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RESEARCH ARTICLE

Effect of *Cinnamomum Zeylenicum* Nees Bark Oil on Drug Induced Diabetic Gastroparesis in Rats

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ABSTRACT

The present study was aimed at investigating the effect of *Cinnamomum zeylenicum* bark oil on drug induced diabetic gastroparesis in rats. A diabetic rat model was established by single intraperitoneal injection with alloxan monohydrate. Rats were divided into five main groups: Normal rats, diabetic rats (Untreated), diabetic rats treated with domperidone (10mg/kg, p.o.), diabetic rats treated with cinnamomum oil (400mg/kg, p.o.) and diabetic rats treated with cinnamomum oil (200mg/kg, p.o.). Gastric emptying rate (GER), intestinal transit rate (ITR), and total gastrointestinal transit were studied in rat after administration of drug. Percentages of GER, ITR, and total gastrointestinal transit time were calculated. Percentages of GER, ITR, and total gastrointestinal transit were decreased in diabetic rats as compared to control rats ($P < 0.05$). In the diabetic rats, bark oil of *Cinnamomum zeylenicum* significantly improved %GER, %ITR and total gastrointestinal transit in a dose dependent manner.

Bark oil of C*innamomum zeylenicum* may become a new choice for patients with diabetic gastroparesis since the benefits are comparable to domperidone.

Keywords: C*innamomum zeylenicum,* Diabetic gastroparesis, Gastric emptying, Intestinal transit.

1. INTRODUCTION

Gastroparesis is a symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction [1]. Gastroparesis is frequent in diabetic patients. It is a well-recognized complication of long-standing diabetes. The symptom complex typically associated with gastroparesis occurs in 25%-55% of patients with long-standing type 1 or type 2 diabetes [2]. Typical symptoms of diabetic gastroparesis are early feeling of satiety, nausea, vomiting, abdominal fullness, epigastric pain, and anorexia [3]. Delayed gastrointestinal transit may be associated with cardiac autonomic neuropathy, blood glucose concentration, and gastrointestinal symptoms. Glycemic control in diabetic patients improves delayed gastric emptying and various symptoms. The pathophysiology of impaired gastrointestinal motility during hyperglycemia still remains unknown. Recent observations indicate that hyperglycemia causes a reversible impairment of motility in various regions of the gastrointestinal tract. Hyperglycemia reduces the number of antral pressure waves propagated abnormally. Hyperglycemia decreases the proximal gastric tone.

Cinnamon belongs to the Lauraceae family. The genus Cinnamomum comprises approximately 250 species which are widely distributed in China, India and Australia. The in vitro investigation of cinnamon has revealed that its extract mimics the function of insulin, which potentiates insulin action in isolated adipocytes. Moreover, cinnamon extract can also improve the insulin receptor function [4]. *Cinnamomum zeylenicum* has been used as antispasmodic, laxative, digestive, antidiabetic, antiseptic, antibacterial, antifungal, and stimulant traditionally. It has been also used in diabetes, dyspeptic complaints, loss of appetite and other abdominal disorder [5]. Cinnamomum bark essential oil is composed of three major and six minor constituents

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by comparison of mass spectral data and retention times of authentic compounds. The three major constituents, cinnamaldehyde, benzaldehyde, and eugenol, comprised 58.1, 12.2 and 5.1% of the oil, respectively [6]. Among these compound cinnamaldehyde and eugenol shows antispasmodic and myorelaxant action mainly improve intestinal transit and gastric emptying [7].

Hence the present study was designed to investigate effect of bark oil of *Cinnamomum zeylenicum*on in diabetic gastroparesis in rats.

2. MATERIALS AND METHODS

2.1. Chemicals

Bark oil of *Cinnamomum zeylenicum* was purchased locally from Mandsaur (M.P. India). Phenol red, alloxan monohydrate and methyl cellulose were purchased from S D fine-Chem limited (Mumbai, India). Other reagents used were of analytical grade and were manufactured in India.

2.2. Animals

Adult wistar rats of either sex weight between 100–150 gm were obtained from central animal house B.R.Nahata college of Pharmacy, Mandsaur. The animals were stabilized for 1 week; they were maintained in standard condition at room temp; 60 ± 5% relative humidity and 12 h light dark cycle. They have been given standard pellet diet and water *ad-libitum* throughout the course of the study.

2.3. Induction of diabetes

Animals were fasted for 24 hours then a single intra peritoneal injection of freshly prepared alloxan (120 mg/kg dissolved in PH - 4.5 acetate buffer) was injected. The diabetes was confirmed by estimation of blood glucose level (BGL) at 3rd day. Rats having BGL more than 250 mg/dl were used for study [8]. Diabetic rats with gastroparesis were evaluated two weeks after alloxan induction of diabetes.

2.4. Assessment of diabetic gastroparesis in alloxan-induced diabetic animals

Rats were divided into five groups (Group-1) Served as normal control; (Group-2) Untreated diabetic rats; (Group-3) Diabetic rats treated with domperidone (10mg/kg); (Group-4) diabetic rats treated with bark oil of *Cinnamomum zeylenicum* (200mg/kg); and (Group-5) diabetic rats treated with bark oil of *Cinnamomum zeylenicum* (400mg/kg). Drugs were orally administered to rats fasted overnight. The untreated diabetic and normal groups were administered the same volume of saline. Then 0.5 h later, assessment of gastrointestinal function was conducted.

2.5. Effect of *Cinnamomum zeylenicum* on *in- vivo* gastric emptying rate of phenol red meals in rats

The GER was determined in rats by measuring the disappearance of phenol red from the stomach. After 30 min of drug administration 1.5 ml of a phenol red meal, consisting of phenol red (0.05%, w/w) in 1.5% methyl cellulose, was given to the rats orally. After 20 min, the rats were sacrificed by cervical dislocation, the abdominal cavity was opened, the gastroesophageal junction and the pylorus were clamped, and the stomach was then extirpated and rinsed in 0.9% saline. The stomach was placed in 100 ml 0.1N NaOH, and homogenized. The suspension was allowed to settle for 1 h at room temperature, and 5ml of the supernatant was then added to 0.5 ml 20% trichloroacetic acid (w/v) and the suspension centrifuged at 3000 rpm for 20 min. The supernatant was mixed with 4ml of 0.5N NaOH, and the absorbance of the sample was read at 560 nm by colorimetric assay. The animals that had been killed immediately after the administration of methyl cellulose solution was used as control group (0% emptying) [11]. The GER in the 20-min period was calculated according to following formula.

GER (%) = {1 − (A_{560} of test / A_{560} of control)} × 100

2.6. *In vivo* intestinal transit rates of charcoal meals in rats

The small intestinal transit in both diabetic and normal animals was measured by the intestinal transit of a charcoal meal. After an overnight fast, a 5% charcoal suspension in olive oil was orally administered at a dose of 10 ml/kg to each animal. After 20 min, the animals were killed by cervical dislocation. The small intestine was immediately excised carefully without stretching and the transit front of the charcoal meals in the small intestine was detected visually. The ITR (%) was expressed as the percentage of the distance traveled by the marker divided by the total length of the small intestine [12].

2.7. Total gastrointestinal transit

Total gastrointestinal transit after the animals were fasted overnight, a 1% (g/100 ml) charcoal suspension in olive oil was orally administered at a dose of 10 ml/kg. The time that animals first defecated black feces was recorded [13].

2.8. Statistical analysis

The value of gastric emptying rates, intestinal transit rates, total gastrointestinal transit between groups are expressed as the mean ± standard error of the mean (SEM). The data were compared using a one-way ANOVA, followed by "Dunnet's test". Data was analyzed using the Graph Pad Software (5.0–demo version) and p value of < 0.05 was considered to be significant.

3. RESULTS

3.1. Effect of bark oil of C*innamomum zeylenicum* on the *in vivo* gastric emptying of phenol red meal in rats

The *in vivo* GERs (%) of phenol red meal during the 20 min period were lower in the untreated diabetic rats (4.89%) than in the normal controls. This decrease was inhibited in diabetic animals after the oral administration of domperidone (63.3%). The %GERs was also increased in diabetic rats treated with bark oil of *Cinnamomum zeylenicum* (45% and 15.6%) at a dose of 400 mg/kg and 200 mg/kg in the untreated diabetic controls (Table 1).

S. No.	Groups	Dose of drugs (mg/kg)	Phenol red remaining in the stomach (mg/kg)	Small intestinal transit of charcoal (%)	Time of the first defecated black feces (min)
1.	Normal rats	-	0.137 ± .009	70.83 ± 1.545	430 ± 26.40
2.	Untreated diabetic rats	-	0.128 ± 0.003	52.40 ± 1.710	892 ± 14.05
3.	Diabetic rats treated with domperidone	10	0.015 ± 0.003***	54.40 ± .0568	776.7 ± 26.03*
4.	Diabetic rats treated with bark oil of Cinnamomum zeylenicum	400	0.051 ± 0.012***	65.60 ± 1.365***	534 ± 2.96***
5.	Diabetic rats treated with bark oil of Cinnamomum zeylenicum	200	0.104 ± 0.006*	59.97 ± 1.586*	653 ± 13.87***

Data are expressed as mean ± SEM. (n = 6). *** $P < 0.001$ is compared to control. * P < $0.05$is compared to control.

Table 1: Parameters of gastrointestinal transit in rats after the oral administration of domperidone and bark oil of *Cinnamomum zeylenicum*.

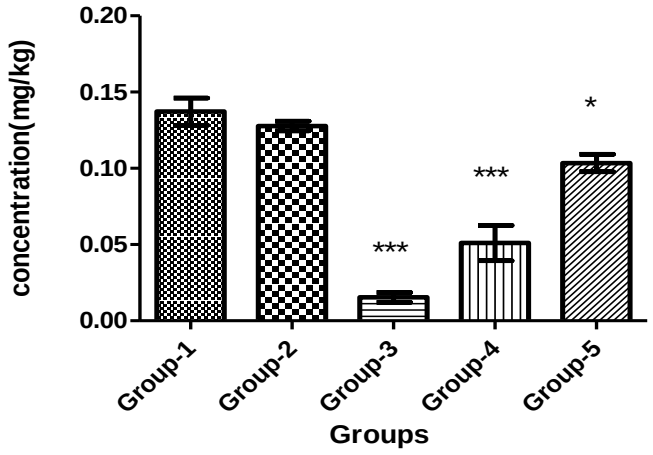

Figure 1: Effect of bark oil of C*innamomum zeylenicum* on the *in vivo* gastric emptying of phenol red meal in rats

3.2. Effect of *Cinnamomum zeylenicum* bark oil on *in vivo* intestinal transit of charcoal meal in rats

The proportion (%) of the distance traveled by the charcoal along the entire length of the small intestine in the untreated diabetic rats (52.40 ± 1.710) was significantly lower than that in normal controls (70.83 ± 1.545), as shown in Table 1. Domperidone had no significant effect on small intestinal transit in the treated diabetic animals (54.40 ± 0.568). Bark oil of *Cinnamomum zeylenicum* at doses of 400 and 200 mg/kg significantly promoted (65.60 ± 1.365 and 59.97 ± 1.586 respectively) small intestinal transit in the treated diabetic animals in a dose-dependent manner.

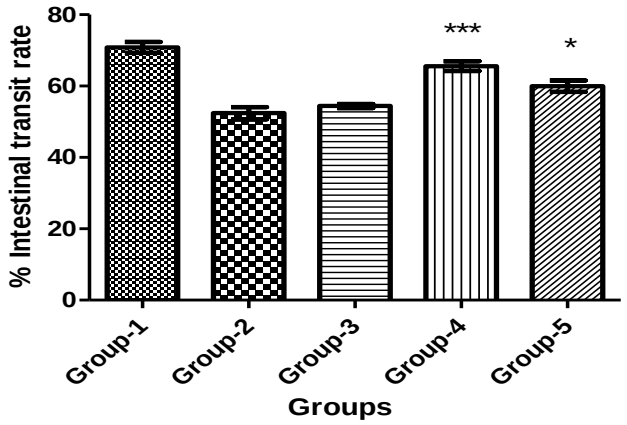

Figure 2: Effect of *Cinnamomum zeylenicum* bark oil on *in vivo* intestinal transit of charcoal meal in rats

3.3. Total gastrointestinal transit

As shown in Table 1, the time to the first black feces was significantly longer in the untreated diabetic animals than in the normal control animals (892 ± 14.05). However, the time was significantly shorter (776.7 ± 26.03) in diabetic rats treated with domperidone than in the untreated diabetic controls. There was also significant reduction (534 ± 2.96 and 653 ± 13.87 respectively) in the time in diabetic groups treated with bark oil of *Cinnamomum zeylenicum*

(400 and 200 mg/kg, respectively) in a dose-dependent manner compared with that in the untreated diabetic controls.

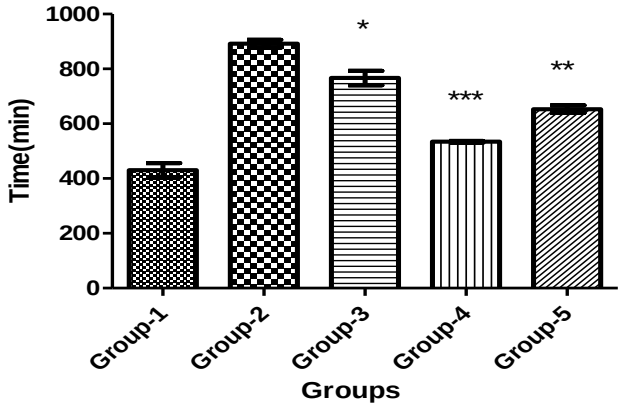

Figure 3: Time of the first defecated black feces (min)

4. DISCUSSION

In the present study, rats with alloxan-induced diabetes had moderate gastroparesis with slow gastric emptying and intestinal transit due to an autonomic neuropathic injury induced by prolonged hyperglycemia as compared with normal controls [8]. Significantly delayed gastric emptying, intestinal transit and total gastrointestinal transit were seen in the rats with alloxan-induced diabetes. Bark oil of *Cinnamomum zeylenicum* was able to accelerate gastric emptying and intestinal transit in the diabetic rats. The most effective dose of bark oil of *Cinnamomum zeylenicum* for accelerating gastrointestinal transit was 400 mg/kg.

Gastrointestinal motility disturbances including esophageal motor dysfunction, gastroparesis, constipation and diarrhea, are common in patients with diabetes mellitus [9]. The pathogenesis of slow gastrointestinal transit in diabetes mellitus patients is not clear, but several mechanisms have been proposed. Among them, autonomic neuropathy, a complication of long-standing diabetes mellitus, has been widely accepted as the culprit. This may lead to the absence of postprandial gastrointestinal response, a reflex that should present in healthy people. Recent studies have shown that an acute change in blood glucose concentration also has a major effect on gastrointestinal motor function. In particular, acute hyperglycemia inhibits both the gastrointestinal and ascending components of peristaltic reflex. Poor glycemic control has the potential to cause delayed gastrointestinal transit in diabetic patients [5].

Cinnamomum zeylenicum comes under the category terpines (monoterpine). The bark contains essential oil-1-2.5% comprising cinnamaldehyde as a major constituent 65-80% of the volatile oil, cinnamic acid, eugenol, and cinnzeylamine [16].

Gastric emptying is delayed because of increased outflow resistance at the level of the pylorus. In diabetes, improperly timed pyloric contractions of abnormal intensity and duration are proposed to lead to pylorospasm and functional outlet obstruction. Cinnamomum oil induced stimulation of gastric emptying and intestinal transit *in vivo* is may be due to active constituents among these compounds, cinnamaldehyde, eugenol, are responsible for antispasmodic and myorelaxant activity [9]. This activity might be due to increased NOs activity (NO-cGMP mediated pathway), inhibition of Na+, K+-ATPase [17]. A preferential decrease in tonus may reduce pylorus and luminal resistance to bulk flow of intestinal contents and helps to maintain the normal tone of gastrointestinal tract. The action displayed by the oil is mainly dependent on the activation of the NO-cGMP pathway. The standard drug Domperidone significantly promoted gastric emptying but it appeared not to improve small intestinal transit although it significantly shortened the time to the first defecated feces in diabetic animals. However, bark oil of *cinnamomum zeylenicum* had significant effects on gastric emptying, small intestinal transit and total gastrointestinal transit in alloxan induced diabetic animals with gastroparesis.

In previously published studies the bark oil of C*innamomum zeylenicum* also showed antidiabetic activity [18] and antioxidant activity [19]. Traditionally it used in abdominal disorder and dyspeptic complaints. Hence on the basis of result obtained we support the traditional claims about the effect of bark oil of *Cinnamomum zeylenicum* on diabetic gastroparesis.

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Conflict of Interest: None Declared

