehicle control (citrate buffer).
Group II: Diabetic control (streptozotocin 65mg/Kg).
Group III: Diabetic rats + glibenclamide (5mg/Kg)
Group IV: 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. Fasting blood glucose was measured using single touch glucometer. Blood samples were withdrawn under mild anaesthesia from tail tip of the overnight fasted animals on 1st, 7th, 14th, and 21st day. 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.

- Biochemical parameters such as
  i. Fasting blood glucose
  ii. Serum glutamic pyruvate transamase (SGPT)
  iii. Serum glutamic oxaloacetate transamase (SGOT)
- Morphological parameter includes
  i) Body weight
- Endogenous antioxidant parameters include
  i. Superoxide dismutase (SOD)
  ii. Catalase (CAT)

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).

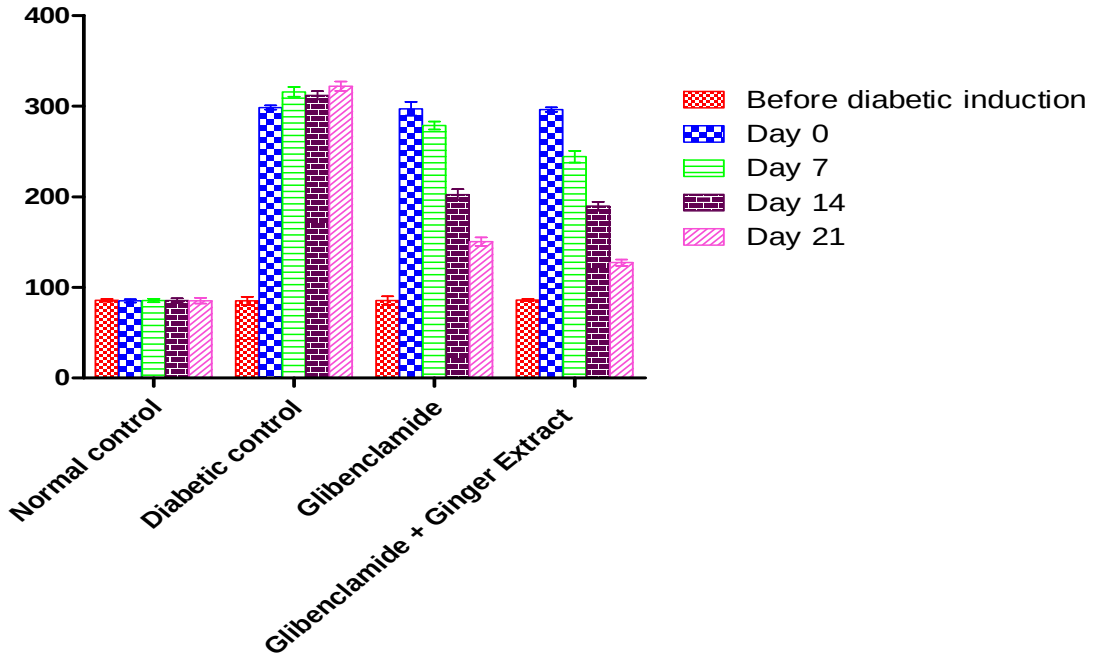
RESULTS:

Effect on fasting blood glucose in STZ induced diabetic rats:
Fasting blood glucose (FBG) level was within the range of 80-90 mg/dl in all the groups prior to STZ administration. Treatment with STZ in normal saline (65 mg/kg, i.p) had increased the FBG level above 290 mg/dl after 48 h. Treatment with glibenclamide and glibenclamide in combination with ginger extract significantly normalized the elevated blood glucose level as shown in Table 1 and Figure 1.

Table 1: Serum Glucose In STZ Induced Diabetic Rats:

Group	Blood glucose level (mg/dl)				
	Before diabetic induction	**Day 0**	**Day 7**	**Day 14**	**Day 21**
Normal Control	85.62±1.38	85.10±1.86	85.34±1.92	85.37±2.56	85.25±3.16
Diabetic control	85.08±4.58	298.45±2.26	315.72±5.36	311.87±4.56	321.91±5.23
Glibenclamide (5mg / Kg)	85.40±4.67	297.08±7.56	278.56±4.32**	202.45±5.92 **	150.46±4.67 **
Glibenclamide (5mg/Kg) + Ginger extract (500mg/ Kg)	85.93±1.132	296.16±2.56	244.21±6.54**	189.59±4.89 **	127.36±3.45 **
Values are mean ± SEM (n=6) one way ANOVA followed by Dunette's test. Where ** represents significant at $p < 0.01$ as compared with diabetic control group					

Figure 1: Serum Glucose In STZ Induced Diabetic Rats



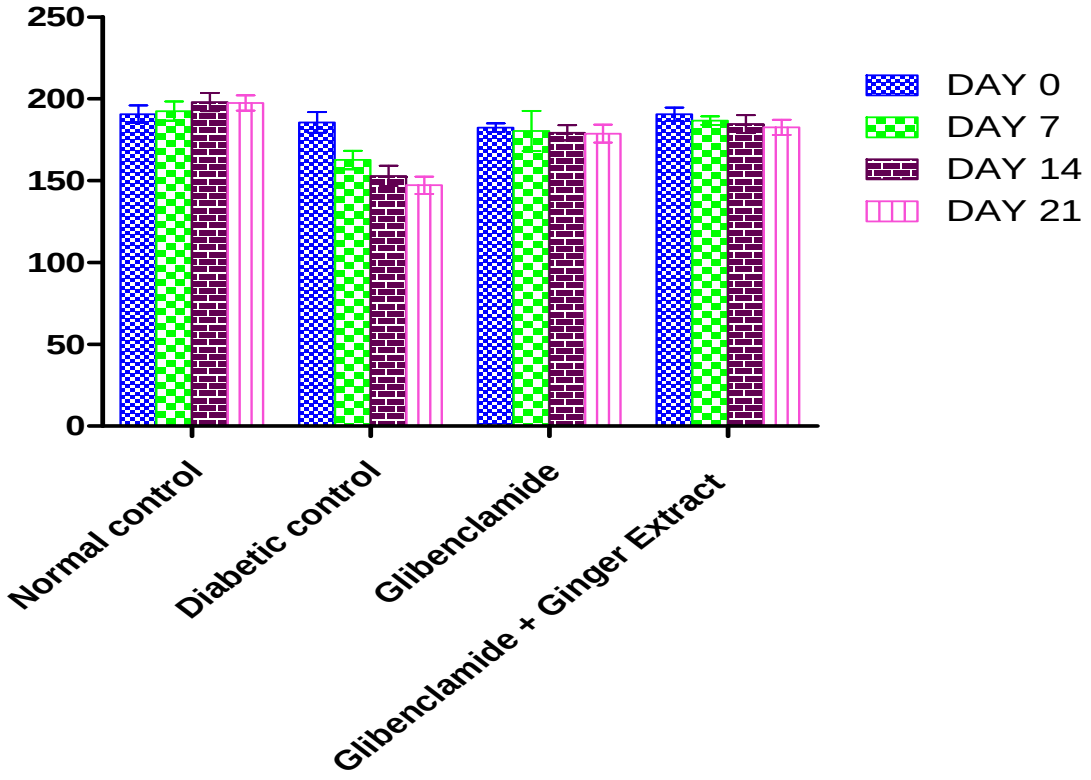
Effect On Body Weight In STZ Induced Diabetic Rats

Body weight of animals in all groups was recorded at 0, 7th, 15th and 21st day. Highest change (decrease) in body weight during study period was found to be in diabetic control group. Glibenclamide and glibenclamide in combination with Ginger extract treated groups showed increase in body weight as compared to diabetic control group as shown in table 2 and figure 2.

Table 2: Body Weight In STZ Induced Diabetic Rats

Group	Body weight (g)				Change in body weight (%)
	Day 0	Day 7	Day 14	Day 21	
Normal Control	185.45±5.38	187.5±4.86	189.55±6.92	192.45±4.66	3.77
Diabetic control	185.32±5.18	166.32±4.32	158.85±6.54	148.32±4.28	-19.96
Glibenclamide (5mg / Kg)	182.45±2.58	180.30±2.26**	179.22±4.67 **	177.75±5.46**	-2.57
Glibenclamide (5mg/Kg) + Ginger extract (500mg/ Kg)	184.51±4.23	182.61±2.56**	181.56±4.39 **	180.18±3.78**	-2.34
Values are mean ± SEM (n=6) one way ANOVA followed by Dunette's test. Where ** represents significant at $p< 0.01$ as compared with diabetic control group					

FIGURE 2: BODY WEIGHT IN STZ INDUCED DIABETIC RATS



SERUM BIOMARKERS:

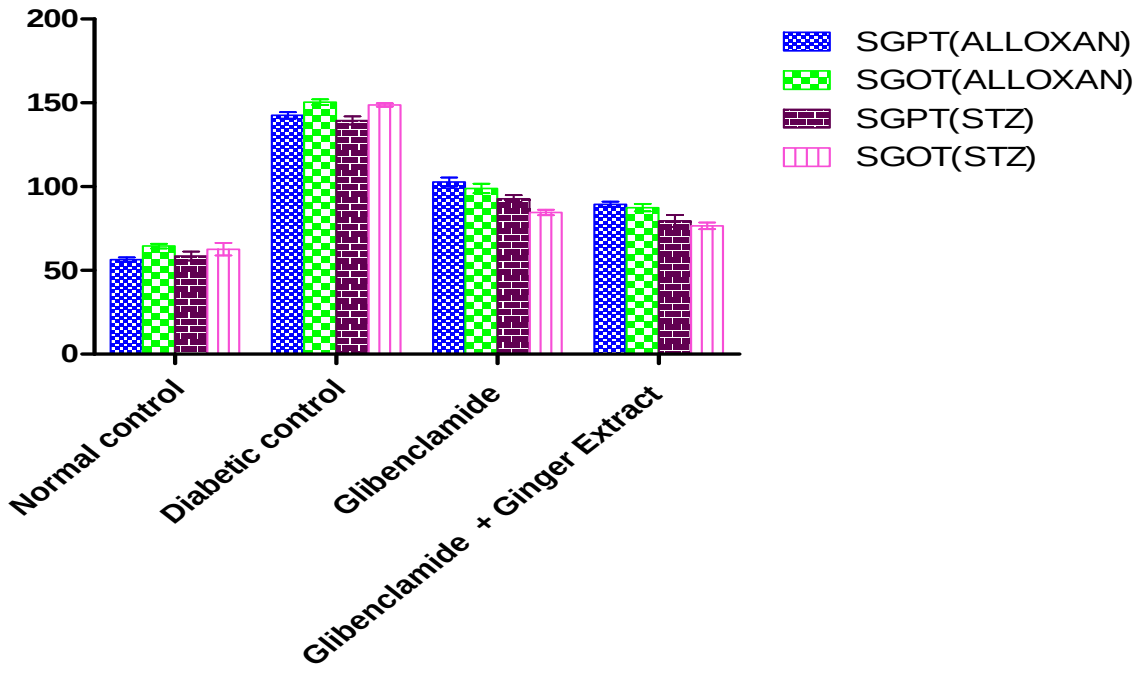
After 21days of experiment, serum biomarkers such as SGPT and SGOT level were significantly elevated in diabetic control group. In animals treated with glibenclamide and glibenclamide in combination with ginger extract, SGPT and SGOT levels were decreased significantly ($p < 0.001$, $p < 0.01$ respectively) as compared to the diabetic control as shown in Table 3 and Figure 3.

Table 3: SGPT And SGOT in Alloxan and STZ 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
Glibenclamide (5mg / Kg)	102.81±2.65 ***	98.91±2.85 **	92.80±2.11 ***	84.64±1.69 **
Glibenclamide (5mg/Kg) + Ginger extract (500mg/ Kg)	89.38±1.65 ***	87.45±2.25 **	79.52±3.54 ***	76.57±1.95 **

Values are mean ± SEM (n=6 except in control) one way ANOVA followed by Dunette's test. Where, ** represents significant at $p< 0.01$, *** represents significant at $p<0.001$ as compared with diabetic control group

FIGURE 3: SGPT AND SGOT IN ALLOXAN AND STZ INDUCED DIABETIC RATS



ANTIOXIDANT PARAMETERS:

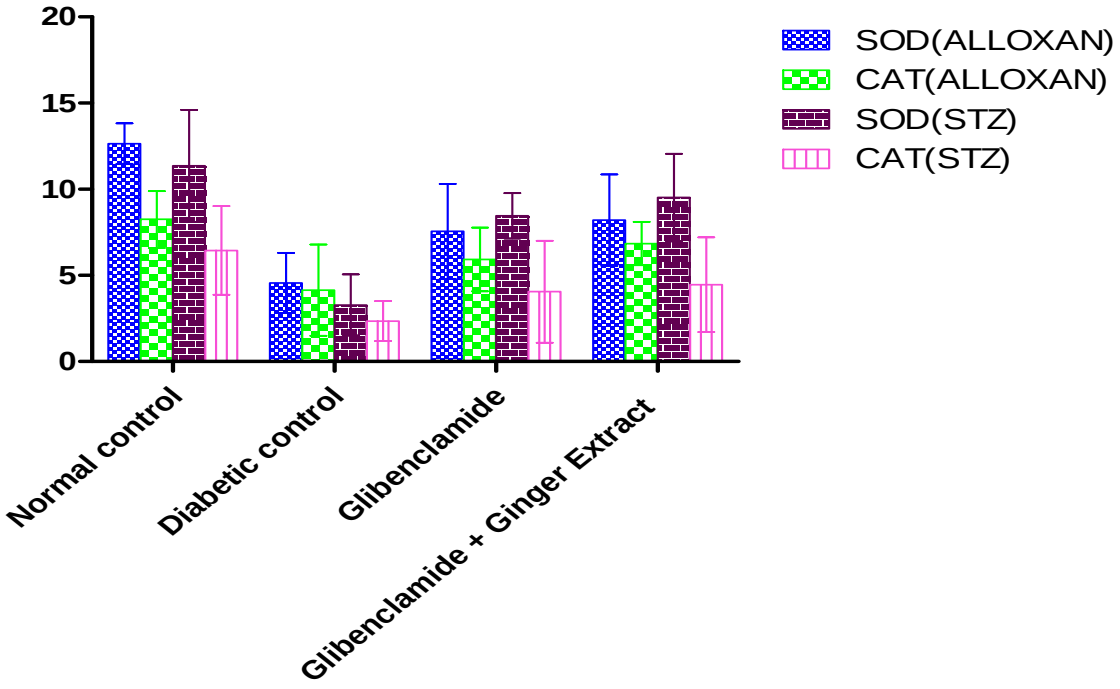
From antioxidant studies, it was found that STZ induced diabetic control animals showed a significant decrease in the levels of SOD and CAT as compared to normal control. Standard group treated with glibenclamide and test group treated with glibenclamide + ginger extract combination showed significant increase in CAT and SOD ($p<0.01$ and $p<0.001$ respectively) as compared to diabetic control as shown in Table 4 and Figure 4.

Table 4: SOD And CAT in 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
Glibenclamide (5mg / Kg)	7.55±2.76***	5.92±1.85**	8.46±1.32***	4.05±2.96**
Glibenclamide (5mg/Kg) + Ginger extract (500mg/ Kg)	8.21±2.65***	6.85±1.25**	9.52±2.54***	4.46±2.75**

Values are mean ± SEM (n=6 except in control) one way ANOVA followed by Dunette's test. Where,** represents significant at $p< 0.01$, *** represents very significant at $p<0.001$ as compared with diabetic control group

Figure 4: SOD And CAT in Diabetic Rat



DISCUSSION:

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 2012 to 2017 reported that 35% of respondents with diabetes used CAM to treat their condition. Herbs are often administered in combination with therapeutic drugs, raising the potential of herb–drug interactions. Currently, 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.[8]

Impaired utilization of glucose due to lack of insulin secretion or its action has been reported to alter the enzymatic activities in diabetic patients as well as in experimental animals. Diabetic animals also showed an increased break down of muscles and other tissues proteins into amino acids due to enhanced proteases activity which in turn resulted into increased urea levels in the blood. Likewise, increased activity of serum glutamic oxaloacetate transminase (SGOT) and of serum glutamic pyruvate transminase (SGPT) in diabetes is of clinical importance because elevated activity of SGOT is suggestive of cardiac damage and that of SGPT liver damage.[9]

Bioavailability and hence bioefficacy of novel classes of drugs can be increased by herbal bioenhancers. In today's era, there is a greater interest and larger healthcare need for the enhancing of bioavailability of many drugs which are less bioavailable. Poorly bioavailable drugs remain sub-therapeutic because a larger portion of a dose never reaches the site of action and shows its biological effect. Larger doses are required which may lead to serious adverse effects. Improvements in bioavailability can results into lowering the dose and also the dose frequency of the drug.[10]

India being a developing country, cost of treatment is a real concern for new allopathic medicine. Innovative methods to reduce these costs of medicine are present demand. Bioenhancers highlights the benefits of integrating of an ancient system with present modern system of medicine in practice. The complementary action of bioenhancer can reduce the dose of rifampin to half, patients need to pay very less of the original treatment This may leads to tremendous economic benefit for the tuberculosis suffering world population. Also if bioenhancer action is applied to other drugs, benefit levels become astonishing. Internationally, many billions of dollars are spent annually due to the poor bioavailability of many drugs.[11]

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. In the present study, diabetes was induced using streptozotocin (STZ). Streptozotocin is a broad spectrum antibiotic, induces diabetes in a wide variety of animal species by damaging the insulin-secreting cells of the pancreas.[12]
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. Induction of diabetes is associated with a characteristic loss of body weight, which is due to increased muscle wasting and loss of tissue proteins. [13]

Insulin deficiency leads to various metabolic aberrations in the rats; the rise in blood glucose level is accompanied by increase in SGPT and SGOT level. 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.[14]

CONCLUSIONS:

The findings of the study suggest that, when glibenclamide is used in combination with ginger extract, the dosage of glibenclamide can be reduced. So it can be considered as a safe supplementary in management of diabetes mellitus.

Intraperitoneal administration of STZ and alloxan produced cardinal symptoms such as 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. So the dose of glibenclamide can be reduced when using in combination with ginger and side effects of glibenclamide can be minimized.

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