CSIR SCIENTISTS AWARDED BY TECHNOLOGY AWARD-2016

for Innovative Ayurvedic Drug for Diabetes

BGR-34™ Tablets

Appreciated by the Hon'ble Prime Minister of India

JOINTLY DEVELOPED BY THE SCIENTISTS OF

CSIR- NBRI
NATIONAL BOTANICAL RESEARCH INSTITUTE (LUCKNOW)

&

CSIR- CIMAP
CENTRAL INSTITUTE OF MEDICINAL & AROMATIC PLANTS, (LUCKNOW)

*Disclaimer : Based on Propotionate consumption from sales data.

Over 20 LAKH* Patients Benefitted

AIOCD Survey Apr.2017

First Time in India an Ayurvedic brand -BGR-34 features in top 20 list of Best Launches in last 2 years amongst more than 6000 allopathic brands.

All Indian Origin Chemists & Distributors Ltd. (AIOCD Ltd)

BGR-34™ Tablets

RANKED No. 1† IN INDIA

in Ayurvedic/Herbal Anti-diabetic market

by imshealth

Data Source – TSA July 2016

RESEARCH TECHNOLOGY TRANSFERRED TO **AIMIL**

A scientifically validated herbal formulation

BGR-34™

jointly developed by the Scientists of
CSIR-National Botanical Research Institute, Lucknow &
CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow

for the management of diabetes.

The product was launched by the Honourable Vice President of India, Mr. M. Hamid Ansari on 22 Feb. 2014 at Vigyan Bhawan, New Delhi and the research technology has been transferred to Aimil Pharmaceuticals (India) Ltd. for the benefit of diabetic sufferers.

Launching Ceremony at Vigyan Bhawan, New Delhi.
Hon'ble vice president of India Mr. M. Hamid Ansari with Dr. C. S. Nautiyal, Director, CSIR-NBRI.

सीएसआईआर–राष्ट्रीय वनस्पति अनुसंधान संस्थान
CSIR-National Botanical Research Institute
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद, नई दिल्ली)
राणा प्रताप मार्ग, लखनऊ – 226 001, उ.प्र., भारत
(Council of Scientific & Industrial Research, New Delhi)
Rana Pratap Marg, Lucknow- 226 001, U. P., India

डॉ. चन्द्र शेखर नौटियाल
टाटा इनोवेशन फैलो, एफएनए, एफएनएएससी, एफएनएएएस
निदेशक
Dr. Chandra Shekhar Nautiyal
TATA Innovation Fellow, FNA, FNASc, FNAAS
Director

FOREWORD

There has been a quest to develop a promising, safe, non-toxic drug regimen to help effectively maintain normal blood glucose levels and reduce the chances of long term complications due to persistent high blood glucose level. It has been highly commendable on the part of scientists at CSIR-NBRI and CSIR-CIMAP to have in depth research studies to evolve scientifically the most desirable formulation that has been validated experimentally to address the disorder with a difference and that too in completely patient friendly manner. Not only that, the product also imparts the much needed good quality life in the patients.

The knowhow for the product has been transferred to Aimil Pharmaceuticals, an organization well known for its innovative quality products for various therapeutic groups in herbal/ayurvedic sector with a strong marketing network spread throughout the country. We wish Aimil Pharmaceuticals all the success in their noble endeavor of serving the mankind by making the benefits of the marvelous research available to the fast increasing number of the patients all throughout the country.

Date : 05.11.2014

Warm regards

(C.S. Nautiyal)

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e-mail : director@nbri.res.in, csnnbri@yahoo.com, Website : http://www.nbri.res.in

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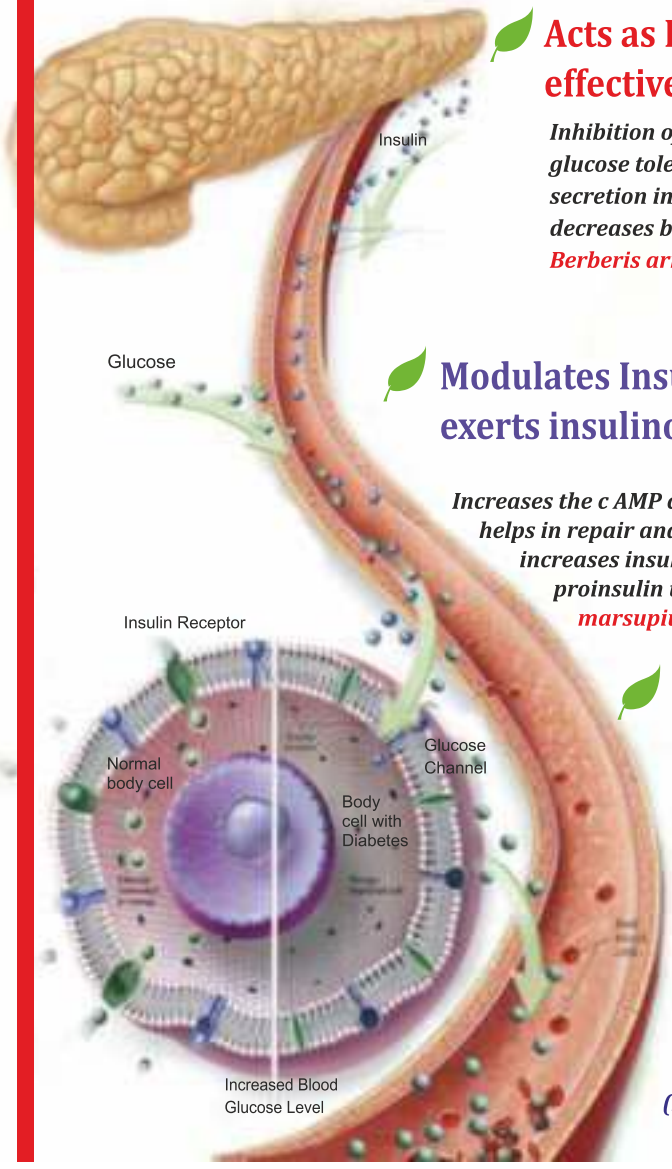
BLOOD GLUCOSE REGULATOR

to manage the lives of suffering Diabetics



Acts as DPP-4 inhibitor to effectively manage Diabetes

Inhibition of DPP-4 provides improved glucose tolerance, increases insulin secretion in response to oral glucose and decreases blood glucose level effectively. - Berberis aristata (Daruharidra)

Modulates Insulin release, exerts insulinogenic effect

Increases the c AMP content of the β-islets, which helps in repair and revival of β-cells of pancreas, increases insulin release & converts proinsulin to insulin. - Pterocarpus marsupium (Vijaysaar)

Manages glucose absorption & uptake

Supplements bioactive constituents like galactomannan, reduces post prandial glucose level because of its property to delay intestinal absorption of glucose and benefits in blood glucose management - Trigonella foenum-graecum (Methi)

Strengthens ß-cell functional Capacity

Protects ß-cells from damage, promotes repairative regeneration of cells, thus increases insulin production by improving the functional capacity of ß-cells- Gymnema sylvestre (Gudmar)

Exerts Cardioprotective Action

Boosts body defence system & anti-oxidant mechanism to protect the cardiovascular system by supplementing essential phyto-constituents - Tinospora cordifolia (Giloe)

Nourishes & Strengthens vital organs

Regulates blood glucose through mitigating oxidative stress, promoting insulin secretion. It helps to restore anti-oxidant enzymes like SOD, catalase, glutathione peroxidase etc. to nourish & protect the vital organs - Rubia cordifolia (Majeeth).

What is special about BGR-34?

BGR-34 is a novel, natural DPP-4 inhibitor and unlike other DPP-4 inhibitors in market, BGR-34 exerts pronounced cardioprotective action. It also exerts powerful anti-oxidant action, helps prevent development of trio-pathic complications. An optimized concentration of synergistically acting extracts makes BGR-34 highly efficacious in management of Diabetes.

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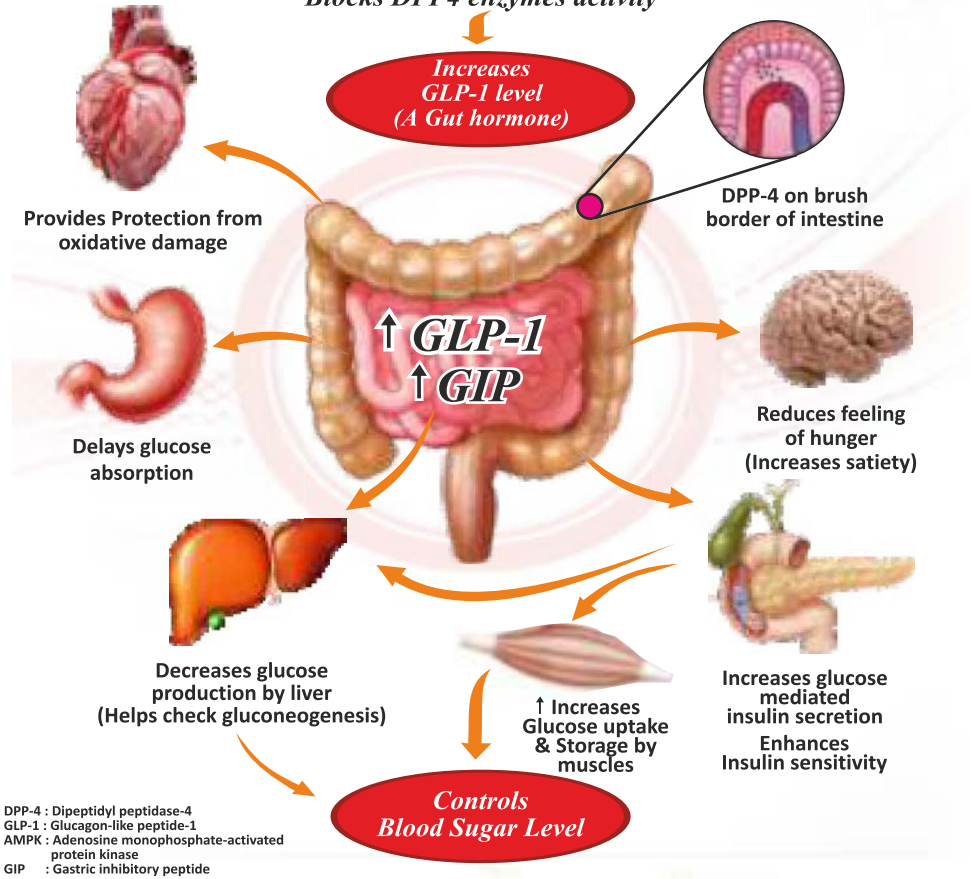
Helps in Effective management of diabetes by inhibiting DPP-4 (GLP-1 & GIP)

Berberine *(Berberis aristata)*

Acts as DPP-4 inhibitor

Blocks DPP4 enzymes activity

Increases GLP-1 level (A Gut hormone)



Controls Blood Sugar Level

DPP-4 : Dipeptidyl peptidase-4
GLP-1 : Glucagon-like peptide-1
AMPK : Adenosine monophosphate-activated protein kinase
GIP : Gastric inhibitory peptide

Improves Insulin action by activating AMPK

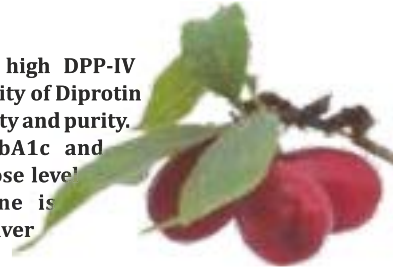
Berberine from ***Berberis aristata*** **(Daruharidra)** has been shown to have a significant beneficial effect on diabetes mellitus type-2, and may be as effective as metformin (500 mg /day). Berberine acts through several mechanisms, including insulin mimicking action, improving insulin action by activating AMPK, reducing insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression inducing glycolysis, and on incretins by promoting GLP-1 secretion and modulating its release, by inhibiting DPP-4.

(Natural Medicine Journal 2(10), 5-6, 2010)

Increases insulin secretion and improves oral glucose tolerance

Berberine from ***Berberis aristata*** **(Daruharidra)** has been shown to antagonize the hyperglycaemic action of glucose and the gluconeogenic action of alanine in experimental subjects and on hepatocyte cell lines. It seems to decrease insulin resistance by raising insulin sensitivity. The DPP IV inhibitory activity could explain the anti-diabetic activity of berberine including the decrease of fasting blood glucose level, the increase in insulin secretion and the improvement in oral glucose tolerance tests (OGTT) was observed in experimental subjects. (Journal of Enzyme Inhibition and Medicinal Chemistry, 24(5): 1061-1066, 2009)

In a study *Berberis aristata* (Daruharidra) extract showed high DPP-IV inhibitory potential. The reason to observe high inhibitory activity of Diprotin A, the standard DPP-4 inhibitor, was due to its tripeptide specificity and purity. Berberine significantly reduced fasting blood glucose, HbA1c and triglycerides in type 2 diabetic patients. It lowered blood glucose level through increasing insulin receptor expression. Berberine is preferred over metformin for hyperglycaemic patients with liver diseases.



(J Natural Products, 4; 158-163, 2011)

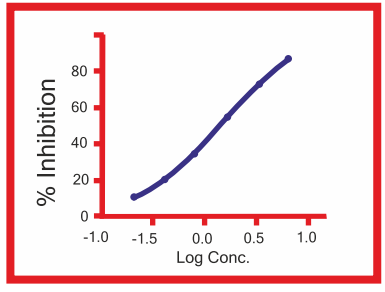


Figure-1: DPP-4 inhibitory activity of Diprotin A, the standard DPP-4 inhibitor

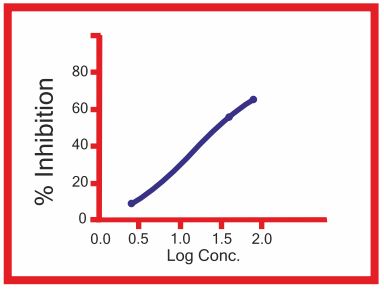


Figure-2: DPP-4 inhibitory activity of *Berberis aristata* ext.

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Repairs & Revives ß-cells, Enhances Insulin Release

A study conducted with **Pterostilbene**, a constituent derived from *Pterocarpus marsupium* **(Vijaysar)** showed hypoglycemic activity in experimental subjects because of presence of tannates in the extract. **Marsupin, pterosupin and liquiritigenin** obtained from vijaysar showed antihyperlipidemic activity. (–)Epicatechin, its active principle, has been found to be insulinogenic, **enhancing insulin release by converting proinsulin to insulin**. Like insulin, (–) epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of experimental subjects diaphragm in a dose-dependent manner.

(J. Clin. Biochem. Nutr., 40, 163–173, 2007)

Flavonoid fraction from Pterocarpus marsupium (Vijaysar) exerts pancreatic β cell regranulation

Converts Pro-insulin to insulin

(-) Epicatechin, an active principle in the extract of ***Pterocarpus marsupium*** **(Vijaysaar)** increases the cAMP content of the β-islets which is associated with the increased insulin release, **conversion of proinsulin to insulin and cathepsin B activity**. The response of the β-islets to the (-)epicatechin stimulation is more pronounced in immature (one month old) than in mature (12 month old) experimental subjects.

(Indian J.Exp. biol. 29(6): 516-520, 1991)

A multicentric trial was carried out to compare the blood glucose lowering effect of ***Pterocarpus marsupium*** **(Vijaysaar)** with pharmacological agent of sulphonyl urea group (Tolbutamide). A total of 365 newly diagnosed or untreated patients with type 2 diabetes mellitus whose fasting blood glucose was< 12.8 mmol/ l were randomized to receive either the trial drug or the standard pharmacological agent for duration of 36 weeks with 4 weekly clinic attendance for review and collection of drug. There were 172 patients in vijaysar treated group and 177 patients in the tolbutamide group. 86% in ***Pterocarpus marsupium*** **(Vijaysaar)** and 94% in tolbutamide group maintained glycaemic control.Thus, it is concluded that vijaysar is effective in blood glucose lowering effect with its hypoglycaemic effect being comparable to that of tolbutamide in treatment of patients with type 2 diabetes and it is free from any significant side effects.

(Diabetologica Croatica, 34-1, 2005)

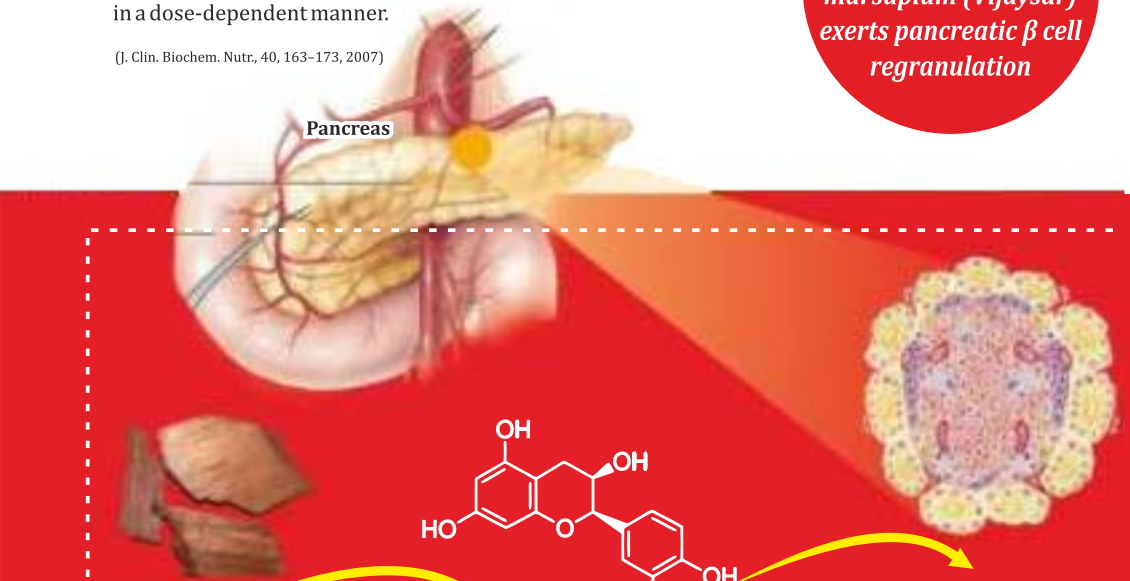
HbA1c (%)

Drug Group	Baseline	At 36 weeks	Mean fall (95%C.I)
Vijaysar (n=45)	10.5	8.9	1.6*
Tolbutamide (n=45)	10.5	8.7	1.8*

* P<0.001 C.I : Cofidence interval

Blood Glucose (mmol/l)

Parameter	Drug group	At Baseline	At 36 weeks	Mean fall (95%C.I)
Fasting	Vijaysar (n=172)	9.4	7.0	2.4
	Tolbutamide (n=177)	9.4	6.7	2.7
Postprandial	Vijaysar (n=172)	13.9	9.6	4.3
	Tolbutamide (n=177)	13.8	9.4	4.4



Vijaysar
(Pterocarpus marsupium)

A rich source of (-)epicatechin

Repairs & Revives ß-cells of islets of Pancreas

Increases glucose mediated insulin secretion

Increases glucose utilisation in tissues

Helps Control Diabetes Mellitus

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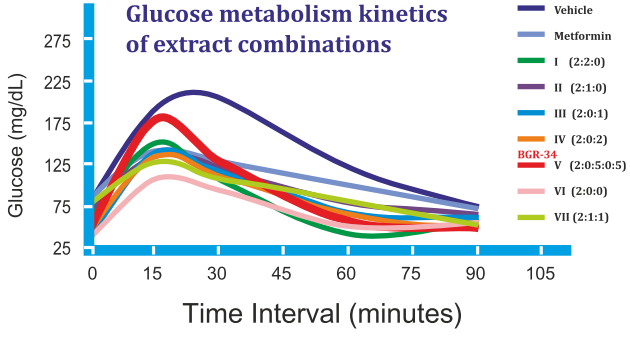
BGR-34 formulation Optimization for best Anti-hyperglycaemic activity

Primary screening of anti-diabetic potential of the herbal combinations in different proportions was undertaken by conducting Oral Glucose Tolerance Test (OGTT) as per the selected parameters. The treatment groups were dosed orally at 2000mg/kg body weight, 30 min. before giving glucose solution. Group 1 of experimental subjects was treated as normal control, and given only glucose solution orally. Group 2 referred as positive control, was treated with Metformin at 250 mg/kg body weight. Group 3-9 were given different combinations of herbs. The blood glucose level at intervals of 15, 30, 60 and 90 min were recorded after giving glucose solution successively. Based on the glucose metabolism kinetics of extract combinations, BGR-34 was found to have most optimum composition with best of anti-hyperglycaemic activity.

BGR-34 maintained the glucose levels significantly when compared to control.

"BGR-34, DELAYS IN ABSORPTION OF GLUCOSE FROM GIT, INHIBITS ADVANCED GLYCATION END PRODUCTS (AGEs) ACCUMULATION, ENHANCES INSULIN RELEASE & INCREASES CONVERSION OF PRO INSULIN TO INSULIN."



Groups	Blood Glucose levels (Time Interval in minutes)				
	0	15	30	60	90
Group-1 Vehicle	89±9.03	202±20.85	215.7±14.65	131±9.97	85.5±3.41
Group-2 Metformin	92.4±4.92	151.3±10.41	138.8±5.90**	109.1±5.88	80.6±4.67
Group-3 I (2:2:0)	70.2±8.03	161.6±29.53	117±24.74***	52.6±9.34***	65.1±4.07
Group-4 II (2:1:0)	80.8±5.32	145.2±36.35	128.6±7.88***	89.4±7.10***	75.3±3.70
Group-5 III (2:0:1)	47.5±3.03	147.4±13.89	126.6±10.21***	76.6±10.46***	71.6±4.80
Group-6 IV (2:0:2)	56.8±6.10	148.8±17.94	123.6±15.15***	77±3.18***	59.75±1.65
Group-7 V (2:0.5:0.5) NBRMAP-DB (BGR-34)	56.5±2.67	183.6±16.70	135.6±4.82***	66±5.68***	58.6±1.40
Group-8 VI (2:0:0)	46.3±6.59	115.75±10.59	104.25±12.65***	60.5±3.48***	63.25±3.09
Group-9 VII (2:1:1)	86.4±5.18	138.2±6.91	117.7±5.91***	90.3±6.20**	62±5.41

**p<0.01, ***p<0.001 Vehicle vs treatment- Metformin at 250mg/kg bd.wt. of combination treatments at 500mg/kg body wt. administered 30 min prior to d-Glucose at 2000mg/kg

CLINICAL STUDY OF BGR-34

Establishing its efficacy and safety in patients with TYPE-II Diabetes

A randomised, double blind, placebo controlled clinical study was conducted in patients with mild to moderately severe type 2 diabetes mellitus at Aggarwal Hospital, New Delhi (India) with BGR-34/placebo taken as adjuvant along with the prescribed anti-diabetic drugs if any. The duration of study was 4 months.

Inclusion Criteria:

- Age: 25 to 60 years
- Patients with type 2 Diabetes mellitus
- Fasting blood glucose >126 mg/dL
- Absence of any other significant disease or clinically significant medical history on physical examination during screening in the view of the investigator.
- Subjects willing to provide written informed consent to participate in the study.

Exclusion Criteria:

- Patients on Insulin
- Patients with acute infections or chronic debilitating diseases, tuberculosis, malignancy, HIV infection etc.
- Any life threatening serious disorder of the liver, kidneys, heart, lungs or other organs
- Pregnancy and lactation
- Patients diagnosed with severe end organ damage
- Unwillingness to give written informed consent for participation in the study.

Demographic profile of patients according to treatment group

Variables	Drug Group (n=28) (mean ± sd)	Placebo (n=28) (mean ± sd)	p value ǂ
Age (years)	47.9 ± 6.7	49.7 ± 5.9	0.318
Weight (kg)	67.04 ± 8.6	70.1 ± 6.9	0.1444
Males (%)	16 (57.1)	14 (50.0)	0.592#
Females (%)	12 (42.9)	14 (50.0)	

ǂ Student's t-test, # Chi square test

56 patients (30 male and 26 females) with type 2 diabetes mellitus completed the study. There were 28 patients in the BGR-34 group (drug arm) and 28 patients in the placebo group (placebo arm). The mean age of patients for BGR-34 and placebo group were 47.9±6.7 years and 49.7±5.9 years respectively. Average body weight in BGR-34 group was 67.04±8.6 kg and in placebo group it was 70.1±6.9 kg.

The difference in age, body weight, number of patients in the drug and placebo groups was not found to be significant.

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Study shows Encouraging Effect on Fasting and PP Blood Glucose

EFFECT ON FASTING BLOOD GLUCOSE

Effect of BGR-34 and Placebo on Fasting Blood Glucose (FBG) mg/dL at baseline and after completion of study

Variables FBG (mg/dL)	Drug Group (n=28) (mean ± sd)	Placebo (n=28) (mean ± sd)	Difference (95% CI)	p value ǂ
Baseline	196.0 ± 32.7	187.2 ± 43.3	8.8 (-11.7 to 29.3)	0.3939
Post intervention	129.3 ± 33.3	162.9 ± 41.59	-33.5 (-53.7 to -13.3)	0.0016
Change (reduction)	66.7 ± 23.2	24.4 ± 14.3	42.3 (31.9 to 52.6)	<0.001
% Change (% reduction)	34.3 ± 10.7	13.2 ± 7.7	21.2 (6.1 to 26.2)	<0.001

ǂ - Student's t test ; FBG- fasting blood glucose

Biochemical results of all patients were analyzed before and after completion of the study. Blood sugar fasting showed significant reduction (p=0.0016) from 196.0 ± 32.7 mg/dL to 129.3 ± 33.3 mg/dL in BGR-34 treated group as compared to placebo group where fasting blood sugar reduced from 187.2 ± 43.3 mg/dL to 162.9 ± 41.6 mg/dL. The percent reduction in the BGR-34 treated group was highly significant (p<0.001) as compared to the placebo group.

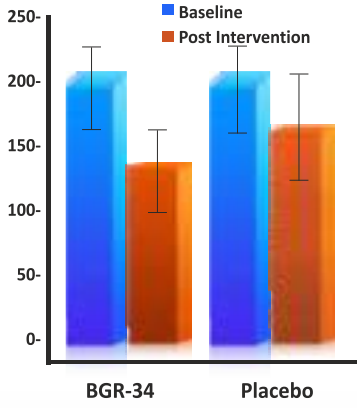


Fig 1: Comparison between means (± sd) of Fasting Blood Glucose (FBG) mg/dL values in drug and placebo arms before and after the treatment

EFFECT ON P.P. BLOOD GLUCOSE

Effect of BGR-34 and Placebo on Post Prandial Blood Glucose (PPBG) mg/dL at baseline and after completion of the study

Variables PPBG (mg/dL)	Drug Group (n=28) (mean ± sd)	Placebo (n=28) (mean ± sd)	Difference (95% CI)	p value ǂ
Baseline	276.8 ± 59.7	294.9±56.3	-18.1 (-49.2 to 12.9)	0.2482
Post intervention	191.9 ± 49.3	262.6 ± 52.9	-70.7 (-98.1 to -43.3)	<0.001
Change (reduction)	84.8 ± 36.3	32.2 ± 18.4	52.6 (37.2 to 68.0)	<0.001
% Change (% reduction)	30.5 ± 10.6	10.9 ± 5.9	19.6 (14.9 to 24.2)	<0.001

ǂ -Student's t test ; PPBG- Post Prandial Blood Glucose

Post prandial blood glucose (PPBG) showed significant reduction (p<0.001) from 276.8 ±59.7 to 191.9 ± 49.3 in BGR-34 treated group as compared to placebo group where PPBS reduced from 294.9±56.3 to 262.6±52.9 mg/dL. Percentage reduction in BGR-34 treated group was highly significant with (p<0.001) as compared to the palcebo group.

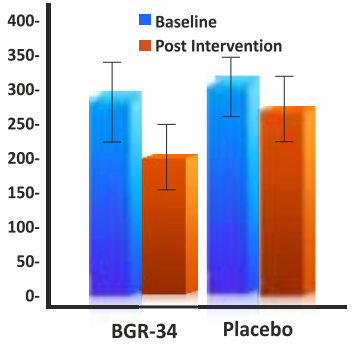


Fig 2: Comparison between means (± sd) of Post Prandial Blood Glucose (PPBG) mg/dL values in drug and placebo arms before and after the treatment

Study shows significant reduction in Glycosylated Haemoglobin (HbA1c)

EFFECT ON HbA1c

Variables HbA1c	Drug Group (n=28) (mean ± sd)	Placebo (n=28) (mean ± sd)	Difference (95% CI)	p value ǂ
Baseline	9.56 ± 1.15	9.91 ± 1.05	-0.35 (-0.94 to 0.25)	0.2469
Post intervention	7.58 ± 0.99	8.86 ± 1.30	-1.28 (-1.90 to -0.66)	0.001
Change (reduction)	1.98 ± 1.02	1.05 ± 0.52	0.93 (0.49 to 1.36)	0.001
% Change (% reduction)	20.31 ± 9.3	10.87 ± 5.94	9.45 (5.26 to 13.63)	<0.001

ǂ - Student's t test ; HbA1c- Glycosylated Haemoglobin

Glycosylated haemoglobin decreased from 9.56 ± 1.15 to 7.58 ± 0.99 which was found to be a highly significant decline in the BGR-34 group (p=0.001). On the other hand in the placebo group there was relatively a lesser reduction in the glycosylated level from 9.91±1.05 to 8.86±1.30 during the 16 week study period.

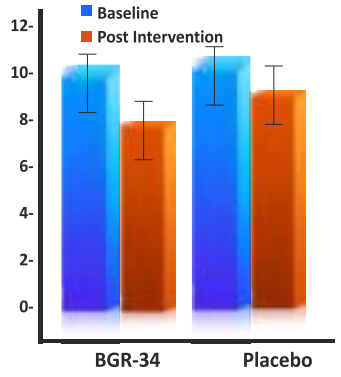
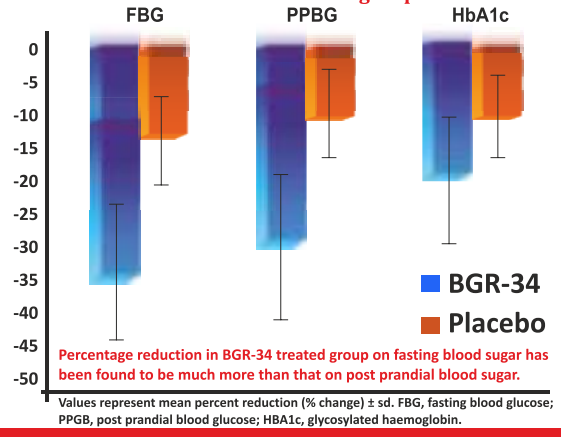


Fig 3:Comparison between means (± sd) of Glycosylated Haemoglobin (HbA1c) values in drug and placebo arms before and after the treatment

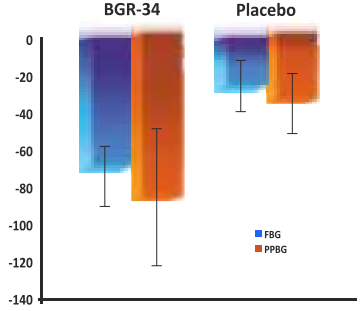
Percent change (reduction) in blood glucose levels between the two groups



Percentage reduction in BGR-34 treated group on fasting blood sugar has been found to be much more than that on post prandial blood sugar.

Values represent mean percent reduction (% change) ± sd. FBG, fasting blood glucose; PPGB, post prandial blood glucose; HBA1c, glycosylated haemoglobin.

Change (reduction) in blood glucose levels between the two groups



Values represent mean reduction (change) ± sd. FBG, fasting blood glucose, PPGB, post prandial blood glucose

Conclusion

BGR-34 showed very promising results with respect to glycemic parameters in patients with type 2 diabetes mellitus. There was a significant improvement in the feeling of wellbeing due to better control of hyperglycemia. The various mechanism through which the drug showed these results may be attributed to i) delays in absorption of glucose from GIT, ii) inhibition of Advanced glycation end products (AGEs) accumulation and iii) enhancing insulin release and conversion of pro-insulin to insulin. It is further suggested that BGR-34 should be further extensively used as a mono therapy/adjunctive therapy for the regulation/ management / control of blood glucose level.

BGR-34 showed very promising results with respect to glycemic parameters in patients with type 2 Diabetes mellitus

BGR-34™

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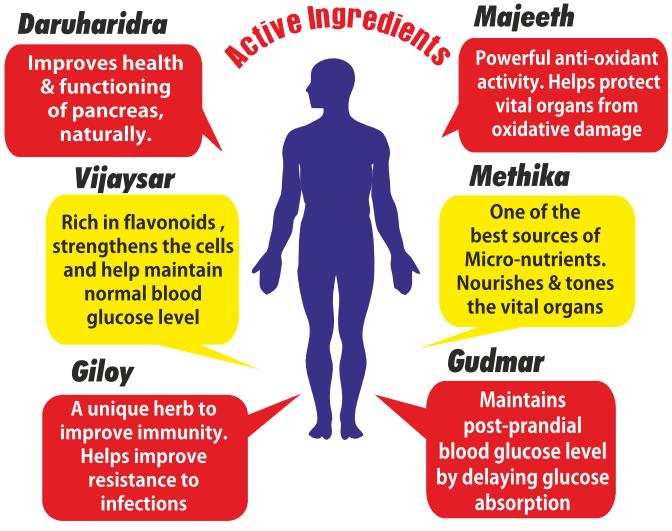
C.S.I.R.

- ✓ Scientifically Proven
- ✓ Clinically Tested
- ✓ Toxicologically Tested

EXCLUSIVE BENEFITS OF BGR-34

- Potential DPP-4 inhibitor with cardioprotective action
- Scientifically proven, optimized formulation
- Enriched with 34 vital Phytoconstituents, derivatives
- Regulates glucose homeostasis
- Converts proinsulin to insulin
- Reduces level of glycosylated Hb
- Exerts Anti-oxidant Action

Active Ingredients



Indications :

- Type II Diabetes Mellitus
- Impaired Glucose Tolerence
- As adjunct to OHG's & Insulin

Dosage : Tablets : 2 tablets twice a day, half an hour before meals or as directed by Physician.