

Evaluation of antidiabetic, hypolipidemic and antioxidant activity of hydroalcoholic extract of leaves and fruit peel of *Punica granatum* in male Wistar albino rats

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Abstract

Background: We investigated anti-diabetic, hypolipidemic and antioxidant activity of hydroalcoholic extract from leaves and fruit peel of *Punica granatum*. **Materials and Methods:** Streptozotocin induced diabetic Wistar rats were used in this study consisting of seven groups of six animals each. Groups (1) normal control, (2) diabetic control, (3) leaves extract 100 mg/kg b.w. of *P. granatum*, (4) leaves extract 200 mg/kg b.w. of *P. granatum*, (5) fruit peel extract 100 mg/kg b.w. of *P. granatum*, (6) peel extract 200 mg/kg b.w. of *P. granatum* and (7) glibenclamide respectively. Fasting blood sugar was recorded on 1st, 7th, 14th, 21st and 28th day. At the end of the experiment Lipid profile and levels of antioxidants were determined. Safety profile of both extracts was evaluated using acute and chronic toxicity studies. **Results:** Higher dose of fruit peel extract of *P. granatum* (PEPG) and glibenclamide significantly lowered blood glucose level from 7th day onwards however glibenclamide was found to be more effective. Leaves extract at higher dose and fruit extract at lower dose also significantly lowered blood glucose level from 14th day onwards. Leaves extract at lower dose also significantly lowered blood glucose level from 21st day onwards. Glibenclamide and higher dose of fruit PEPG extract significantly reduced the total cholesterol, triglyceride levels and significantly increased the high density lipoprotein cholesterol level. Glibenclamide followed by higher dose was found more effective in reducing plasma thiobarbituric acid reactive substances and increasing levels of antioxidant enzymes (superoxide dismutase and catalase). No toxicity was observed even when both extracts were administered at 10 times of higher dose used in this study and no significant changes were seen when it were used chronically. **Conclusion:** Leaves and fruit PEPG possesses significant anti-diabetic, hypolipidemic and antioxidant properties. This study supports the traditional use of *P. granatum* in diabetes. Fruit peel which is normally thrown by many while eating pomegranate fruit is having anti-diabetic, hypolipidemic and Antioxidant activity. Furthermore high therapeutic index is safe for chronic use.

Key words: Anti-diabetic, antioxidant, glibenclamide, hypolipidemic, *Punica granatum*, streptozotocin

INTRODUCTION

Diabetes is a chronic endocrine disorder associated with several secondary complications.^[1-3] Despite the currently available anti-diabetic drugs, there is need for alternatives

which are economical and safe.^[4] Many Indian medicinal plants recommended for the treatment of diabetes mellitus lack rigorous scientific justification. *Punica granatum*, commonly known as pomegranate is one of the plants that have long been used in traditional herbal medicine against diabetes and other disorders.^[5-8]

Many scientific studies have reported anti-diabetic activity of flower and juice of the pomegranate seeds.^[9-11] However, only few studies have evaluated the anti-diabetic property of fruit peel and leaves of *P. granatum*. Hence, the present study was designed to scientifically validate and compare the anti-diabetic as well as the antioxidant effect of fruit peel and leaves of *P. granatum*.

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MATERIALS AND METHODS

Collection of the plant materials

The leaves of *P. granatum* were collected in the month of October from Nagpur, Maharashtra, India and were then authenticated by Mr. Hivarkar botanist of local Science College. The fruits of *P. granatum* were purchased from local fruit shop and peel was removed from it after authenticated by Botanist.

Preparation of extract of leaves of *P. granatum*

Fresh leaves of *P. granatum* were carefully cleaned, shade dried, powdered and stored in airtight containers until it was used for further studies. Hydroalcoholic extract was prepared.^[12] A total of 40 g of dried powder was packed in the tumbler of Soxhlet apparatus and was extracted using 95% ethanol refluxing at 50-70°C which yielded a dark brown extract. The stock extract was preserved in airtight glass container and stored at 4°C.

Preparation of extract of fruit peel of *P. granatum*

Fruit peel of *P. granatum* was carefully removed, cleaned, shade dried, powdered and stored in airtight containers until it was used for further studies. Hydroalcoholic extract was prepared as above.

Chemicals

Streptozotocin (STZ) was obtained from Sigma Chemicals, Bangalore, India. Glibenclamide of Cipla Company was procured from local medical store. The solvents and chemicals of analytical grade were used and obtained from Swastik Chemicals Nagpur. Kits to estimate total cholesterol (TC), triglycerides (TGs) and high density lipoprotein cholesterol (HDL-C) kit were purchased from Merck, Mumbai India.

Equipment

The glucometer manufactured by Prestige Company (Prestige IQ) was used for estimation of blood glucose for study.

Animals

A 70-80-day-old healthy adult Wistar male albino rats 1 (60 ± 10 g) were used. The animals were maintained under standard laboratory conditions (light period of 12 h/day and temperature 27°C ± 2°C) with access to water *ad libitum*. The animals were used in groups of six for all the studies.

Ethical clearance

Ethical clearance was taken from Institutional Animal Ethics Committee of the institute before commencement of the study where the research was conducted (MG/IAEC/3/2010).

Acute toxicity study and dose selection

Healthy adult male albino Wistar rats were used for this study. Pilot study was performed using three doses 500 mg/kg body weight, 1000 mg/kg body weight and 2000 mg/kg body weight of the leaves and fruit peel extract of *P. granatum* (PEPG). The doses selected were 5, 10 and 20 times more than the earlier study.^[13] The animals were observed continuously for 4 h and then occasionally for further 4 h and finally overnight. Animals were observed for tremors, clonic convulsions, tonic extensions, catatonia, spasticity, opisthotonus, ataxia, sedation, ptosis, respiration. After a period of 24 and 72 h they were observed for any lethality or death.

Induction of diabetes mellitus

The anti-diabetic activity of *P. granatum* was assessed using Streptozotocin (STZ) induced diabetes in rats. Diabetes mellitus was induced in overnight fasted male Wistar albino rats weighing 160 ± 10 g by single intraperitoneal injection of freshly prepared STZ at dose of 40 mg/kg body weight in 0.1 M citrate buffer (pH = 4.5). After 7 days of STZ administration, blood was collected from tail vein and blood glucose level was determined. Rats with blood glucose level above 200 mg/dl were considered diabetic and included in the study.

Experimental design

In the experiment a total of 42 rats (6 normal; 36 STZ diabetic surviving rats) were used. Only those animals with fasting blood sugar (FBS) between 200 and 300 mg/dl were selected for the study. Rats were divided into seven groups of six animals each as follows (1) normal control, (2) diabetic control, (3) diabetic + leaves extract of *P. granatum* 100 (LEPG @ 100/mg/kg), (4) diabetic + LEPG @ 200/mg/kg, (5) diabetic + fruit PEPG @ 100/mg/kg, (6) diabetic + PEPG @ 200/mg/kg and (7) diabetic + standard control glibenclamide (600 µg/kg) respectively. Normal control and diabetic control rats were given normal lab diet *ad libitum* up to 28 days. All extracts/drugs dissolved in distilled water were administered once orally/day in the morning between 9 and 10 am for 28 days. In all groups fasting blood glucose (FBG) levels were recorded on 1st (First time recording FBS levels), 7th, 14th, 21st and 28th day. FBS levels were taken after overnight fasting. Body weights of animals were also recorded on 1st, 14th and 28th day in all groups.

Estimation of lipid profile and antioxidant levels

At the end of the experiment, rats were euthanized by cervical decapitation and blood was collected by direct cardiac puncture. Serum was separated by centrifugation at 3000 rpm for 10 min. It was then kept frozen at -20°C until analysis. TC level was calculated by enzymatic method and expressed in mg/dl. HDL-C level was calculated

using polyanion precipitation and expressed as mg/dl. Low density lipoprotein cholesterol level was calculated using Friedewald's equation and expressed in mg/dl. TG in serum was converted to glycerol and then estimated using glycerol kinase enzyme based kinetic method and expressed in mg/dl.

Liver was removed immediately and washed with ice-cold physiological saline and then stored at -20°C until analysis. The antioxidant action of the leaves and fruit PEPG was assessed by measuring thiobarbituric acid reactive substances (TBARS) in tissues.^[14] Superoxide dismutase (SOD) activity^[15] and catalase activity.^[16]

Chronic toxicity studies

Animals were divided into three groups of six animals each. First group was control and received laboratory food *ad libitum*, second group was given LEPG 200 and third group was given PEPG 200. Plant extracts were dissolved in distilled water and given twice daily orally for 3 months. The various parameters such as food intake, any gross change in behavior and motor activity were observed on 1st, 30th and 60th day.

Statistical analysis

Data was analyzed using SPSS statistical software version 17.0 produced by SPSS Inc. Results are expressed as mean \pm standard deviation statistical analysis was performed using analysis of variance followed by *post-hoc* test (Bonferroni). $P < 0.05$ was considered as statistically significant.

RESULTS

Acute toxicity study of leaves and fruit PEPG in rats

Acute toxicity studies showed the non-toxic nature of the leaves as well as fruit PEPG up to dose of 2000 mg/kg body weight. There was no mortality of any animals when observed for 72 h. There was no lethality or any toxic reactions found at any of the doses selected until the end of the study period [Table 1].

Effect of leaves and fruit PEPG on streptozotocin induced diabetes

There was sustained increase in the mean blood glucose level until 28th day after induction of diabetes by streptozotocin in diabetic group. In diabetic control group mean blood glucose level was 261.50 ± 6 mg/dl on day 1 and was 264.83 ± 3.189 mg/dl on 28th day.

LEPG 100 group showed a significant drop in the mean blood glucose level from 21st day onwards. On 1st day mean blood glucose level was 266.00 ± 4.05 mg/dl, which significantly dropped to 222.00 ± 4.51 mg/dl on 28th day. LEPG 200 group was found better than LEPG 100 and showed a significant drop in the mean blood glucose level from 14th day onwards. On 1st day mean blood glucose level was 266.00 ± 7.40 mg/dl, which significantly dropped to 196.17 ± 8.95 mg/dl on 28th day. PEPG 100 group showed a significant drop in the mean blood glucose level from 14th day onwards (264.17 ± 6.70 mg/dl at day 1- 211.17 ± 3.06 mg/dl on 28th day). PEPG 200 group showed a significant drop in the mean blood glucose level from 7th day onwards (266.17 ± 3.86 mg/dl at day 1- 152.33 ± 5.57 mg/dl on 28th day). Glibenclamide group showed a sustained drop in the mean blood glucose levels when compared between 1 and 28th days (268.00 ± 6.06 mg/dl on day 1- 130.33 ± 7.42 mg/dl on 28th day) and was found better than all extracts of *P. granatum* in lowering the blood glucose levels [Table 2]. The reduction in mean blood glucose levels was 51.33%, 16.51%, 26.24%, 20.03% and 42.75% in glibenclamide, LEPG 100, LEPG 200, PEPG 100 and PEPG 200 groups respectively [Table 3].

Effect of leaves and fruit PEPG on serum lipid profile

There was increased level of TC, TGs and decreased level of HDL-C in diabetic rats compared with the normal control. Administration of leaves and fruit PEPG extract at all doses for 28 days significantly reduced the TC, TG levels and significantly increased the HDL-C level when compared with diabetic rats. PEPG 200 was significantly better than its lower dose and leaves extract at both the doses. Standard drug glibenclamide was found better than all the extracts of *P. granatum* [Table 4].

Table 1: Signs in different doses of leaves and fruit peel extract of *P. granatum* (n = 6)

Treatment	Respiration	Gait	Convulsion	Opisthotonus	Sedation	Ataxia
LEPG 500	N	N	No	Ab	No	NM
LEPG 1000	N	N	No	Ab	No	NM
LEPG 2000	N	N	No	Ab	No	NM
PEPG 500	N	N	No	Ab	No	NM
PEPG 1000	N	N	No	Ab	No	NM
PEPG 2000	N	N	No	Ab	No	NM

LEPG 500: Leaves extract of *P. granatum* at dose of 500 mg/kg body weight, LEPG 1000: Leaves extract of *P. granatum* at dose of 1000 mg/kg body weight, LEPG 2000: Leaves extract of *P. granatum* at dose of 2000 mg/kg body weight, PEPG 500: Fruit peel extract of *P. granatum* at dose of 500 mg/kg body weight, PEPG 1000: Fruit peel extract of *P. granatum* at dose of 1000 mg/kg body weight, PEPG 2000: Fruit peel extract of *P. granatum* at dose of 2000 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation

Table 2: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on streptozotocin induced diabetic rats ($n = 6$)

Group	Day 1 (mg/dl)	Day 7 (mg/dl)	Day 14 (mg/dl)	Day 21 (mg/dl)	Day 28 (mg/dl)
Normal control	124.83±5.60	123.17±4.16	125.0±4.147	125.67±5.16	124.17±4.95
Diabetic control	261.50±6.41	260.83±6.08	263.67±4.41	263.67±4.41	264.83±3.18
Diabetic+LEPG 100	266.00±4.05	258.83±2.78	255.83±5.94	247.83±6.85*	222.00±4.51*
Diabetic+LEPG 200	266.00±7.40	237.50±4.63	235.00±4.29*	222.50±5.71*	196.17±8.95*
Diabetic+PEPG 100	264.17±6.70	241.83±5.77	227.33±4.22*	224.00±7.07*	211.17±3.06*
Diabetic+PEPG 200	266.17±3.86	239.33±4.54*	204.33±7.42*	175.00±5.17*	152.33±5.57**
Diabetic+glibenclamide	268.00±6.06	182.00±7.09*	175.00±8.07*	150.00±5.51*	130.33±7.42*

Results were expressed in mean±SD. *Significant P value (<0.05) with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with diabetes control. LEPG 100: Leaves extract of *P. granatum* at dose of 100 mg/kg body weight, LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 100: Fruit peel extract of *P. granatum* at dose of 100 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation

Table 3: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on percentage reduction of mean blood glucose levels ($n = 6$)

Group	Day 7 (%)	Day 14 (%)	Day 21 (%)	Day 28 (%)
Diabetic+LEPG 100	2.67	3.82	6.82	16.51*
Diabetic+LEPG 200	10.67	11.61	16.34*	26.24*
Diabetic+PEPG 100	8.39	13.89	15.16*	20.03*
Diabetic+PEPG 200	10.06	23.21*	34.23*	42.75*
Diabetic+glibenclamide	32.06*	34.71*	43.98*	51.33*

Results were expressed in mean±SD. *Significant P value (<0.05) with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with diabetes control. LEPG 100: Leaves extract of *P. granatum* at dose of 100 mg/kg body weight, LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 100: Fruit peel extract of *P. granatum* at dose of 100 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation

Table 4: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on lipid profile in STZ induced diabetic rats after 28 days ($n = 6$)

Group	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)
Normal control	83.40±3.36	61.58±1.57	68.3183±2.92
Diabetic control	115.62±4.10	123.18±2.48	31.3817±2.43
Diabetic+LEPG 100	98.37±5.51*	92.65±2.49*	42.3550±3.08*
Diabetic+LEPG 200	89.28±2.25*	84.00±3.24*	60.7100±3.69*
Diabetic+PEPG 100	86.04±4.04*	91.61±1.94*	46.2167±3.71*
Diabetic+PEPG 200	84.11±2.83*	77.21±1.06*	71.2333±1.92*
Diabetic+glibenclamide	93.69±2.58*	92.42±3.78*	73.6733±4.04*

Results were expressed in mean±SD. *Significant P value (<0.05) with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with diabetes control. LEPG 100: Leaves extract of *P. granatum* at dose of 100 mg/kg body weight, LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 100: Fruit peel extract of *P. granatum* at dose of 100 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation, STZ: Streptozotocin, TC: Total cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol

Effect of leaves and fruit PEPG on TBARS and antioxidant levels

In diabetic control group a marked increase in the TBARS levels and a concomitant decrease in the antioxidant levels were observed. However, administration of LEPG at dose of 200 mg/kg and fruit PEPG at both doses significantly reduced the TBARS. PEPG 200 was significantly better compared to other extracts. The activities of SOD and CAT in liver were significantly lower in diabetic rats compared to control rats. Treatment with LEPG 200 and fruit PEPG at both doses showed a significant increase in SOD and CAT activity in the diabetic rats but less compared to glibenclamide group [Table 5].

Effect of Leaves and fruit PEPG on body weight

Significant decrease in body weight was observed in diabetic control group. Although, significant increase in

body weight was observed in fruit PEPG treated groups in both doses and glibenclamide group when compared with diabetic control rats but no change in body weight was observed in both doses of LEPG treated groups [Table 6].

Chronic toxicity of leaves and fruit PEPG on rats

The photoactometer readings in control group were 156.33 ± 11.76 , 164.33 ± 8.43 and 162.67 ± 7.005 on 1st, 30th and 60th day respectively. LEPG 200 group didn't show any significant change in photoactometer readings on 30th and 60th day, whereas the PEPG 200 group showed significant change in photoactometer readings at the end of 30th and 60th day. There was no change in gross behavior of animals but food intake was less in group which received LEPG [Table 7].

Table 5: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on levels of TBARS, SOD and catalase in STZ induced diabetic rats after 28 days ($n = 6$)

Group	TBARS (mmol/100 g)	SOD (Umin/mg protein)	Catalase (Umin/mg protein)
Normal control	0.93±0.51	3.27±0.35	82.41±3.45
Diabetic control	2.75±0.78	1.85±0.15	40.02±4.51
Diabetic+LEPG 100	2.33±0.62*	2.03±0.28*	51.23±3.78*
Diabetic+LEPG 200	1.57±0.43*	2.47±0.31*	64.22±4.32*
Diabetic+PEPG 100	1.65±0.28*	2.32±0.35*	60.23±5.26*
Diabetic+PEPG 200	1.17±0.18*	2.82±0.29*	70.23±5.13*
Diabetic+glibenclamide	1.03±0.07*	2.74±0.27*	69.29±4.26*

Results were expressed in mean±SD. *Significant P value (<0.05) with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with diabetes control. LEPG 100: Leaves extract of *P. granatum* at dose of 100 mg/kg body weight, LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 100: Fruit peel extract of *P. granatum* at dose of 100 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation, TBARS: Thiobarbituric acid reactive substances, SOD: Superoxide dismutase, STZ: Streptozotocin

Table 6: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on body weight in STZ induced diabetic rats ($n = 6$)

Treatment	Day 1	Day 14	Day 28
Normal control	161.00±2.36	167.00±2.83	175.33±2.66
Diabetic control	159.50±2.66	151.83±3.13	149.17±2.23
Diabetic+LEPG 100	161.17±2.85	160.83±4.02	163.33±2.94
Diabetic+LEPG 200	160.33±2.94	160.00±2.53	161.33±2.66
Diabetic+PEPG 100	162.33±1.03	168.50±1.05*	170.50±1.76*
Diabetic+PEPG 200	161.17±1.83	169.33±2.07*	175.33±1.97*
Diabetic+glibenclamide	161.83±1.16	171.33±2.34*	178.83±2.04*

Results were expressed in mean±SD. *Significant P value (<0.05) with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with diabetes control. LEPG 100: Leaves extract of *P. granatum* at dose of 100 mg/kg body weight, LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 100: Fruit peel extract of *P. granatum* at dose of 100 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*, SD: Standard deviation

Table 7: Effect of oral administration of leaves and fruit peel extract of *P. granatum* on spontaneous motor activity in rats ($n = 6$)

Treatment	Day 1	Day 30	Day 60
Normal control	156.33±11.76	164.33±8.43	162.67±7.05
LEPG 200	154.67±11.43	160.67±11.43	162.67±7.05
PEPG 200	154.67±9.69	161.67±6.59*	175.33±4.96*

*Significant P value with One-way ANOVA followed by *post-hoc* test Bonferroni when compared with normal control. LEPG 200: Leaves extract of *P. granatum* at dose of 200 mg/kg body weight, PEPG 200: Fruit peel extract of *P. granatum* at dose of 200 mg/kg body weight, *P. granatum*: *Punica granatum*

DISCUSSION

The study showed the anti-diabetic activity of leaves as well as fruit PEPG in STZ induced diabetic rats.^[17-21] Leaves and fruit peel extracts of *P. granatum* decreased the elevated blood sugar levels. The possible mechanism for this anti-diabetic action of leaves and fruit peel extracts of *P. granatum* may be improving glycemic control and insulin secretion from pancreatic beta cells in diabetic rats. The study done by Das and Sarma also showed the anti-diabetic activity of fruit PEPG.^[22] Diabetes induced by STZ leads to loss of body weight due to the increased muscle wasting.^[23] Fruit PEPG extract for 28 days significantly increased the body weight when compared with diabetic control in dose dependent manner. The increase in weight could be due to control of hyperglycemia by fruit PEPG. However, the

animals received LEPG at both doses showed no increase in body weight. As shown by Lei *et al.* this effect appears to be partly mediated by inhibiting the pancreatic lipase activity and suppressing energy intake.^[24]

The level of serum lipids are usually raised in diabetes and such an elevation represents a risk factor for coronary heart disease.^[25,26] We have noted a significant increase in TC, TG and significant decrease in HDL-C levels in streptozotocin induced diabetic rats. Fruit peel and LEPG extract significantly decreased TGs and significantly increased HDL-C levels in dose dependent manner. Higher dose of peel extract was found better than both leaves extract and peel extract at lower dose. Since lipid abnormalities accompanied with premature atherosclerosis is the major cause of cardiovascular diseases in diabetic patients, therefore ideal treatment for diabetes, in addition to glycemic control, should have a favorable effect on lipid profile.^[27-30] Free reactive oxygen species generated due to sustained hyperglycemia causes lipid peroxidation.

Treatment with fruit peel and LEPG extract for 28 days significantly decreased TBARS levels in dose dependent manner. The increase in the levels of lipid peroxidation might be indicative of a decrease in the enzymatic antioxidant defense mechanism.^[31-34] In the present study significant increase in SOD and catalase activity was

observed following treatment with the extracts, which is in concurrence with previous reports on hypoglycemic, antioxidant and hypolipidemic effect of *P. granatum* flower extract.^[35] The hypoglycemic, antioxidant and hypolipidemic effect of leaves and fruit peel extract could be due to the presence of phytochemicals such as alkaloids, flavonoids, saponins and tannins. As per the previous study done by Elfalleh *et al.* fruit peel of *P. granatum* has the most antioxidant content followed by flower, leaves and seed.^[36] This could be the reason for better activity of fruit peel extract than the LEPG.

CONCLUSION

Fruit peel and LEPG has shown anti-diabetic and hypoglycemic activity. Fruit PEPG has better anti-diabetic activity than leaves extract. Further elaborative work is necessary for the better understanding of the mechanism of their anti-diabetic activity. Detailed clinical studies in this direction are required to potentiate this claim in human beings.

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