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Efficacy Appraisal of Some Antidiabetic Herbal Preparations Available in Bangladesh

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MRA and MRZ wrote the protocol, managed the literature searches and wrote the first draft of the manuscript. Author BR designed the study, managed the experimental process of the study, statistical analysis of data of the study performed. Authors BR and MM replied to the reviewers comments. All authors read and approved the final manuscript.

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ABSTRACT

Antidiabetic Herbal Preparations (ADHP) are being used for the management of diabetes mellitus (DM) but their efficacy in controlling hyperglycemia is not scientifically evaluated. This study was undertaken to evaluate the antihyperglycemic potency of some selected antidiabetic HPs (herbal preparations) manufactured locally and readily available in Bangladesh. Six ADHPs were collected from herbal medicine shops in Dhaka city produced by five different local herbal pharmaceuticals

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companies. Acute and chronic responses of the selected ADHPs on glycemic status were determined by feeding test on streptozotocin induced type 2 diabetic model rats. Plasma glucose concentrations were measured at baseline and after oral administration of ADHPs. Acute responses were investigated after 30 and 60 minutes of oral glucose load when ADHPs were administered simultaneously or 30 minutes before oral glucose load. Chronic responses were investigated at 14 and 28 days after ADHPs administration in two different doses. Data were expressed as mean±SD. Statistical analysis within groups was done using paired't'- test. Comparison between groups was done using one-way ANOVA with post Hoc Bonferroni test. Among the six ADHPs tested, only ADHP-3 showed significant reduction of plasma glucose levels compared to control. It was effective at 30 ($p<0.05$) and 75 ($p<0.01$) minutes when ADHPs were administered simultaneously with oral glucose load. ADHP-3 was also effective at 60 and 105 minutes ($p<0.01$ at both time points) when ADHPs were administered 30 minutes before oral glucose load. In case of chronic responses evaluation, ADHP-3 at a dose of 200 mg/kg/day insignificantly reduced blood glucose levels compared to baseline ($p=0.342$) at 28 days but at a dose of 400 mg/kg/day significantly reduced blood glucose levels ($p=0.040$).

Keywords: Antidiabetic herbal preparations; diabetes mellitus.

1. INTRODUCTION

Global health burden is increasing due to upward trend in non-communicable diseases (NCDs) and diabetes mellitus (DM) is considered as one of the most important component of NCDs. Diabetes mellitus remains a major global epidemic in the 21st century, driven by population growth and ageing. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030 [1] with type 2 diabetes mellitus (T2DM) accounting for about 90% of cases. The incidence of DM is increasing worldwide and rising rate is higher in developing countries [2]. For the management of DM and its complications, modern therapeutics (MT) as well as herbal preparations (HP) are being used. The side effects & adverse effects of MTs have been reported [3]. There are several types of glucose-lowering drugs including insulin sensitizers, insulin secretagogues, DPP 4 inhibitors and α-glucosidase inhibitors. Most glucose-lowering drugs, however, have side effects, such as severe hypoglycemia, idiosyncratic liver cell injury, lactic acidosis, permanent neurological deficit, digestive discomfort, headache, and dizziness. Lazarou et al. [3] showed that a large number of people died and seriously injured due to the adverse effects of modern drugs. According to World Health Organization (WHO, 2001 [4]), it has been globally accepted that allopathic drugs are not in reach of large proportion of human population for their healthcare because of high price and non-availability. On the other hand, HPs are believed to be safe as they are obtained from natural sources. Beside this HP is readily available at relatively low cost. Eighty percent of population of developing country rely on herbal medication for the management of diabetes [5]. Therefore, consumption of these plant based therapeutics or botanicals has grown rapidly.

Although a large number of world populations use and rely on HP for their healthcare it has several drawbacks like inadequate and unacceptable evidence of safety, efficacy and inconsistent quality [6]. In United State of America, out of about 20,000 herbal preparations only four are considered as effective [7]. Modern pharmaceuticals are prepared following stringent standard operational procedures. However, no such regulated procedures are followed for preparing herbal products. Identification of the plants, their origin and parts, substitution, extraction procedures and the climatic condition of growing the plants are important factors in preparing a quality herbal drug by using a single or multiple plant materials. Therefore, HPs may not be considered scientifically valid unless has been authenticated and categorized in order to ensure reproducibility. The use of herbal products is increasing and will likely continue to do so. Several herbal preparations for the treatment of diabetes are available in Bangladesh and are used without any proper scientific proof. Therefore, herbal medicines are now a very important concern regarding the scientific proof for beneficial clinical effect and quality. The assessment of the efficacy of herbal medicines should be done by following more authentic scientific techniques. Therefore, the present study was undertaken to evaluate the efficacy of some antidiabetic herbal preparations available in Bangladesh. The six ADHPs which were tested are used for the treatment of not only diabetes but other diseases also (*i.e.*ADHP-2 for

generalized weakness, spermatorrhoea, leucorrhoea, ADHP-3 and ADHP-4 for Diabetes Insipidus, ADHP-6 for obesity).

2. MATERIALS AND METHODS

In this study six ADHPs were collected from herbal medicine shops in Dhaka produced by five different local herbal pharmaceuticals companies. To evaluate the anti-hyperglycaemic effects acute and chronic response in glycemic status were determined by feeding test on type 2 diabetic model rats. Chronic effect was evaluated by feeding ADHPs consecutively once in a day for 28 days.

2.1 Development of Diabetic Rat Model

Feeding test (acute and chronic) was carried out on type 2 diabetic model rats (Long-Evans strain) following the ethical guidelines approved by Bangladesh Association for Laboratory Animal Science. Type 2 diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 90 mg/kg body weight to 48 hours old pups as described by Bonner of Weir et al[7]. Experiments were carried out 3 months after STZ injection administration. Model rats were selected for the experiments after confirming with an oral glucose tolerance test. Rats having blood glucose level of 144-216 decimal (mg/dL) at fasting condition were taken as type 2 diabetic model to carry out the experiments.

2.2 Investigation of Acute Effects

Acute effect of herbal preparations on blood glucose level was determined by single feeding in type 2 diabetic model rats. For the evaluation of the antidiabetic activity, the herbal preparations were administered orally to the rats at a dose of 1.25 g/kg body weight. The dose (1.25 g/kg body weight) of ADHPs that has been administered orally to the rats is an arbitrary dose determined from our long experience and trials that we use for screening of antidiabetic plants in our laboratory. For all the *in vivo* studies, the drug glibenclamide (as a positive control) was administered orally at a dose of 5 mg/kg body weight and the control groups received only water. Acute experiments were performed on streptozotocin induced diabetic rat model in the fasting and postprandial states, for simultaneous administration with glucose load (2.5 g/kg body weight) and when fed 30 min before the glucose load. Blood samples were collected from tail tips by cutting at 0, 30 and 75 min for fasting condition; at 0, 30 and 75 min for simultaneous feeding with glucose load and at 0, 60 and 105 min when the herbal drug was fed 30 min before glucose load.

2.3 Investigation of Chronic Effects

Chronic experiments were carried out for the duration of 28 days. Streptozotocin induced diabetic rats were fed with a single feeding everyday with different herbal preparations and blood was collected on days 0 and 14 days by cutting the tail tip and on the 28^{th} day by decapitation. Body weight of the rats were checked in every week. Two doses (200 mg/kg body weight and 400 mg/kg body weight) of herbal preparation were fed orally to type 2 model rats for the chronic test.

2.4 Biochemical Analysis

Serum glucose concentrations were determined by glucose-oxidase method using micro-plate reader (Bio-Tec, USA).

2.5 Statistical Analysis

Data were expressed as mean±standard deviations. One way analysis of variance (ANOVA) and two tailed paired‘t’ test were done to compare variables among and between groups using statistical software Graph Pad Prism version 5.04 for Windows. A p-value of <0.05 was denoted as statistically significant.

3. RESULTS

3.1 Acute Effects

The acute response of different antidiabetic herbal preparation (ADHP) on blood glucose level by feeding simulteneously and before 30 minutes of oral glucose load are presented in Table 1. Compared to control, at 0 minute no significant difference of blood glucose levels were observed for any ADHP. As it was shown in the Table 1, only ADHP-3 showed a significant reduction of blood glucose levels at 30 ($p<0.05$) and 75 ($p<0.01$) minutes. When ADHPs were administered 30 minutes before oral glucose load, no significant difference of blood glucose levels were found for any ADHP except ADHP-3. ADHP-3 was found to be effective in reducing blood glucose levels at 60 ($p<0.01$) and 105 ($p<0.01$) minutes.

Table 1. Acute effect of antidiabetic herbal preparations on blood glucose level of type 2 diabetic rats

Group	Acute response-1			Acute response-2		
	Min 0 (mmol/L)	Min 30 (mmol/L)	Min 75 (mmol/L)	Min 0 (mmol/L)	Min 60 (mmol/L)	Min 105 (mmol/L)
Water control n=14	8.50±1.60 (100%)	15.39±1.70 (187%)	15.91±2.64 (187.17%)	8.55±1.34 (100%)	15.32±2.43 (179.18%)	15.42±2.31 (180.35%)
Glibenclamide n=14	8.86±1.26 (100%)	15.06±2.68 (169.98%)	12.58±3.17* (141.99%)	9.68±1.18 (100%)	12.88±2.81* (133.05%)	10.44±4.39** (107.65%)
ADHP-1 n=07	7.92±1.65 (100%)	15.60±1.30 (196.96%)	15.45±1.29 (195.08%)	7.37±1.41 (100%)	14.13±2.21 (191.20%)	13.38±2.27 (181.06%)
ADHP-2 n=07	8.51±1.36 (100%)	15.04±2.96 (176.73%)	15.20±3.1 0 (178.61%)	8.52±0.85 (100%)	15.08±1.40 (196.99%)	14.15±2.04 (166.07%)
ADHP-3 n=06	8.95±1.45 (100%)	13.92±2.10* (155.53%)	12.16±2.33* (135.68%)	8.20±1.17 (100%)	9.84±3.89** (120%)	9.94±2.99** (121.21%)
ADHP-4 n=06	9.63±0.73 (100%)	16.37±1.51 (169.98%)	16.40±2.0 (170.30%)	9.07±1.64 (100%)	16.91±2.02 (186.44%)	15.98±3.24 (176.18%)
ADHP-5 n=08	8.42±1.21 (100%)	15.22±0.93 (180.76%)	15.88±1.40 (188.60%)	8.82±1.71 (100%)	16.34±1.23 (185.26%)	16.31±1.78 (184.92%)
ADHP-6 n=08	8.43±2.22 (100%)	16.16±2.37 (191.70%)	15.79±2.37 (187.30%)	9.82±1.53 (100%)	16.97±1.19 (172.82%)	16.85±0.93 (171.59%)

*Data are expressed as mean±standard deviation (M±SD). One-way ANOVA (Bonferroni test) was done for comparing between different groups; *p<0.05; **,p<0.01; when compared with water control and ADHP-3 treated groups; n=number of rats*

Acute response-1, effects of ADHP on blood glucose levels of Type 2 diabetic rats when fed simultaneously with glucose load; **Acute response-2,** Acute effects of ADHP on blood glucose levels of Type 2 diabetic rats when fed 30 minutes before to glucose load;

3.2 Chronic Effect

The chronic effect of ADHP-3 was appraised for 28 days with consecutive administration of two different doses (200 and 400 mg/kg/day) and are presented in Fig. 1. The mean plasma glucose concentrations at baseline were 8.01±1.31, 8.68±1.39, 8.47±0.85 and 7.97±1.11 mmol/L in diabetic rats treated with water control, glibenclamide, ADHP-3 (200 mg/Kg/day) and ADHP-3 (400 mg/kg/day), respectively. No significant difference was found on blood glucose levels among different groups at baseline. The positive control (glibenclamide) revealed significant reduction of blood glucose levels compared to baseline levels ($p<0.019$) at 28 days. ADHP-3 at a dose of 200 mg/kg/day insignificantly reduced blood glucose levels compared to baseline ($p=0.342$) at 28 days. On the other hand ADHP-3 at a dose of 400 mg/kg/day significantly reduced blood glucose levels compared to baseline ($p<0.05$) and blood glucose levels in control ($p<0.001$) at 28 days.

4. DISCUSSION

Herbal preparations are frequently used for the management of diabetes mellitus world wide as well as in Bangladesh [8]. Locally produced ADHPs are claimed to be effective antihyperglycemic agents. However, scientific assessment regarding their efficacy is rare. This study was designed to investigate the efficacy of some locally produced ADHPs.

In this study, among six ADHPs only one (ADHP-3) was an effective antihyperglycemic herbal preparation as found by evaluating acute effects by feeding ADHPs simultaneously with glucose load and by administering ADHPs 30 minutes before to glucose load. As this preparation showed significant improvement of glycemic status compared to others, ADHP-3 at two different doses (200 mg/kg, 400 mg/kg) were further subjected to assess for the chronic effect on blood glucose in type 2 diabetic rat model. Though ADHP-3 at a dose of 200 mg/day reduced blood glucose levels but it was not significant ($p=0.342$). ADHP-3 at a dose of 400 mg/kg/day significantly ($p=0.040$) reduced blood

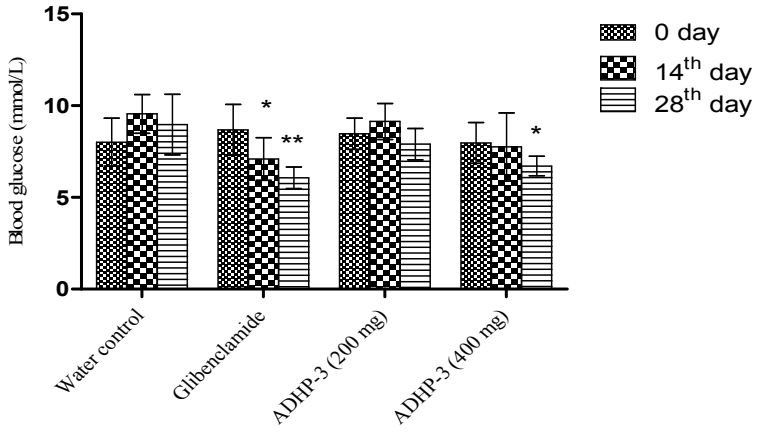

Fig. 1. Chronic effect of ADHP-3 with different doses on plasma glucose levels in type 2 diabetic rat model. (*, p<0.05; **, p<0.01)

glucose levels. Since ADHP-3 contains the herb *Gymnema sylvestre* in its composition which has been claimed to enhance endogenous insulin secretion. This enhancement of endogenous insulin secretion from the leaves of *Gymnema sylvestre* is probably due to the regeneration/revitalization of the residual β cells in Type 1 animals [9] and on human subjects [10]. Gymnemic acid, a compound derived from *Gymnema sylvestre* leaves showed antihyperglycemic effect in mice by insulin releasing action [11]. Also a pure compound, condritol, isolated from *Gymnema sylvestre* showed significant hypoglycemic effect on Type 1 diabetic rats [12]. Therefore, the obtained hypoglycaemic activity in ADHP-3 is probably due to the presence of the leaves of Gymnema *sylvestre* in it as an active ingredient.

5. CONCLUSION

The results of this study indicate that the preparation of herbal medicine particularly that claimed to be effective as antidiabetic agents may not be prepared by following validated or regulated procedures. Therefore, identity of the plant, their parts, origin, substitution, extraction procedure and the climatic condition of growing the plants are important variables and these factors need to be considered scientifically in preparing a quality herbal drug by using single or multiple plant materials.

CONSENT

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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