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Preliminary clinical assessment and non- toxicity evaluation of an ayurvedic formulation BGR-34 in NIDDM

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ABSTRACT

In view of the overall health impact of NIDDM, inventers understand the necessity of improving glycemic control in adults with type 2 diabetes. BGR-34 provides an effective treatment option for adults with type 2 diabetes who have been inadequately controlled on lifestyle with or without other oral hypoglycemic agents (OHGAs) such as metformin, sulfonylurea, or a glitazones. BGR-34 is an appropriate option to consider for addition to a managed care drug formulary. Treatment with BGR-34 produced clinically relevant and statistically significant reductions in all three key measures of glucose control studied —FPG, PPBG and HbA1c— when compared with placebo. BGR-34, showed the promising result with respect to glycemic parameters in NIDDM patient with a significant reduction in fasting blood sugar by 34.3%, postprandial blood sugar 35.5% & glycosylated haemoglobin by 20.31% as compared to placebo group showing a reduction by 13.2%, 10.9% & 10.87% respectively. The trial has also been registered to CTRI, India. This study has been registered in the clinical trial registry-India.

1. Introduction

Diabetes is nowadays considered as a global epidemic with 415 million patients recorded in 2015, and around 642 million patient expected by 2040.[1,2] Diabetes is categorized into two main types insulin-dependent (IDDM) and non-insulin dependent (NIDDM). The most widely drug used for treatment of NIDDM, are metformin, glimepiride, repaglinide, pioglitazone, sitagliptin, and acarbose.[3] The use of these oral hypoglycaemic drugs may be effective in controlling blood glucose level, but may not prevent all the complications of diabetes.[4] Keeping in view the possibility of above side effect, World Health Organization Expert Committee on diabetes has encouraged that traditional medicinal herbs should be investigated on large scale for discovering safe and effective oral anti-diabetic agents. Therefore, there is a clear need for exploring alternate source of anti-diabetic drugs. The present study was directed to polyherbal anti-diabetic drug BGR-34, developed by Council of Scientific & Industrial Research, India (CSIR). It is the combination of *Berberis aristata*, *Tinospora cordifolia*, *Pterocarpus marsupium*, *Gymnema sylvestre*, *Rubia cordifoila* & *Trigonella foe-numgraecum* already known for controlling diabetes mellitus.[5–10] Aimil Pharmaceuticals (India) Ltd is licensee for manufacturing and marketing of BGR-34 worldwide. The Pre-clinical studies of BGR-34, produced promising outcomes on diabetes induced experimental rats without producing adverse effect on liver, heart and kidney (unpublished data CSIR).

The aim of the present study is, to evaluate the safety & clinical efficacy of BGR-34 with following objectives:

i. To setup the safe limits of BGR-34 dosage through acute and sub-acute toxicity in rats.

Abbreviations: NIDDM, noninsulin-dependent diabetes mellitus; CSIR, council of scientific & industrial research, india; CTRI, clinical trial registry-India; OHGAs, other oral hypoglycemic agents; FPG, fasting plasma glucose; PPBG, post-prandial blood glucose; HbA1c, glycosylated haemoglobin; OECD, organization for economic co-operation and development; CPCSEA, committee for the purpose of conduct and supervisions of experiments on rats; TLC, TOTAL leukocyte count; DLC, differential leukocyte count; Hb, haemoglobin; SGPT, serum glutamate pyruvate transaminase; SGOT, serum glutamate oxaloacetate transaminase; ALP, alkaline phosphatase; BBN, total bilirubin; HDL, high-density lipoproteins; OPD, out Patient Department.

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ii. To estimate the anti-diabetic efficacy of BGR-34 in Indian NIDDM patients on blood glucose regulation.

2. Materials and methods

2.1. Plant material collection

The medicinal plants (Table 1) were procured, from the local herbal market and authenticated in-house by Dr. H.B Singh, former chief scientist, Raw Materials Herbarium and Museum, NISCAIR, New Delhi. Authenticated voucher samples of raw material were preserved in research and development section of Aimil Pharmaceuticals (I) Ltd.

2.2. Preparation of BGR-34

BGR-34 was prepared at Aimil Pharmaceuticals (I) Ltd as per methodology mentioned in know how document received from CSIR- NBRI-CIMAP, India.

2.3. Toxicity studies

An acute and sub-acute oral toxicity studies were conducted in accordance with the Organization for Economic Co-operation and Development[11–13] Guideline 425 and 407 respectively. The experimental protocol has been approved by the Institutional Animal Ethics Committee of Shree Dhanvantry Pharmaceutical Analysis and Research Centre Pvt. Ltd. with the Experimental Protocol Approval Number SDPARC/IAEC/2015/046 and SDPARC/IAEC/2015/051 respectively prior to the initiation of the study. Experiments were performed as per the instructions prescribed by the Committee for the Purpose of Conduct and Supervisions of Experiments on Rats (CPCSEA), Ministry of Environment and Forest, Government of India.

2.4. Experimental rats

Female albino Wistar (Mahaveer Enterprises, Hyderabad) weighing 180–200 g ± 20 were maintained under standard laboratory conditions of temperature (22 ± 3 °C) and humidity 30–70% with 12 h day: 12 h night cycle. Rats had free access to water and rodent pellet diet (Hindustan Lever Ltd, Bangalore, India).

2.5. Acute oral toxicity study

Acute oral toxicity study of BGR-34 was carried out in 15 adult female Wistar as per the[11,12] test guidelines 425. All rats were dosed orally once in a stepwise manner i.e next higher dose level was administered to next animal after observation of the previous animal for any mortality for 48 h. Dose levels were progressed in geometric progression with the factor of 2. Dosing was started by oral administration of 250 mg/kg bw of BGR-34 to Ist test animal. As no mortality was observed in Ist animal when observed for 48 h, next animal was treated with 500 mg/kg bw dose and observed in a similar manner and so on up to 2000 mg/kg bw. A total of 5 rats were tested, at test dose 2000 mg/kg bw and observed for any clinical sign of toxicity for a total of 14 days. Dosage progression has been depicted in Table 2.

Table 1
Composition: each tablet contains following ingredients.

Drug name	Botanical name	Part used
Daruharidar	*Berberis aristata*	Stem
Vijaysar	*Pterocarpus marsupium*	Heart wood
Gudmar	*Gymnema sylvestre*	Leaf
Manjeeth	*Rubia cordifolia*	Root
Methika	*Trigonella foenum graceum*	Seed
Giloy	*Tinospora* cordifolia	Stem

2.6. Sub-acute oral toxicity

For sub-acute toxicity study, a total of 50 Wistar (25 males and 25 females) were used. They were subdivided into 5 groups of 10 rats each (5 males and 5 females), according to[13] guideline 407. The first group (G1), was the control group which received distilled water while the next three test groups (G2, G3, G4), were served BGR-34 orally at the doses of 1500; 750 and 375 mg/kg bw/day respectively the equivalent high, normal and low dosage for. The duration of treatment and observation for these first four groups was 28 days. The last group, called satellite group/reversible group (G5) was treated in similar manner with high dose level (1500 mg/kg bw/day) for 28 days and further observed without medicine for next 14 days post-treatment for the reversibility, persistence, or delayed occurrence of toxic effects of BGR-34 and were sacrificed on 43 day. During this period, all the rats were observed daily for signs of toxicity and mortality. The changes in body weight, food and water intake and clinical signs were also observed and recorded.

2.7. Blood analysis

On the end of dosing and observation period, blood was collected from retro orbital sinus from all rats for hematological study viz haematocrit (%), haemoglobin (gm %), Total leukocyte count (TLC) and Differential leukocyte count (DLC) were estimated by following method of Docie.[14]

2.8. Clinical biochemistry

To investigate major toxic effects in tissues and, specifically, effects on kidney and liver, blood samples obtained from all rats just prior to killing the rats for biochemical examinations were performed at the end of the test period: the analysis of blood glucose,[15] serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT)[16,17]; alkaline phosphatase (ALP), total bilirubin (BBN),[18] Urea[19]; total protein; albumin[20] and creatinine[21]; Cholesterol, HDL Cholesterol[22] and Triglyceride[23] were estimated in serum.

2.9. Histopathological studies

After collecting a blood sample, the vital organs (brain, heart, lung, kidney, and liver) were excised and their wet weight was taken as soon as possible after dissection to avoid drying. These

Table 2
Dosage progression for LD $_{50}$ determination of BGR-34 in single dose oral toxicity study.

Day	Animal no.	Dose (mg/kg bw)	Outcome
1	1	250	No death
3	2	500	No death
5	3	1000	No death
7	4	2000[a]	No death
9	5	2000[a]	No death
11	6	2000[a]	No death
13	7	2000[a]	No death
15	8	2000[a]	No death

[a] 2000 mg/kg bw is the limit test dose.

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