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Research Article

Comparative Phyto-Remedial Effect of *Zingiber officinale* and *Cuminum cyminum* on Hepatocytes of Alloxan Induced Diabetic *Mus musculus*

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ABSTRACT

Diabetes mellitus is a metabolic disorder that causes chronic hyperglycemia. Diabetes and its crippling complications are a significant cause of morbidity and mortality. This study evaluates the comparative antihyperglycemic and hepatoprotective effects of alcoholic extracts of rhizome of *Zinger officinale* plant and seed extract of *Cuminum cyminum* plant on alloxan-induced diabetic mice. Mice were divided into four groups (one normal control, one diabetic control and two diabetic groups treated with the two extracts). Mice were induced diabetes by intraperitoneal administration of alloxan. Normal control and diabetic control mice received normal saline water during the treatment period while diabetic mice were administrated with ethanolic extracts of ginger rhizome @100mg/kg/BW and cumin seeds extract @80mg/kg/BW for 16 weeks. At the end of the experiment, animals were sacrificed, and biochemical as well as histopathological examinations were carried out. Hyperglycaemia with increased SGPT and bilirubin have been observed in diabetic mice. However, normoglycemic conditions along with restored liver marker enzymes have been observed in diabetic rats treated with extracts. Histopathological examination showed that alloxan administration causes damage to hepatic cells. Conversely, in ginger and cumin-treated diabetic groups, a significant improvement in the architecture of hepatic cells has been observed, which showed the ability of the extracts to repair the damaged tissue. Thus, this study safely submitted that ginger and cumin significantly reduce the blood glucose level, with ginger having greater potential as a hepatoprotective agent than cumin.

INTRODUCTION

Diabetes mellitus is a heterogeneous group of disorders with multiple aetiologies characterized by hyperglycemia due to defects in insulin secretion, insulin resistance/action, or a combination of both of these factors. It is the third leading cause of morbidity and mortality after a heart attack and cancer.^[1,2] It arises due to the impaired metabolism of glucose that affects the human body at multiple organ levels, thus making it difficult to follow a precise treatment protocol.^[3] Chronic hyperglycemia is associated with several liver diseases such as non-alcoholic fatty liver, abnormal glycogen deposition, and

viral hepatitis.^[1,4] An array of side effects of synthetic drugs on disease progression highlights the need for newer therapies that minimize the frequency and severity of diabetes exacerbations.^[5,6] Medicinal plants present valuable therapeutic agents in traditional and modern medicine. However, only a small number of these plants have gained medical and scientific assessment to assess their usefulness and safety. Some of these plants are accessible worldwide as polyherbal formulations and are being prescribed by medical practitioners to treat diabetes.^[7] Anti-oxidant supplements from the diet are considered alternatives for the treatment of

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diabetes, e.g., ginger (*Zingiber officinale*) and cumin (*Cuminum cyminum*).

Ginger (*Zingiber officinale*; family: Zingiberaceae) and Cumin (*Cuminum cyminum*; family: Apiaceae) originated from Southeast Asia are used as spices globally.^[8] These two plants have been documented for numerous diseases in centuries-old Ayurveda and Unani medicinal systems. They have been claimed for a wide range of pharmacological properties such as antibacterial, anti-oxidant, anti-inflammatory, anti-hyperglycaemic, and anti-carcinogenic.^[9-11] The Ginger plant has been documented to contain numerous bioactive phytochemicals such as gingerols, shogaols, and gingerols. It has been reported that dietary ginger has a hypoglycaemic effect that enhances insulin synthesis in rats and has high anti-oxidant activity with the likely mechanisms of malondialdehyde, which acts as a scavenger of oxygen radicals.^[12]

Cuminum cyminum (cumin), belonging to the *Apiaceae* family and native to India, has been documented to contain essential oil and cymene, cumin aldehyde, γ -terpinene, and $(-)$ - β -pinene as its main components.^[9,13] This plant has anti-oxidant and anti-diabetic properties.^[14] The effective component of cumin is cumin aldehyde or 4-isopropyl Benzaldehyde which is the enzyme inhibitor of α -glucosidase and aldol reductase of carbohydrate metabolism.^[13]

Currently, medicinal plants are explored as alternative medicines to achieve effective treatment without any side effects with lower costs for most diseases such as hyperlipidemia, diabetes mellitus, etc. Contrarily, allopathic medicines have many side effects and sometimes fail to treat. Since both plants are common have several therapeutic potentials, the present study is designed to evaluate the anti-diabetic and hepatoprotective effect of ethanolic extract of *Zingiber officinale* and *Cuminum cyminum* in diabetic mice.

MATERIALS AND METHODS

Experimental Animal and Plant Extract

The healthy *Mus musculus* (BALB/c) was brought up at Mahavir Cancer Sansthan and Research Centre, Patna, Bihar, India in the animal house in the age group of 12 weeks old with 30 ± 5 g body weight. The mice were kept at standard environmental conditions $20 \pm 2^\circ\text{C}$, relative humidity $50 \pm 10\%$, and 12 h dark-light cycle with food and water *ad libitum*. All experiments were conducted in accordance with the guideline of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, with ethical approval letter number IAEC-2020/1E-27/08/20. The alcoholic rhizome extract of plant *Zingiber officinale* and seed extract of *Cuminum cyminum* have been prepared for oral administration to experimental mice.

Chemicals

Alloxan was purchased from Loba Chem Pvt. Ltd., Mumbai, and is used to make a diabetic model in the experimental mice. After making the solution of alloxan in distilled water, it was injected intraperitoneally at 110 mg/kg/BW/day to overnight (12 hours) fasted mice. After the injection, mice were allowed food and water *ad libitum*. Mice were allowed to stabilize for three days, and blood samples were collected from the tail end for blood glucose estimation. The prevalence of the diabetic model was analysed after 2 weeks before starting the treatment.

Study Design

The alcoholic rhizome extract of plant *Zingiber officinale* (100 mg/kg/BW) and seed extract of *Cuminum cyminum* (80mg/kg/BW) have been orally administered to three of the four mice groups for 16 weeks as follows: a) group I (normal control) received distilled water and standardized food orally, b) group II (diabetic control) not treated received standardized food only, c) group III (diabetic + ginger administrated group) received an ethanolic extract of ginger 100mg/kg/BW orally once a day and d) group IV (diabetic + cumin administrated group) received an ethanolic extract of cumin 80mg/kg/BW orally by gavage method once a day for 16 weeks. Mice in groups I and II were sacrificed after sixteen weeks, while mice in groups III and IV were sacrificed at the interval of 4th, 8th, 12th, and 16th weeks after the termination of the last dose. Hepatic tissues were removed and fixed in 10% formalin for the light microscopic study. Serum was collected for glucose, SGPT, and bilirubin analysis using the standard protocol of CORAL TEST Kits.

Statistical Analysis

Results were expressed as mean $\pm$ SD. Statistical analysis was performed by one-way analysis of variance "ANOVA" with the help of Dunnett's Multiple Comparisons Test using graph pad in stat version 5.03.

RESULTS

The Serum Glucose Level in Ginger and Cumin Administrated Group

The glucose level was 90.00 ± 0.5774 mg/dL in the control group, while in the diabetic group, it was 222.0 ± 0.5774 mg/dL. It was 127.3 ± 17.68 mg/dL in 4 weeks, $93.92.50 \pm 13.56$ mg/dL in 8 weeks, 93.67 ± 4.177 mg/dL in 12 weeks, and 112.0 ± 1.732 mg/dL in 16 weeks, in the *Z. officinale* extract administered group (Table 1; Fig. 1). While it was 143.3 ± 16.46 mg/dL after 4 weeks, 86.50 ± 3.753 mg/dl after 8 weeks, 75.88 ± 1.732 mg/dL after 12 weeks, and 96.67 ± 10.27 mg/dl after 16 weeks in *C. cyminum* extract administered group. (Table 1 Fig. 1).



Serum SGPT Level in Ginger and Cumin Administrated Group

SGPT levels in ginger administered group of mice were as follows; 23.90 ± 1.320 U/L in the control group; while in the diabetic group it was 214.0 ± 1.732 mg/dL. It was 168.3 ± 1.167 U/L after 4 weeks, 172.9 ± 1.012 U/L after 8 weeks, 155.0 ± 0.4041 U/L after 12 weeks, and $171.0 \pm 0.69.28$ U/L after 16 weeks (Table 1; Fig. 2), while it was 213.0 ± 1.443 U/L after 4 weeks, 122.0 ± 1.270 U/L after 8 weeks, 164.0 ± 0.9238 U/L after 12 weeks, and 169.4 ± 0.913 U/L after 16 weeks *Cuminum cyminum* administered group (Table 1; Fig. 2).

Serum Bilirubin Level in Ginger and Cumin Administrated Group

Bilirubin was 0.6000 ± 0.1893 mg/dL in control group; while in diabetic group it was 1.500 ± 0.5774 mg/dL. In *Z. officinale* extract administered mice group it was found to be 1.00 ± 0.144 mg/dl after 4 weeks, 1.33 ± 0.16 mg/dl after 8 weeks, 0.7700 ± 0.1270 mg/dL after 12 weeks and 1.383 ± 0.1922 mg/dL after 16 weeks, (Table 1; Fig. 3). In *C. cyminum* extract treated group it was 1.333 ± 0.3333 mg/

dL after 4 weeks, 1.01 ± 0.15 mg/dl after 8 weeks, 1.13 ± 0.29 mg/dL after 12 weeks, and 0.90 ± 0.57 mg/dl after 16 weeks (Table 1; Fig. 3).

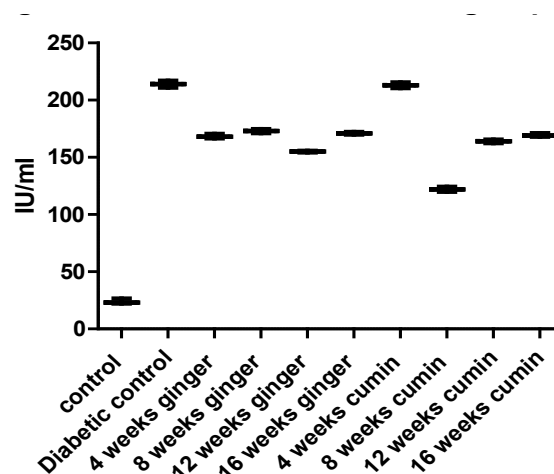


Fig. 2: SGPT level in different mice groups

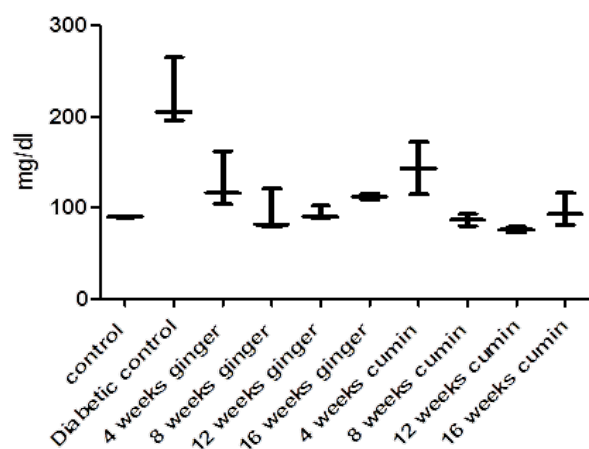


Fig. 1: Glucose level in different mice groups

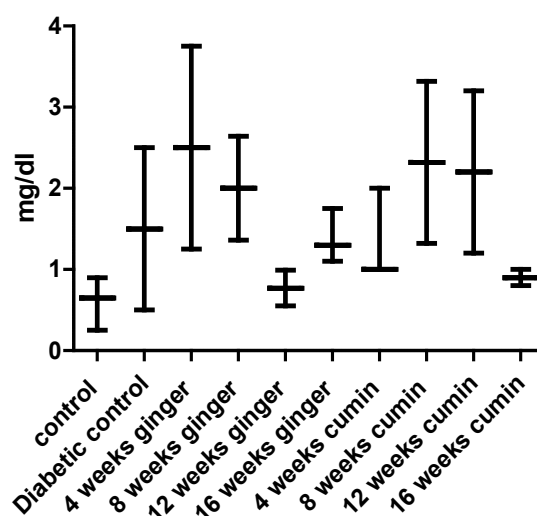


Fig. 3: Bilirubin level in different mice groups

Table 1: Effect of ethanolic extract of ginger and cumin on glucose and liver function parameters

Group	Glucose mg/dL	SGPT U/L	Bilirubin mg/dL
Control	90.00 ± 0.57	23.90 ± 1.32	0.6000 ± 0.18
Diabetic control	222.0 ± 0.57##	214.0 ± 1.73	1.500 ± 0.57
4-week ginger administrated	127.3 ± 17.68*	168.3 ± 1.16	1.00 ± 0.14
8-week ginger administrated	93.92 ± 13.56**	172.9 ± 1.01	1.330 ± 0.16
12-week ginger administrated	93.67 ± 4.177**	155.0 ± 0.40	0.7700 ± 0.12
16 weeks ginger administrated	96.67 ± 10.27**	171.0 ± 0.69	1.383 ± 0.19
4-week cumin administrated	143.3 ± 16.46*	213.0 ± 1.44	1.33 ± 0.33
8-week cumin administrated	86.50 ± 3.753**	122.0 ± 1.27	1.01 ± 0.15
12-week cumin administrated	75.88 ± 1.732**	164.0 ± 0.92	1.13 ± 0.05
16 weeks cumin administrated	96.67 ± 10.27**	169.4 ± 0.91	0.90 ± 0.57

Values are mean ± SD for three animals analyzed by ANOVA followed by Dunnett's test. #: value differs significantly from normal control group ## (p < 0.001). levels of significance *p < 0.05 and **p < 0.01, between diabetic control and ginger, treated groups

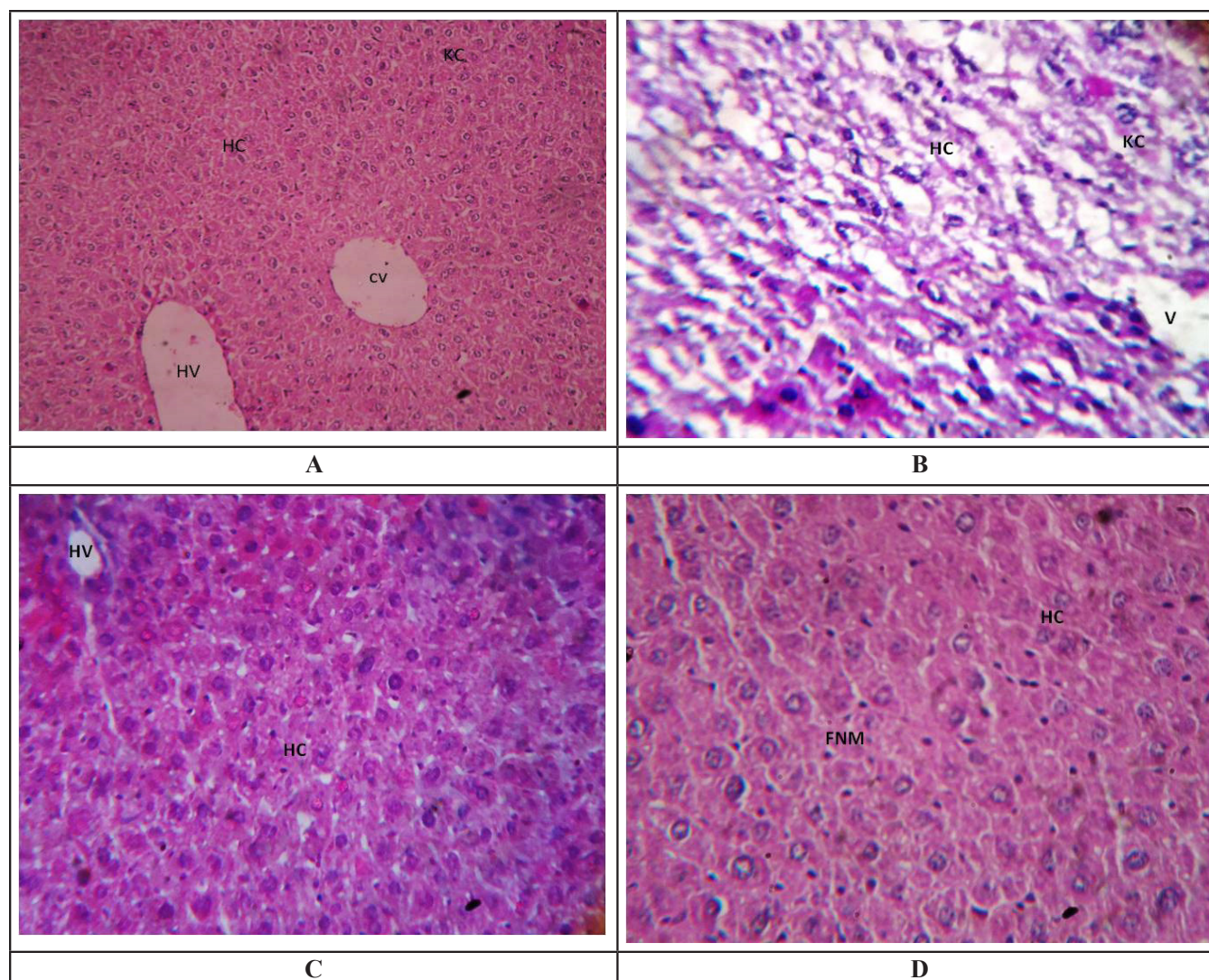


Fig. 4: Microphotograph of the hepatic tissue stained with H & E (200X). (A) Normal control tissue showed well-organized hepatic cells with a prominent central and hepatic vein. (B) The tissue of diabetic control showed degenerated hepatic cells (HC), Kupffer's cells (KC) clustered nucleus, and degenerated cytoplasmic materials with many vacuolated (V) spaces in the cytoplasm. (C) The tissue of diabetic mice followed by 16 weeks of *Z. officinale* extract treatment showing near normal hepatic vein (HV) and least vacuolization. The tissue of diabetic mice followed by 16 weeks of *C. cyminum* extract administration showed complete vacuolization in hepatic cells' nuclear material with regeneration in cytoplasmic material and fragmented nuclear materials (FNM).

Histopathology of Liver

The control group of the liver showed the normal structure of hepatic tissue central vein and hepatic vein (Fig. 1) while in the diabetic group degenerated hepatic cells, a central vein is not prominent and many vacuolated spaces were observed (Fig. 2) but in ginger administrated group it restores the normal architecture of liver in 16 weeks it shows better restoration less vacuolization and well defined hepatic cells (Fig. 3) while least restoration was observed in hepatocyte of 16 weeks cumin administered group (Fig. 4).

DISCUSSION

Diabetes is one of the most common causes of death throughout the world.^[1] Elevated glucose level produces

oxidative stress, which damages the tissue and alters its function. Since alloxan is β -cytotoxic and induces diabetes by damaging the β -cell due to the structural similarity of glucose, it enters into β -cell by GLUT-2 transporters. It leads to glucokinase inhibition and reactive oxygen species generation resulting in high blood glucose levels.^[1-3] In our study, we observed significant increases in blood glucose levels in mice after administration of alloxan. It has been well documented that the extract of ginger effectively reduces the blood glucose level.^[15] The plant extracts increase of uptake of glucose and glycogen synthesis by increasing the phosphorylation of the insulin receptor.^[16] Ethanolic extract of ginger showed reduced blood glucose levels in streptozotocin-induced diabetic mice.^[17] Our study observed that ginger extract



started to reduce the blood glucose level in the 4th week. It consistently maintained its glucose level in the 8th and 12th weeks, while its effect is more prominent in the 16th week.

It has been well documented that ginger's phenols, polyphenolic compounds, and flavonoids are responsible for hypoglycaemic and other pharmacological activities.^[1,2,6] In the case of diabetes, liver marker enzyme SGPT, SGOT, and bilirubin levels were significantly increased in diabetic mice.^[18] We have also observed that the diabetic group has an elevated level of liver marker enzyme SGPT, SGOT, and bilirubin. It has been documented that active phytoconstituents from ginger reduce the glucose levels, SGPT, and SGOT levels in streptozotocin-induced mice.^[1,19] We further observed a declining trend in SGPT and SGOT levels in diabetic mice and ameliorated the damaged liver tissue after administering an aqueous extract of ginger. The Ginger plant has numerous bioactive phytochemicals like gingerols, shogaols, and gingerols impart cytoprotective effect. Other researchers observed similar findings. According to these studies, ginger exerts its anti-diabetic effects through restorative effects on pancreatic β -cells, increasing insulin sensitivity, insulin-like action, and peripheral utilization of glucose.^[20,21]

Extract of cumin seeds has been documented for reducing the blood glucose level as well as the glycosylated hemoglobin. It improved serum insulin and glycogen content in diabetic mice.^[9,22] In our study, we observed that 4th weeks cumin-treated group reduces the blood glucose level although it was not in the normal range while maintaining the normal glucose range when continued up to 16 weeks. Extract of cumin has also been documented for effectively reducing the SGPT, SGOT and ALP marker levels and repairing the damaged hepatic cells in diabetic albino mice.^[23] The hepatoprotective nature of cumin has been documented due to the presence of saponins, tannins, glycosides, terpenes, and sterols. Tannins are well recognized as hepatoprotective components as it has been found to repair the liver tissue in diabetic rat.^[1,24] In our study, we have observed that at the end of the 4th week, there is no significant reduction of SGPT levels, but after the 8th, 12th, and 16th week it reduces effectively. In contrast, SGOT and bilirubin were also reduced in the diabetic group but did not achieve the normal range.

In our study, extract possesses an anti-diabetic effect in diabetic rats through reduction of plasma glucose levels and elevation of insulin in plasma. We have also observed that alloxan-induced diabetic liver sections stained with hematoxylin and eosin showed degenerated hepatic cells. The central vein and the hepatic vein are not prominent. Much vacuolated space was observed in the cytoplasm clustered nucleus, and degenerated hepatic cells were observed.^[1,20] The liver of diabetic mice followed by

16 weeks zingiber extract treatment showed normal hepatic vein. Damaged hepatic cells got improved to the normal state with fewer vacuolization in the cytoplasm. The liver of diabetic mice followed by 16-week cumin treatment showed minor necrosis in the cytoplasm. Less vacuolization was also observed in the nucleus of hepatic cells imparting the bioactivity of cytoprotective action as well as other therapeutic applications. The anti-oxidant activity and anti-diabetic effect may be due to the presence of total phenolic and flavonoids compounds as observed in the present study, similar in line with other studies.^[25-27]

CONCLUSION

Thus, we can safely submit that ginger and cumin's ethanolic extract significantly reduces the glucose level, but ginger consistently maintains the normal range compared to cumin. Liver marker enzymes were also reduced but did not achieve the normal range. However, at the tissue level, both plants show the restoration in hepatic cells to some extent in which ginger is more effective as compared to cumin, probably due to its anti-oxidant effect. Therefore, ginger can be a better hepatoprotective agent and a potent anti-diabetic agent as compared to cumin.

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