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Research Article

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Oral glucose tolerance and analgesic activity evaluation with methanolic extract of fruits of *Momordica cochinchinensis*

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ABSTRACT

In oral glucose tolerance tests conducted with methanolic extract of fruits of Momordica cochinchinensis, the extract at doses of 50, 100, 200 and 400 mg per kg dose-dependently reduced blood glucose levels in glucose-loaded mice by 23.6, 27.4, 39.5, and 47.5%, respectively. A standard antihyperglycemic drug, glibenclamide, at a dose of 10 mg per kg, reduced blood glucose level by 35.4%. In standard acetic acid-induced pain model in mice, the extract at the afore-mentioned four doses reduced the number of pain-induced abdominal constrictions in mice, respectively, by 44.1, 50.0, 52.9, and 55.9%. A standard analgesic drug, aspirin, when administered to mice, reduced the number of abdominal constrictions by 47.1 and 61.8, respectively. Taken together, the methanolic extract demonstrated significant antihyperglycemic and analgesic potential and so can be a source for efficacious blood glucose lowering and pain-relieving drug(s).

Key words: *Momordica cochinchinensis*, Cucurbitaceae, OGTT, analgesic, antihyperglycemic

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INTRODUCTION

Momordica cochinchinensis (Lour) Spreng is a vinous plant belonging to the Cucurbitaceae family and is widely cultivated in the Southeast Asian countries including Bangladesh for its fruits, which are cooked and consumed as vegetable. It is known as Spiny Bitter Gourd in English and as kakroal in Bengali. The plant has ethnomedicinal uses and several pharmacological activities have been reported for the plant or plant parts.

In Rajshahi Division of Bangladesh, paste of leaves and fruits are used topically for treatment of lumbago, ulceration and fracture of bones. The seeds are used as aperients and in the treatment of ulcers, sores, and obstruction of liver and spleen. The roots are given in rheumatism [1]. The fruits and seeds are used to treat flatulence in Greater Khulna Division of Bangladesh [2]. A hypoglycemic oleanane triterpenoid, 2'-O-beta-D-glucopyranosylmomordinIc has been reported from leaves of the plant [3]. Chondrillasterol has been reported from the tubers of the plant [4]. A triterpenoid ester 3,29-di-O-(p-methoxy)benzoylmultiflora-8-ene-3alpha,29-diol-7-one has been reported from seeds [5]. Carotenoids like beta-carotene, lycopene, zeaxanthin and beta-cryptoxanthin has been isolated from fruits [6].

Aqueous extract of fruit reportedly inhibited the growth of colon 26-20 adenocarcinoma cell line, transplanted in Balb/c mice [7]. Extract of seeds was found to have a beneficial effect on healing of gastric ulcers [8]. Seed extract has been shown to induce apoptosis and cell cycle arrest in human gastric carcinoma cell lines SGC7901 and MKN-28 cells [9]. Seed extract also suppressed migration and invasion of human breast cancer ZR-75-30 cells [10].

Various solvent extracts of seeds also has anthelmintic potential [11]. Two tripenoidal saponins, namely, gypsogenin 3-O-β-D-galactopyranosyl(1→2)-[α-L-rhamnopyranosyl(1→3)]-β-D-glucuronopyranoside and a quillaic acid glycoside has been isolated from seeds, the latter compound demonstrating anti-inflammatory activity in RAW 264.7 cells [12]. Fruit extract has been reported to exert a hypoglycemic effect in alloxan-induced diabetic rats [13].

Diabetes is a chronic disease when the pancreas cannot produce enough insulin or the body cannot effectively utilize the insulin produced by the pancreas. The disease is characterized by high blood glucose levels and can rapidly give rise to other complicated factors like cardiovascular disorders, diabetic retinopathy, nephropathy, and neuropathy. The World Health Organization (WHO) estimates that more than 220 million people worldwide had diabetes in 2004, and diabetes deaths will double between 2005 and 2030. Almost 80% of diabetes deaths occur in low and middle income countries [14]. The disease is rapidly reaching endemic proportions in Bangladesh. In a demographic study conducted with 7541 adults aged 35 years or more, it was found that 9.7% had diabetes and 22.4% had pre-diabetes [15]. Juvenile diabetes is also on the rise in Bangladesh [16]. The problem is compounded by the fact that the rural and urban slum population of Bangladesh cannot afford or lack access to proper diagnostic clinics, modern doctors, and diabetic medications. Furthermore, daily injections of insulin appear cumbersome to many people.

Pain is another common affliction suffered by millions of people in Bangladesh and indeed throughout the world on a daily basis. Pain can arise from injuries or sprain or can be a problem associated with diseases like cancer and rheumatoid arthritis. The majority of the people of Bangladesh are rural and urban slum dwellers. Agriculture involves hard labour resulting in body pain. A huge section of the urban slum dwellers work as construction labourers or rickshaw pullers, which again involves hard labour, resulting in body, muscle or joint pain. While over-the-counter drugs like aspirin or paracetamol can alleviate pain, these drugs can produce gastric ulceration or hepatotoxicity from over-dosage or prolonged use [17, 18]. The illiterate rural and urban slum dwellers take these drugs without proper consultation with physicians, and end up with adverse effects of these drugs. Although no proper statistics are available, anecdotal evidence suggests that these drugs are being over used by the people.

The plant kingdom can form a novel source for affordable and newer efficacious drugs. Towards an effective mitigation of diabetes and pain, we had been systematically screening the common plants of Bangladesh, which can help the poorer segments of the urban population as well as the rural population to more readily treat these afflictions [19-26]. Towards that objective, the aim of the present study was to evaluate the antihyperglycemic (through oral glucose tolerance tests or OGTT) and analgesic (through acetic acid-induced pain model test) potential of the fruits of *M. cochinchinensis*, which fruits are readily available in the country and affordable by all segments of the population.

EXPERIMENTAL SECTION

Plant material collection

Fruits of *M. cochinchinensis* were collected during August 2013 from a local market in Dhaka city, Bangladesh, and taxonomically identified at the Bangladesh National Herbarium (Accession Number 38,758).

Preparation of methanolic extract of fruits

Fruits were cut into small pieces, air-dried in the shade, and 100g of dried and powdered fruits were extracted with methanol (w:v ratio of 1:5, final weight of the extract 9.5g).

Chemicals and Drugs

Glibenclamide, aspirin, and glucose were obtained from Square Pharmaceuticals Ltd., Bangladesh. All other chemicals were of analytical grade.

Animals

Swiss albino mice, which weighed between 17-20g were used in the present study. The animals were obtained from International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). The animals were acclimatized for three days prior to actual experiments. The study was conducted following approval by the Institutional Animal Ethical Committee of University of Development Alternative, Dhaka, Bangladesh.

Oral glucose tolerance tests for evaluation of antihyperglycemic activity
Oral glucose tolerance tests were carried out as per the procedure previously described by Joy and Kuttan [27] with minor modifications. Briefly, fasted mice were grouped into six groups of five mice each. The various groups received different treatments like Group 1 received vehicle (1% Tween 80 in water, 10 ml/kg body weight) and served as control, Group 2 received standard drug (glibenclamide, 10 mg/kg body weight). Groups 3-6 received methanolic fruit extract (MEMC) at doses of 50, 100, 200 and 400 mg per kg body weight. All substances were orally administered. Following a period of one hour, all mice were orally administered 2g glucose/kg of body weight. Blood samples were collected 120 minutes after the glucose administration through puncturing heart. Blood glucose levels were measured by glucose oxidase method [28]. The percent lowering of blood glucose levels were calculated according to the formula described below.

Percent lowering of blood glucose level = $(1 – W_e/W_c) X 100$,

where W_e and W_c represents the blood glucose concentration in glibenclamide or MEMC administered mice (Groups 2-6), and control mice (Group 1), respectively.

Analgesic activity evaluation through abdominal writhing test
Analgesic activity of MEMC was examined as previously described [29]. Mice were divided into seven groups of five mice each. Group 1 served as control and was administered vehicle only. Groups 2 and 3 were orally administered the standard analgesic drug aspirin at doses of 200 and 400 mg per kg body weight, respectively. Groups 4-7 were administered MEMC at doses of 50, 100, 200 and 400 mg per kg body weight, respectively. Following a period of 60 minutes after oral administration of standard drug or MEMC, all mice were intraperitoneally injected with 1% acetic acid at a dose of 10 ml per kg body weight. A period of 5 minutes was given to each animal to ensure bioavailability and onset of chemically induced irritation of acetic acid [30], following which period, the number of abdominal constrictions (writhings) was counted for 10 min. The percent inhibitions of abdominal constrictions were calculated according to the formula given below.

Percent inhibition = $(1 – W_e/W_c) X 100$

where W_e and W_c represents the number of abdominal constrictions or writhings in aspirin or MEMC administered mice (Groups 2-7), and control mice (Group 1), respectively.

Acute toxicity test
Acute toxicity test was conducted as previously described [31]. Mice were divided into nine groups, each group consisting of six animals. Group 1 was given 1% Tween 80 in normal saline (2 ml per kg body weight). The other eight groups (Groups 2-9) were administered, respectively, 100, 200, 300, 600, 800, 1000, 2000 and 3000 mg of MEMC per kg body weight. All animals were closely observed for the next 8 hours to notice any behavioural changes or mortality and were kept under close observation for the next two weeks.

Statistical analysis
Experimental values are expressed as mean ± SEM. Independent Sample t-test was carried out for statistical comparison. Statistical significance was considered to be indicated by a p value < 0.05 in all cases [26].

Preliminary phytochemical screening
Preliminary phytochemical analysis of MEMC for presence of saponins, tannins, alkaloids, and flavonoids were conducted as described before [32].

RESULTS AND DISCUSSION

Toxicity evaluation
The crude extract (MEMC) did not show any toxicity in mice even at the highest dose tested. There were no changes in behavioral pattern and mortality was not observed.

Preliminary screening of phytochemicals
Various tests conducted for presence of phytochemicals in MEMC indicated the presence of alkaloids, flavonoids, saponins, and tannins.

Antihyperglycemic activity evaluation through OGTT

Significant and dose-dependent oral glucose tolerance was observed in glucose-loaded mice following administration of MEMC. At extract doses of 50, 100, 200 and 400 mg per kg, MEMC reduced blood glucose concentrations by 23.6, 27.4, 39.5, and 47.5%, respectively, compared to control animals. A standard antihyperglycemic drug, glibenclamide, when administered at a dose of 10 mg per kg, reduced blood glucose concentrations by 35.4%. The results are shown in Table 1, and suggest that the extract had potent antihyperglycemic activity, in fact better than that of glibenclamide at doses of 200 and 400 mg per kg. It may be noted that antihyperglycemic activity has been reported before with fruit extract in alloxan diabetic rats [13]. Thus our results are in agreement with previous results and indicate that the extract needs to be further explored for isolation and identification of the phytochemical constituents responsible for the antihyperglycemic effect. The results further suggest that the extract itself may be used as a crude drug to lower blood glucose in hyperglycemic patients.

Table 1: Effect of crude methanol extract of *M. cochinchinensis* fruits (MEMC) on blood glucose level in hyperglycemic mice following 120 minutes of glucose loading

Treatment	Dose (mg/kg body weight)	Blood glucose level (mmol/l)	% lowering of blood glucose level
Control	10 ml	5.26 ± 0.15	-
Glibenclamide	10 mg	3.40 ± 0.30	35.4*
(MEMC)	50 mg	4.02 ± 0.28	23.6*
(MEMC)	100 mg	3.82 ± 0.21	27.4*
(MEMC)	200 mg	3.18 ± 0.37	39.5*
(MEMC)	400 mg	2.76 ± 0.20	47.5*

*All administrations were made orally. Values represented as mean ±SEM, (n=5); *P < 0.05; significant compared to hyperglycemic control animals.*

Analgesic activity evaluation results

Dose-dependent and significant reductions in the number of abdominal constrictions (writhings or squirms) induced by intraperitoneal administration of acetic acid were observed with MEMC. At doses of 50, 100, 200 and 400 mg per kg body weight, MEMC was observed to reduce the number of writhings, respectively, by 44.1, 50.0, 52.9, and 55.9%. A standard analgesic drug, aspirin, when administered to experimental animals at doses of 200 and 400 mg per kg body weight, reduced the number of constrictions by 47.1 and 61.8%, respectively. Thus, even a dose of 100 mg/kg MEMC was better than that of 200 mg/kg aspirin. The results are shown in Table 2 and suggest that the extract possesses significant analgesic properties. Since analgesic activity has previously not been reported from the whole plant or any part of the plant to our knowledge, the results suggest possible presence of potentially new analgesic phytoconstituents in fruits.

Table 2: Analgesic effect of crude methanol extract of *M. cochinchinensis* fruits (MEMC) in acetic acid-induced pain model mice

Treatment	Dose (mg/kg body weight)	Mean number of abdominal constrictions	% inhibition
Control	10 ml	6.8 ± 0.37	-
Aspirin	200 mg	3.6 ± 0.40	47.1*
Aspirin	400 mg	2.6 ± 0.51	61.8*
(MEMC)	50 mg	3.8 ± 0.37	44.1*
(MEMC)	100 mg	3.4 ± 0.68	50.0*
(MEMC)	200 mg	3.2 ± 0.80	52.9*
(MEMC)	400 mg	3.0 ± 0.32	55.9*

*All administrations (aspirin and extract) were made orally. Values represented as mean ±SEM, (n=5); *P < 0.05; significant compared to control.*

The identification of the phytochemical constituent(s) responsible for the observed antihyperglycemic and analgesic effects was not done in this preliminary study and is currently undergoing in our laboratory. However, phytochemical analysis of the extract indicated presence of alkaloids, flavonoids, saponins, and tannins. Interestingly, these groups of phytochemicals have been reported to demonstrate antihyperglycemic as well as analgesic activities in such studies conducted with extracts of other plants.

Ethanolic extract of whole plant of *Tridax procumbens* showing hypoglycemic activity in STZ-diabetic rats revealed the presence of alkaloids, flavonoids, and tannins [33]. Hot water extract of seeds of *Persea americana* reportedly demonstrated hypoglycemic activity in alloxan-diabetic rats; phytochemical screening of the extract showed the

presence of alkaloids, flavonoids, and tannins [34]. Ethanolic root extract of *Sida cordifolia* demonstrating acetic acid-induced writhing inhibition in mice indicated presence of alkaloids [35]. The hypoglycemic effect of stem bark extract of *Tamarindus indica* in alloxan-diabetic rats has also been attributed to presence of alkaloids, flavonoids, and tannins among other groups of compounds [36]. Analgesic activity has been seen with aqueous leaf extract of *Lagenaria breviflora*; phytochemical analysis revealed the presence of alkaloids, flavonoids, and tannins in the extract [37].

Also interestingly, other species belonging to the *Momordica* genus have been reported to have hypoglycemic effects or being beneficial in diabetes. The most widely studied and reported is *Momordica charantia*. Studies have shown that *M. charantia* fruit repairs damaged pancreatic beta-cells, increases insulin levels, and also enhance the sensitivity of insulin. Furthermore, it inhibits the absorption of glucose by inhibiting glucosidase, and improves glycemic control [38, 39]. Methanolic extract of fruits have been shown to exert hypoglycemic activity in alloxan induced diabetic rats [40]. Antidiabetic activity of a triterpenoid saponin isolated from *Momordica cymbalaria* has been reported [41]. Fruits, leaves, and tuberous roots of *Momordica dioica* are used as a folk remedy for diabetes mellitus (DM) in India. The antioxidative effect of fruits has been seen in alloxan induced diabetic Wistar rats, which effect can be useful in relieving oxidative stress during diabetes [42].

The analgesic effect of seed extract of *M. charantia* has been observed in mice [43]. The analgesic and anti-pyretic effect of ethanolic fruit extract of *M. charantia* has also been reported [44]. Various plant parts of *Momordica balsamina* have also been in a recent review mentioned as to have among others, analgesic and hypoglycemic properties [45]. Thus it appears that the *Momordica* genus is a useful genus containing plants with the potential to reduce blood glucose and to alleviate pain. The present study adds to the list of species in the *Momordica* genus with antihyperglycemic and analgesic potential.

The fruits of *M. cochinchinensis* need to be further analyzed for isolation and identification of antidiabetic and analgesic constituents. The fruits are eaten in the cooked form in Bangladesh. It would be interesting to study whether consumption of cooked fruits can also produce antihyperglycemic and analgesic effects. If found to be so, the fruits can form a readily available form of blood glucose lowering and pain relieving agent and so can be a boon to people suffering from diabetes or pain. Even if the cooking process destroys the antihyperglycemic and analgesic properties of the fruits, the methanol extract of fruits can be an affordable and readily available source for antihyperglycemic and analgesic drugs with the further potential to isolate the individual responsible constituents and so increasing their efficacy.

CONCLUSION

The experimental results suggest that the methanolic extract of fruits of *M. cochinchinensis* possess antihyperglycemic and analgesic potential.

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