An in-vivo study on postprandial hyperglycemia to assess antidiabetic activity of alcoholic extract of *Cinnamomum verum* bark

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Background and objective
Cinnamomum verum bark is locally known as 'Daruchini' and is traditionally reputed as an Ayurvedic medicine, which is used in the treatment of flatulence, toothache, heart diseases, fever, cough, cold, headache, and many others. In this study, we intended to explore the effectiveness of its activity on hyperglycemia.
Materials and methods
To evaluate its antihyperglycemic activity, we used various experimental designs, including the effect of plant extract on gastrointestinal (GI) motility in the Swiss albino mice model and intestinal disaccharidase enzyme activity and carbohydrate digestion and absorption in the gut of the Long Evans rats.
Results and discussion
The plant extract significantly ($P<0.001$) increased the GI motility rate by ~16% than the control (distilled water, 10 ml/kg body weight) and indicated that it interfered with the rate of glucose absorption in the gut. Furthermore, treatment with *C. verum* caused a significant ($P<0.05$) dose-dependent reduction of intestinal disaccharidase enzyme activity from 1.63 to 1.21 μmol/mg protein/h in fasting Long Evans rats. Besides, the extract produced a similar effect in the acute oral sucrose (2.5 g/kg body weight) load assay, in which a substantial amount of unabsorbed sucrose was found in six different parts of the GI tract after sucrose administration. This indicates that *C. verum* can liberate GI content and reduce or delay glucose absorption.
Conclusion
All the findings of the present study point to the conclusion that *C. verum* has the potential to exert postprandial antihyperglycemic activity within type 2 diabetic animal models through reducing or delaying carbohydrate digestion and absorption in the gut.

Keywords:
antidiabetic, antihyperglycemic, intestinal disaccharidase, postprandial hyperglycemia

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Introduction

Diabetes is one of the most prevalent diseases and is a heterogeneous group of metabolic disorders characterized by hyperglycemia due to insulin secretion defects, insulin action or both. According to the National Diabetes Statistics Report, 2020, a total of 34.2 million people has diabetes, of which 21.4% are still undiagnosed [1], and about 8.4 million people in Bangladesh are affected by this disease, according to the International Diabetes Federation [2]. The prevalence is predicted to double from 2005 through 2030. Asia, Africa, and South America will account for the highest proportion of this rise [3–6].

While we have advanced diagnostic methods and treatment protocols, the lack of information on the pathways underlying disease pathogenesis causes a high incidence of morbidity that significantly disturbs the quality of life. Understanding the underlying mechanisms of the pathogenesis of the disease can enable better targeting of changes that lead to glycemic control and improvement in overall outcomes [7,8].

Cinnamomum verum belongs to the Lauraceae family and from several investigations, it was found that the plant possesses antiulcerant [9], antipyretic [10,11], antioxidant [12], anesthetic [13], and anti-allergenic activities [14]. It has also been reported that in the thin-layer chromatographic assay of the volatile oils found in the bark of the stem and root of *C. verum*,

cinnamaldehyde and eugenol were seen to be present in high amounts [15]. Moreover, some other components, namely, linaloon, alpha-terpineol, acetyl eugenol, and some unknown compounds, were present in low to trace amounts [16]. Previous research on *C. verum* revealed that cinnamaldehydes have a variety of biological activities, including peripheral vasodilation, antifungal, cytotoxic, and antimutagenic properties [17–20].

The present study aims to evaluate the pharmacological effect of C. verum bark on hyperglycemia after a meal in laboratory animals by observing the methanolic extract effect on gut absorption. This study tries to draw a comprehensive picture of the effects of C. verum on gastrointestinal (GI) motility, carbohydrate absorption, and intestinal enzyme functions.

Materials and methods

Material collection and processing

The plant sample of *C. verum* was collected from the market and botanically authenticated. Voucher specimens were deposited in the National Herbarium, Bangladesh (DACB Accession Number: 55821). The plant materials were processed in the laboratory of the East West University. The materials were initially washed several times with clean water to avoid unwanted parts and dust. Then these were partially dried in air and fully dried in the oven at a temperature below 40°C for 2 days. The drying process was carried out with great caution to avoid loss of the volatile oils. Fully dried samples of plants were finely ground to a powdered form and methanolic extraction was carried out. During this process, we used 2500 ml of 90% methanol for 500 mg of powder sample, and after 7 days, it was filtered by cloth, cotton, and finally Whatman filter paper 1. The filtrate was obtained by rotary evaporator filtration. Then the extract was stored in the refrigerator under 4°C until the experiment was started. The plant extract was named methanolic extract of C. verum (MECV).

Animal model preparation

Two types of animal models were used for this study.

(1) The Long Evans rat model was selected for the disaccharidase activity test and to evaluate the effect on sucrose absorption from the gut, because it is large in size and more enzymes can be easily extracted.

(2) The Swiss albino mice model was chosen for the GI motility test because this test is not enzyme dependent, we just need the length of the gut.

Both animal models were collected from the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR'B) Animal Resource Centre, Dhaka, Bangladesh. The test animals were kept in a fasting state for 16–20 h before the experiments. The total study method was presented and accepted by the Ethics Committee on Animal Research, East West University, Dhaka, Bangladesh.

Effect of methanolic extract of *Cinnamomum verum* extract on gastrointestinal motility

GI motility is the movement of the digestive system and the transit of the contents within it. The primary functions of the small intestine are the digestion and absorption of nutrients. The small intestinal motor activity enables access to the mucosal surface of the luminous contents [21–25]. $BaSO_4$ milk was used to determine GI motility according to the previously delineated Chatterjee [26] method.

Twenty-four Swiss albino mice (male and female) were randomly selected for this experiment, separating the mice into two groups (standard control and MECV), each comprising eight mice per group. A 10% (w/v) $BaSO_4$ solution was mixed with 0.5% carboxymethyl cellulose to form a suspension of $BaSO_4$ milk. Orally, MECV (500 mg/kg) was introduced to the test groups, with only distilled water (10 ml/kg) for the control group. Bisacodyl, marketed under the brand name Duralax-5mg by Opsonin Pharma Ltd, Dhaka, Bangladesh, was used as a standard drug at doses of 1 mg/kg body weight of the mice. After 1 h of water, bisacodyl, and MECV administration to the control, standard, and test groups, respectively, $BaSO_4$ milk was administered to all groups. Then after 15 min, the mice belonging to all groups were killed and the small intestine was isolated. The result was defined as a percentage of the total length of the small intestine passing through the $BaSO_4$ milk, which was measured with a tape measure ribbon, and the test group data were then compared with the control and standard group data.

Effect of methanolic extract of *Cinnamomum verum* on sucrose absorption from the gut

Postprandial hyperglycemia is an abnormally high increase in blood sugar after eating. The pancreas secretes insulin all the time in people who do not have diabetes. It boosts its secretion as blood glucose levels rise after meals [27]. For this experiment, 16 Long Evans rats (both male and female) were selected

randomly, then divided into a control and test group, each group containing eight rats. A sucrose solution (2.5 g/kg body mass) was administered orally with MECV (500 mg/kg) to the test group and only sucrose solution to the control group. Both test and control groups were killed to determine the unabsorbed sucrose content at 30, 60, 120, and 240 min time intervals, and then the GI tract was excised and separated into six segments: the stomach, upper 20 cm, middle and lower 20 cm of the small intestine, the cecum, and the large intestine. After washing the segments with 10 ml ice-cold normal saline, 2N H_2SO_4 was added to acidify it and finally centrifuged at 3000 rpm for 10 min. Then the supernatant was boiled for 2 h in paraffin oil, and then after the addition of 1 N sodium hydroxide to neutralize the H_2SO_4 content, the final volume was recorded. The GI sucrose content was determined using the in-situ gut technique from the volume of released glucose [28,29].

Effect of methanolic extract of *Cinnamomum verum* on disaccharidase activity

For the experiment, randomly selected 12 Long Evans rats were divided into the test control and the standard group, each containing four rats in each group and administered with MECV (500 mg/kg body weight), an equal volume of water (10 ml/kg body weight), and acarbose (15 mg/kg body weight) to each group, respectively. The rats were killed after 1 h of administration; then the small intestine was isolated from just below the duodenum to just above the cecum, and washed out with 50 ml of normal ice-cold saline. The intestine was cut longitudinally on an ice-cold glass plate to collect mucosa and homogenized mucosa in 10 ml of normal saline for 20 s at medium speed. Finally, 40 mM sucrose was added to aliquots of the homogenate and incubated at 37°C. The activity of the disaccharidase enzyme was assessed as μmol/mg protein/hour from the concentration of glucose converted from sucrose measured using the Lowry protein estimation method, where the total protein concentration is determined by the change in the color of the sample solution in proportion to the protein concentration in the absence of sucrose [30,31].

Methods of analysis

To achieve the different objectives of this study, appropriate statistical methods for analyzing the data were adopted. The *t* test and the analysis of variance tests were used to examine the effects of the variables. The Statistical Package for Social Sciences, 25 version (IBM Corporation, Armonk, New York, NY, USA) and GraphPad Prism were used for management, analysis, and graphical presentation of data.

Results

Effect of plant extracts on gastrointestinal motility

MECV increased the %GI motility significantly at doses of 500 mg/kg body weight of mice. Table 1 demonstrates the data of %GI motility as a mean ±SEM (n=8).

Effect of plant extracts on sucrose absorption from the gut

The unabsorbed sucrose content after the administration of sucrose (2·5 g/kg body weight) to MECV was increased significantly more than the control group in the stomach, upper 20 cm of the small intestine, middle intestine, lower 20 cm of the small intestine, cecum, and large intestine at doses of 500 mg/kg body weight of rats after 30, 60, 120, and 240 min time intervals of dose administration. Table 2 displays the data for unabsorbed sucrose content (mg) as mean±SEM (n=8).

Effect of plant extract on disaccharidase enzyme activity

MECV significantly decreased the disaccharidase activity at a dose of 500 mg/kg body weight of rats. Table 3 demonstrated the data of disaccharidase activity (μmol/mg/h) as mean±SEM (n=8).

Discussion

Nowadays, postprandial hyperglycemia is widespread in diabetic patients and is difficult to regulate due to elevated high blood glucose levels, which can cause activation of the polyol pathway, elevation of protein glycation, and insulin resistance. Lowering carbohydrate absorption may thus be a beneficial approach to diabetes treatment [32,33]. Although the mechanism of action of MECV antidiabetic properties at the tissue level is yet to be investigated, our present study has assisted in evaluating the antidiabetic properties of a methanolic extract of the bark of C. verum on laboratory animals where the plant extract was given orally. In addition, unpublished preliminary screening data of this plant showed highly promising hypoglycemic activity. MECV

Table 1 Effect of methanolic extract of *Cinnamomum verum* (500 mg/kg body weight) on gastrointestinal motility in mice (mean±SEM, n=8)

Groups	%GI motility
Control	53.73±2.29
MECV	70.06±1.98***
Bisacodyl (reference)	86.63±0.58***

GI, gastrointestinal motility; MECV, methanolic extract of *Cinnamomum verum*. ***Significant through *t* test at *P* value less than 0.001.

Table 2 Data of the carbohydrate absorption test to determine the effect of methanolic extract of *Cinnamomum verum*

Segments	Group	30 min	60 min	120 min	240 min
Stomach	Control	54.13 ±1.7	34.04 ±3.94	8.50±0.60	1.32 ±0.32
	MECV	64.23 ±0.93*	52.37 ±1.56*	18.50 ±2.30	3.55 ±0.11*
Upper 20 cm	Control	14.69 ±0.89	11.68 ±0.66	4.56±1.08	0.95 ±0.15
	MECV	19.06 ±1.62*	18.31 ±0.15*	7.30 ±0.06*	1.67 ±0.06*
Middle intestine	Control	20.17 ±1.95	17.48 ±0.72	7.99±0.05	1.26 ±0.08
	MECV	32.49 ±1.70*	31.74 ±0.55*	11.30 ±0.03*	1.97 ±0.06*
Lower 20 cm	Control	5.57±0.7	3.24 ±0.73	1.26±0.56	0.98 ±0.02
	MECV	5.97 ±0.16	7.32 ±0.48*	6.17 ±0.26*	1.53 ±0.04*
Cecum	Control	2.7±0.4	2.01±0.0	1.76±0.04	0.74 ±0.08
	MECV	5.50 ±0.03**	6.81 ±0.65*	5.60 ±0.08**	1.54 ±0.06*
Large intestine	Control	1.32 ±0.22	0.94 ±0.06	0.96±0.15	0.48 ±0.01
	MECV	5.39 ±0.20*	5.70 ±0.25**	5.40 ±0.07***	1.02 ±0.03*

MECV, methanolic extract of *Cinnamomum verum*. Significant through one-way analysis of variance test: ***P value less than 0.001, **P value less than 0.01, *P value less than 0.05.

Table 3 Effect of methanolic extract of *Cinnamomum verum* (500 mg/kg body weight) on disaccharidase activity [(n=8, Long Evan rats), mean±SEM]

Groups	Disaccharidase activity (μmol/mg/h)
Control	1.64±0.026
MECV	1.21±0.031***
Acarbose (reference)	1.01±0.02

MECV, methanolic extract of *Cinnamomum verum*. Significant through t test at ***P value less than 0.001.

significantly increased the GI motility where the test group showed ~1.3 times better effect (control group=53.73% and test group=70.06%) after administration of MECV. There are various enzymes that get secreted in the brush border membrane of the intestine and they are highly necessary for food absorption. Since MECV increases GI motility, the food ingested gets to spend less time in contact with the brush border membrane, hence getting less opportunity to get absorbed by those abundant digestive enzymes. Thus, MECV inhibits glucose absorption from the small intestine, ultimately leading to a lower chance of developing postprandial hyperglycemia [34].

Disaccharidase is found in the brush border membrane of the small intestine and it is an essential digestive enzyme that breaks down the disaccharides and helps in the terminal stage of carbohydrate digestion. Inhibition of the disaccharidase enzyme helps eliminate postprandial glucose increases by reducing the additional pressure on beta cells to secrete insulin, which can be used to detect a new therapeutic strategy for diabetic patients [35].

The six-segment test showed a significant availability of sucrose (a disaccharide) in different portions of the intestinal tract of the Long Evans rat, which indicates that the sucrose remained undigested and hence it was not absorbed through the intestine. It can further be justified by the evidence of the decreased disaccharidase enzyme activity in the rat intestine. In our GI tract, disaccharides need to be converted into monosaccharides by different types of disaccharidase enzymes before absorption [36], which suggests that the reduction in the disaccharidase enzyme activity by MECV has led to a decreased conversion of sucrose to glucose, resulting in a higher amount of residual undigested sucrose in the gut. Since complex carbohydrates and disaccharides have to first be broken down into simpler monosaccharides, it follows that any inhibition of this catabolic process would retard sugar absorption, which would, in turn, be shown as a lower glycemic peak [37].All the discussion in our present study demonstrates that our results can be fully attributed to the significant increased amount of unabsorbed sucrose that remained in six different parts of the intestine and the decrease in disaccharide enzyme activity, which validates the antihyperglycemic activity of MECV.

Conclusions

The present study showed that MECV bark possessed hypoglycemic and antihyperglycemic activities in a Long Evans rat model by reducing the absorption of sucrose and activity of the disaccharidase enzyme. Besides, we have evaluated that it is capable of slowing the absorption of glucose by increasing GI motility in the Swiss albino mice model. These findings reveal the presence of biologically active constituents in C. verum bark extracts that may be worth further investigation and elucidation.

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Authors' Contributions: J.M.A. Hannan: conceived and designed experiments. Iqbal H. Nayan: collect the plant material, performed the experiments, analyzed, and interpreted the data, and wrote the manuscript. Mohibul Alam, Abrar Jamil: preliminary reviewing and editing the paper. Iqramul Haq, Ismail Hossain: final reviewing of the manuscript.

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Conflicts of interest
There are no conflicts of interest.

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