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Antidiabetic Potential of The Leaf Extracts of *Phragmanthera incana* (Schum.) Balle Harvested on *Albizia lebbeck*

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Abstract

Introduction: This comparative study investigated the antidiabetic potentials of the various organic solvents of the leaf extracts of *Phragmanthera incana* with the aim of determining the best organic solvent for its antidiabetic activity.

Methodology: The pulverized leaves of the plant were subjected to successive extraction using different organic solvents to obtain its *n*-hexane (HPI), chloroform (CPI), ethyl acetate (EPI), methanol (MPI) and aqueous butanol (BPI) extracts. The hypoglycaemic and antihyperglycaemic effects of the extracts were carried out on normoglycaemic and glucose-induced hyperglycaemic rats, respectively at 100, 200 and 400 mg/kg using glibenclamide (5 mg/kg) as positive control. The most effective antihyperglycaemic doses of the extracts were used to determine its anti-diabetic activity on streptozotocin-induced diabetic rats. The results obtained from the study were subjected to analysis of variance (ANOVA), followed by Student–Newman-Keuls post hoc tests and $p< 0.05$ was considered significant.

Results: CPI and BPI extracts lacked hypoglycaemic effect on normal rats while HPI, EPI and MPI extracts gave significantly ($p< 0.05$) lower hypoglycaemic effect than glibenclamide. HPI (400 mg/kg) with 54 % blood glucose level reduction at 4 h was the most active antihyperglycaemic extract, followed by EPI (400 mg/kg) with 48 % activity while BPI (200 mg/kg), MPI (200 mg/kg) and CPI 400 (mg/kg), were comparable in activity with 34, 34 and 38 % blood glucose level reduction, respectively at 4 h. In the streptozotocin- induced diabetic rats, HPI gave a significantly ($p<0.05$) better hyperglycaemia lowering effect than glibenclamide (5 mg/kg) on days 4 and 7 and comparable ($p>0.05$) effect on days 10, 14 and 21. The 57 and 70 % antidiabetic effect of CPI given on days 14 and 21 were comparable to 62 and 75 % of activity elicited on the same days. MPI and BPI with comparable 63 and 66 % effect, respectively on day 21 that were significantly less active than glibenclamide were the least active extracts.

Conclusion: The study concluded that all the leaf extracts of *Phragmanthera incana* from the different organic solvents possessed antidiabetic activity to various degrees in both glucose and streptozotocin-induced hyperglycaemic rats. The n-hexane extract (HPI), with the highest antihyperglycaemic effect in the two models used in the study confirmed that the extract contained the highest concentration of the active constituents and hence, *n*-hexane was the best solvent for extraction.

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Introduction

Diabetes mellitus is a major and fastest growing global health emergency characterized by chronic hyperglycaemia which may be the result of immune-mediation (type 1 diabetes), insulin resistance (type 2 diabetes), gestational diabetes, or others (neonatal, insipidus) [1, 2]. Hyperglycaemia leads to frequent urination (polyuria), increased thirst (polydipsia) and increased hunger (polyphagia), which leads to the development of micro and macrovascular complications, resulting in nerves, heart, kidneys, skin, and retina diseases [3]. In 2019, about 463 million adults (20 to 79 years) were living with diabetes and this number could increase to 700 million by 2045, causing 4.2 million deaths worldwide [2].

Glycaemic control is achieved by administration of antidiabetic medications which exist in different classes and their choice varies according to several factors, such as the nature of diabetes, age, and progression of the disease [1, 2]. Several treatment options are available for diabetes patients today than ever before but most of the complications of diabetes still result from uncontrolled hyperglycaemia because no therapy in widespread use can consistently halt, reverse, or cure type 1 or type 2 diabetes. Moreover, the intensive therapy to achieve normal glucose levels is not without risk. The treatments still have significant drawbacks such as limited efficacy, unwanted side effects, and inconvenient dosing. Some of these adverse effects include; weight gain, gastrointestinal disorder, fluid retention with associated oedema, heart failure, myocardial infarction, bladder cancer, hypoglycaemia, nausea, abdominal discomfort, headache, hypersensitivity, skin reactions (including photosensitivity), abnormal liver function tests, dizziness, diarrhoea, constipation, arthralgias, headache, cough, abdominal pain, diarrhoea, flatulence, acute pancreatitis, vomiting, mycotic infections (vulvovaginitis, balanitis, urinary tract infections) and anorexia . In addition, observational studies indicate that the presence of diabetes increases the risk of other co morbidities such as fractures and certain cancers and the treatment choice may affect risk [4, 5]. Although the number of diabetes treatments has substantially increased in the past two decades, today's therapies are considered far from ideal [4]. Thus, there is need for therapies that are effective, easy to use, safe, tolerable and affordable.

Complementary and alternative medicine is increasingly becoming an important aspect of the management of chronic diseases and is classified into five categories which include alternative medicine systems, mind-body interventions, biologically based therapies, manipulative and body-based therapies and energy therapies. Biologically based therapies which refer to substances found in nature such as herbal products, vitamins and dietary supplements are commonly used in African settings [6]. *Phragmanthera incana* is an example of a plant that is used in biological based therapies. *Phragmanthera incana* (Schum) Balle, (Loranthaceae), is a member of the African mistletoe. It is a woody parasitic shrub, which is very variable in form, common, widely distributed and grows on different host plants of economic importance, including shea butter, neem, citrus, cocoa, kolanut, bush mango and rubber [6, 7]. Some of the uses of *P. incana* are listed in the table 1 below:

Material and Methods

Plant material

Fresh leaves of *P. incana* were collected from University of Lagos campus, Nigeria. The plant was authenticated at the Herbarium of the Department of Botany, University of Lagos, by Mr. Daramola and Mr. Odewo. Voucher specimen was deposited with reference number, LUH 1863.

Preparation and extraction of plant material

The leaves of *P. incana* were washed with distilled water to remove sand and dirt. The leaves were air-dried at room temperature and milled into powder. The pulverized powder (5.0 kg) was extracted successively with *n*-hexane, chloroform, ethyl acetate, methanol and butanol/water (50:50) to obtain their corresponding solutions that were concentrated *in vacuo* and coded, HPI (250 g), CPI (370 g), EPI (186 g), MPI (215 g) and BPI (526 g) respectively.

Table 1: Ethno- and pharmacological uses of *Phragmanthera incana*

Uses	Indication	References
Ethnopharmacological uses	Cancers and inflammations.	[8]
	Restores the immune system, hypertension, diabetes and inflammatory-related disorders. Skin diseases and prostate cancer. Hypertension, diabetes, insomnia, hepatitis, stroke, cancer, infertility and nervous disorders.	[7, 9] [6, 10]
	Gastro-intestinal tract infections, wound, diarrhoea, dysentery and skin infections.	[11]
Pharmacological uses	Antibacterial and antifungal activities.	[11 12]
	Metabolic activity.	[13]
	Antidiabetic and antioxidant properties.	[9, 14]
	Antihypertensive, antioxidant and anti-inflammatory properties.	[7]

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Bioassays

Animals

Healthy albino rats (120–160 g) of both sexes bred under standard conditions (temperature 25 ± 3 °C) at the animal house, Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria were used for the experiment. They were fed on a standard pellet diet (Vital Feeds, Nigeria) and water was given *ad libitum*.

Hypoglycaemic effect of the extracts

Five groups of five normoglycaemic rats each were fasted for 24 h and orally administered with either 1% Tween 80 (negative control), extract (100, 200, 400 mg/kg), or glibenclamide (5 mg/kg), (positive control). A drop of blood taken from the tip of the tail of each rat at 0.0, 0.5, 1.0, 2.0 and 4.0 h were dropped onto a glucometer strip and the blood glucose (bg) level read off directly. The blood glucose levels at 0.0 h (To) were taken as 100 % while those at other times were expressed as percentage of these values [15].

Anti hyperglycaemic effect of the extracts

A glucose tolerant test was carried out by giving glucose (10 g/kg, *p.o.*) to rats that were fasted for 24 h. Those with high blood glucose level (blood glucose level ≥ 7 mmol/L (126 mg/dL) after 0.5 h (time point 0 h, T_o) were divided into groups of five and administered (*p.o.*) with 1 % tween 80 in normal saline (negative control), extract (100, 200 and 400 mg/kg), or glibenclamide (5 mg/kg) to determine their blood glucose level reduction activity. A drop of blood, taken from the tip of the tail of each rat, was dropped onto a glucometer strip and the blood glucose (bg) level read off directly. The blood glucose levels at 0 h (T_o) were taken as 100 % while those at other times were percentages of these values. Their blood glucose (bg) levels were determined and recorded at 0, 0.5, 1, 2 and 4 h after administration of the normal saline/ extract/drug [16].

Anti-diabetic effect of the extracts on streptozotocin-induced diabetic rats

Diabetic rats were obtained by intraperitonial injection of streptozotocin (65 mg/kg) that was dissolved in freshly prepared 0.1M sodium citrate buffer with a pH of 4.5 on pH meter. Rats with fasting blood glucose levels ≥ 14 mmol/L after 72 h of injection of streptozotocin were considered to be diabetic. The diabetic rats were divided into three groups of 10 rats each. They were given 1 % tween 80 in normal saline, extract (the most active dose from glucose-induced hyperglycaemia assay) or glibenclamide (5 mg/kg) for 21 days. Their fasting blood glucose levels were determined on days 1, 4, 7 and 10, 14 and 21 [17]. This study was performed in strict accordance with the Institute for Laboratory Animal Research Division on Earth and Life Studies guidelines for the care and use of laboratory animals (National Research Council Publication, 2011) and was approved by the Institutional Animal Care and Use committee of National Academy of Sciences (Washington, DC, USA) [18]. Analysis of variance (ANOVA) was first used followed by Bonferroni t-test to determine the source of significant differences for all determinations and $p < 0.05$ was considered to be statistically significant.

Glibenclamide (5 mg/kg) gave 45, 54, 51 and 44 % blood glucose level reduction at 0.5, 1, 2 and 4 h, respectively in normoglycaemic rats which showed its hypoglycaemic side effect as an antidiabetic drug [19]. The *n*-hexane leaf extract of *P. incana* gave a significantly ($P < 0.05$) lower hypoglycaemic effect than glibenclamide at all the tested doses indicating that the extract may not precipitate hypoglycaemia coma in normal subjects. However, 33 % activity of the extract at 400 mg/kg at 4 h with significantly higher effect than both 100 and 200 mg/kg indicated caution in the use of the extract at high doses (Table 2).

Table 2: Dose related hypoglycaemic effect of n-hexane extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
NS	100	115.64±12.08^c	108.22±8.62^c	101.25±10.30^c	102.81±5.23^c
HPI (100)	100	108.76 ± 5.7^{5}c	93.12 ± 6.98^b	99.39 ± 8.25^c	98.18 ± 10.81^c
		5.95%	13.95%	1.84%	4.50%
HPI (200)	100	93.35 ± 3.69^b	86.35 ± 3.30^b	83.99 ± 3.28^b	80.25 ± 5.50^c
		19.28%	20.21%	17.05%	21.94%
HPI (400)	100	90.58 ± 7.25^b	81.46 ± 4.93^b	77.45 ± 3.2^{2}b	68.84 ± 4.36^b
		21.67%	24.73%	23.51%	33.04%
GLI (5)	100	68.04±6.88^a	50.22±4.14^a	50.02±2.36^a	57.76±4.41^a
		44.62%	53.59%	50.59%	43.82%

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), $n = 5$. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: 1 % of Tween 80 in normal saline (negative control); **HPI**: Hexane extract of *Phragmathera incana* leaves; **GLI**: Glibenclamide.

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In the chloroform extract of *P. incana* leaves, all the tested doses and at all time points elicited a significantly lower hypoglycaemic effect than the positive control which suggested that the extract lacked any potential to cause hypoglycaemic coma in non-diabetic subjects. This result also showed that chloroform extract did not contain the constituents of the extract that were responsible for its hypoglycaemic effect like n-hexane (Table 3).

Similar to the chloroform leaf extract of *P. incana,* its ethyl acetate extract was significantly less active than glibenclamide (5 mg/kg) at all the tested doses. However, ethyl acetate extract caused more hypoglycaemic effect on the animals than the chloroform extract, even at 100 mg/kg (Tables 2 and 3). The hypoglycaemic effect of the n-hexane extract was pronounced at 400 mg/kg while that of the ethyl acetate extract was mostly observed at 100 mg/kg (Tables 2 and 4).

Generally, methanol extract of *P.* leaves exhibited a significantly lower hypoglycaemic effect at the tested doses than glibenclamide (5 mg/kg) which showed its safety in normal humans. However, 31 and 28 % blood glucose level reduction after 4 h caused by 200 and 400 mg/kg called for caution in its use when extracted with this solvent.

Butanol/water extract of *P. incana* leaves did not cause hypoglycaemia in the rats at all the tested doses while glibenclamide gave a significantly higher hypoglyvaemia than the extract at all the tested doses and time points (Table 6). This indicated that the extract may not lead to excessive decrease in blood glucose when administered to non-diabetic humans.

Antihyperglycaemic activity of the crude extracts of *P. incana* leaves

The results of antihyperglycaemic studies using

Table 3: Dose related hypoglycemic effect of chloroform extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
NS	100	115.64±12.08^b	108.22±8.62^b	101.25±10.30^b	102.81±5.23^b
CPI (100)	100	117.64 ± 9.04^b	111.94 ± 6.77^b	109.05 ± 9.30^b	109.15 ± 8.60^b
		(-1.73 %)	(-3.44 %)	(-7.70 %)	(-6.17 %)
CPI (200)	100	111.85 ± 3.46^b	105.99 ± 9.05^b	113.87 ± 5.00^b	103.09±10.14^b
		(3.28%)	(2.06%)	(-0.12 %)	(-0.27 %)
CPI (400)	100	114.19 ±11.35^b	109.91 ± 4.41^b	107.39 ± 9.89^b	106.67±10.99^b
		(1.25%)	(-1.56 %)	(-6.06 %)	(-3.75 %)
GLI (5)	100	68.04±6.88^a	50.22±4.14^a	50.02±2.36^a	57.76±4.41^a
		(44.62%)	(53.59%)	(50.59%)	(43.82%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: 1 % of Tween 80 in normal saline (negative control); **CPI**: Chloroform extract of *Phragmathera incana* leaves; **GLI**: Glibenclamide.

Table 4: Dose related hypoglycemic effect of ethyl acetate extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
NS	100	115.64±12.08^b	108.22±8.62^b	101.25±10.30^c	102.81±5.23^c
EPI (100)	100	91.65 ± 2.63^b	88.25 ± 2.92^b	80.62± 3.54^b	72.92± 2.90^b
		(20.74%)	(18.45%)	(20.38%)	(29.07%)
EPI (200)	100	97.44 ± 1.60^b	90.78 ± 2.80^b	85.08 ± 2.70^b	77.90 ± 4.04^b
		(15.74%)	(16.12%)	(15.97%)	(24.23%)
EPI (400)	100	96.21 ± 0.89^b	93.96 ± 1.17^b	88.00 ± 1.45^b	83.49± 2.37^b
		(16.80%)	(13.18%)	(13.09%)	(18.79%)
GLI (5)	100	68.04±6.88^a	50.22±4.14^a	50.02±2.36^a	57.76±4.41^a
		(44.62%)	(53.59%)	(50.59%)	(43.82%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: 1 % of Tween 80 in normal saline (negative control); **EPI**: Ethylacetate extract of *Phragmathera incana* leaves; **GLI**: Glibenclamide.

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Table 5: Dose related hypoglycemic effect of methanol extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
NS	100	115.64±12.08^b	108.22±8.62^c	101.25±10.30^c	102.81±5.23^c
MPI (100)	100	95.31 ± 2.68^b	97.05 ± 5.76^b	90.41 ± 2.33^b	83.34 ± 3.83^b
		(17.58%)	(10.32%)	(10.71%)	(18.94%)
MPI (200)	100	101.30 ± 8.84^b	88.08 ± 5.34^b	79.16 ± 5.72^b	71.44 ± 6.85^b
		(12.40%)	(18.61%)	(21.82%)	(30.51%)
MPI (400)	100	96.66 ± 2.86^b	86.52 ± 1.63^b	86.42 ± 3.17^b	73.75 ± 4.19^b
		(16.41%)	(20.05%)	(14.65%)	(28.27%)
GLI (5)	100	68.04±6.88^a	50.22±4.14^a	50.02±2.36^a	57.76±4.41^a
		(44.62%)	(53.59%)	(50.59%)	(43.82%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: 1 % of Tween 80 in normal saline (negative control); **MPI**: Extract of *Phragmathera incana* leaves; **GLI**: Glibenclamide.

Table 6: Dose related hypoglycemic effect of butanol /water extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
NS	100	115.64±12.08^b	108.22±8.62^b	101.25±10.30^b	102.81±5.23^b
BPI (100)	100	111.25 ± 6.47^b	107.07 ± 5.80^b	99.47 ± 5.31^b	95.94 ± 5.53^b
		(3.80%)	(1.06%)	(1.76%)	(6.68%)
BPI (200)	100	99.69 ± 1.64^b	99.36 ± 2.11^b	101.91 ± 3.37^b	92.59 ± 4.91^b
		(13.69%)	(8.19%)	(-0.65 %)	(9.94%)
BPI (400)	100	98.55 ± 2.78^b	104.76 ± 2.65^b	104.19 ± 3.43^b	100.52 ± 3.97^b
		(14.78%)	(3.20%)	(-2.9 %)	(2.23%)
GLI (5)	100	68.04±6.88^a	50.22±4.14^a	50.02±2.36^a	57.76±4.41^a
		(44.62%)	(53.59%)	(50.59%)	(43.82%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: 1 % of Tween 80 in normal saline (negative control); **BPI**: Butanol/water extract of *Phragmathera incana* leaves; **GLI**: Glibenclamide.

glucose-loaded rat model and insulin-stimulating drugs like glibenclamide as positive controls can be extrapolated to type 2 diabetes state in humans [20]. There was an observed time dependent (0.5-4 h) reduction in blood glucose levels of normal rats in the negative control group that received 10 g/kg glucose solution of distilled water in 1 % Tween 80. This was due to the released insulin by the rats pancreas in response to hyperglycaemia caused by the glucose load [21]. Glibenclamide with early extra-pancreatic and late insulin stimulating mechanisms of action was used as the standard drug in this study [22] to investigate possible mechanism of action of the extract [23]. Generally, the extract at 100, 200 and 400 mg/kg gave a time dependent antihyperglycaemic activity similar to the positive control with highest effect at 4 h indicating insulin stimulation as the major mechanism of action of the extract like glibenclamide. The activity of the extract at 100-400 mg/kg was comparable (P>0.05) at 0.5-2 h but the 200 and 400 mg/kg doses were significantly more active than the 100 mg/kg at 4 h. Similarly, 200 and 400 mg/kg of the extract were significantly more active than glibenclamide at 4 h but gave comparable activity at 2 h (Table 7).

Similar to the n-hexane extract of *P. incana* leaves, its chloroform extract also gave comparable activity at all the tested doses and at all time points with the exception of 100 mg/kg, that gave a significantly higher effect at 1 h. Also, the activity of the extract, 100-400 mg/kg was comparable to glibenclamide at 2-4 h suggesting insulin release as its major mechanism of action. The *n*-hexane extract, 200 and 400 mg/kg with 51 and 54 % blood glucose level reduction at 4 h showed a significantly better effect than its chloroform

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Table 7: Dose related glucose lowering effect of n-hexane extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of To (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
GLU (10 g/kg)	100	84.32 ± 6.40^{b}	82.16 ± 4.20^{b}	76.52 ± 3.11^{b}	71.86 ± 6.62^{c}
HPI (100)	100	80.52 ± 4.80^{b}	72.15 ± 7.17^{b}	65.64 ± 4.80^{a,b}	44.55 ± 4.93^{b}
		(4.51%)	(12.18%)	(14.22%)	(38.00%)
HPI (200)	100	81.97 ± 7.77^{b}	70.50 ± 7.30^{b}	61.39 ± 7.36^{a}	35.50 ± 5.38^{a}
		(2.79%)	(14.19%)	(19.77%)	(50.60%)
HPI (400)	100	83.40 ± 3.10^{b}	81.20 ± 4.70^{b}	57.27 ± 5.33^{a}	33.38 ± 4.42^{a}
		(1.09%)	(1.17%)	(25. 16)	(53.55%)
GLI (5)	100	72.2±0.41^{a}	67.0 ± 0.20^{a}	56.6±0.20^{a}	43.3±0.30^{b}
		(14.37%)	(18.45%)	(26.03%)	(39.74)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **GLU**: Glucose in 1 % of Tween 80 in normal saline (negative control); **HPI**: Hexane extract of *Phragmanthera incana* leaves; **GLI**: Glibenclamide.

Table 8: Dose related glucose lowering effect of chloroform extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of To (reduction in blood glucose relative to negative control at Tt)				
(mg/ kg)	0.0 h	0.5 h	1 h	2 h	4 h
GLU (10 g/kg)	100	84.32 ± 6.40^{c}	82.16 ± 4.20^{c}	76.52 ± 3.11^{b}	71.86 ± 6.62^{c}
CPI (100)	100	60.04 ± 3.37^{a}	54.92 ± 1.68^{a}	57.58 ± 7.1^{9}a	50.35± 7.46^{a,b}
		(28.80%)	(33.15%)	(24.75%)	(29.93%)
CPI (200)	100	61.53 ± 9.09^{a}	65.88 ± 10.86^{b}	59.57 ± 9.3^{4}a	51.76 ± 8.10^{a,b}
		(27.03%)	(19.81%)	(22.15%)	(27.97%)
CPI (400)	100	55.53 ± 10.90^{a}	63.46 ± 9.24^{b}	53.38 ± 7.46^{a}	44.25 ± 6.79^{a}
		(34.14%)	(22.76%)	(30.24%)	(38.42%)
GLI (5)	100	72.2±0.41^{b}	67.0 ± 0.20^{b}	56.6±0.20^{a}	43.3±0.30^{a}
		(14.37%)	(18.45%)	(26.03%)	(39.74%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **GLU**: Glucose in 1 % of Tween 80 in normal saline (negative control); **CPI**: Chloroform extract of *Phragmanthera incana* leaves; **GLI**: Glibenclamide.

Table 9: Dose related glucose lowering effect of ethyl acetate extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of To (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
GLU (10 g/kg)	100	84.32 ± 6.40^{c}	82.16 ± 4.20^{c}	76.52 ± 3.11^{c}	71.86 ± 6.62^{c}
EPI (100)	100	69.25 ± 11.64^{b}	71.16 ± 12.80^{b}	64.68 ± 8.87^{b}	44.83 ± 7.46^{a}
		(17.87%)	(13.39%)	(15.47%)	(37.61%)
EPI (200)	100	62.38 ± 10.69^{a}	63.32 ± 9.81^{b}	63.89 ± 10.97^{b}	59.65 ± 11.95^{b}
		(26.02%)	(22.93%)	(16.51%)	(16.99%)
EPI (400)	100	52.55 ± 9.94^{a}	49.15 ± 8.70^{a}	40.90 ± 6.28^{a}	37.07 ± 6.53^{a}
		(37.68%)	(40.18%)	(46.55%)	(48.41%)
GLI (5)	100	72.2±0.41^{b}	67.0 ± 0.20^{b}	56.6±0.20^{b}	43.3±0.30^{a}
		(14.37%)	(18.45%)	(26.03%)	(39.74%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **GLU**: Glucose in 1 % of Tween 80 in normal saline (negative control); **EPI**: Ethyl acetate extract of *Phragmanthera incana* leaves; **GLI**: Glibenclamide.

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extract with 28 and 38 % effect, respectively at the same time (Tables 7 and 9).

The ethylacetate extract of *P. incana* leaves gave similar and comparable profile of activity at 100 mg/kg with glibenclamide showing possible mechanism of action of the extract and glibenclamide. At 400 mg/kg, it elicited significantly higher antihyperglycaemic activity than glibenclamide at 0.5-2 h indicating additional extrapancreatic activity of the extract at this dose. Furthermore, 38, 40, 47 and 48 % blood glucose level reduction of 400 mg/kg that was significantly higher than those of 100 and 200 mg/kg showed 400 mg/kg as the most effective dose (Table 9).

The antihyperglycaemic effect elicited by 100 and 400 mg/kg of the methanol extract of *P. incana* leaves was comparable at all time points while its 200 mg/kg gave a significantly higher effect at 1-4 h showing it as the most active dose. Higher activity of the extract at 0.5-1 h of the extract at 200 mg/kg indicated additional extrapancreatic action at this dose similar to 400 mg/kg of ethylacetate extract (Table 9 and 10). Furthermore, the extract at 200 mg/kg was comparable in activity to glibenclamide at 1-2 h.

Butanol/water extract of *P. incana* leaves lacked appreciable antihyperglycaemic effect at both 100 and 400 mg/kg. However, its 200 mg/kg gave a comparable activity to glibenclamide at 0.5 and 2-4 h while the 31 % reduction in blood glucose level at 1 h is indicative of extrapancreatic effect of the extract in addition to its insulin stimulation (Table 11). MPI and BPI showed similar (33 % at 4 h) antihyperglycaemic effect at the same dose (200 mg/kg) with additional extrapancreatic effect.

The various solvent extracts of *P. incana* were tested in the streptozotocin-induced diabetic rats model using the most active dose of the extract in the glucose induced hyperglycaemic rats model in order to further establish the

Table 10: Dose related glucose lowering effect of methanol extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of To (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
GLU (10 g/kg)	100	84.32 ± 6.40^{b}	82.16 ± 4.20^{c}	76.52 ± 3.11^{b}	71.86 ± 6.62^{c}
MPI (100)	100	63.87 ± 4.25^{a}	64.32 ± 6.2^{0}b	71.25 ± 7.10^{b}	58.31 ± 6.59^{b}
		(24.25%)	(21.71%)	(6.89%)	(18.86%)
MPI (200)	100	62.57 ± 8.71^{a}	52.64 ± 8.45^{a}	55.31 ± 8.84^{a}	47.63 ± 10.17^{a}
		(25.79%)	(35.93%)	(27.72%)	(33.72%)
MPI (400)	100	62.66 ± 8.23^{a}	70.09 ± 10.50^{b}	68.84 ± 9.06^{b}	58.91 ± 5.97^{b}
		(25.69%)	(14.69%)	(10.04%)	(18.02%)
GLI (5)	100	72.2±0.41^{b}	67.0 ± 0.20^{b}	56.6±0.20^{a}	43.3±0.30^{a}
		(14.37%)	(18.45%)	(26.03%)	(39.74%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **GLU**: Glucose in 1 % of Tween 80 in normal saline (negative control); **MPI**: Methanol extract of *Phragmanthera incana* leaves; **GLI**: Glibenclamide.

Table 11: Dose related glucose lowering effect of butanol/water extract of *P. incana* leaves

Dose of extract	Blood glucose level as percentage of T_o (reduction in blood glucose relative to negative control at Tt)				
(mg/kg)	0.0 h	0.5 h	1 h	2 h	4 h
GLU (10 g/kg)	100	84.32 ± 6.40^{b}	82.16 ± 4.20^{b}	76.52 ± 3.11^{b}	71.86 ± 6.62^{b}
BPI (100)	100	81.56 ± 2.62^{b}	83.56 ± 2.99^{c}	80.80 ± 1.20^{b}	63.41 ± 8.37^{b}
		(3.27%)	(-1.70 %)	(-5.59%)	(11.76%)
BPI (200)	100	64.28 ± 9.03^{a}	56.86 ± 7.29^{a}	54.22 ± 8.18^{a}	47.70 ± 6.66^{a}
		(23.77%)	(30.79%)	(29.14%)	(33.62%)
BPI (400)	100	81.76 ± 5.66^{b}	78.65 ± 4.99^{b}	71.17 ± 7.04^{b}	65.55 ± 7.71^{b}
		(3.04%)	(4.27%)	(6.99%)	(8.78%)
GLI (5)	100	72.2±0.41^{a}	67.0 ± 0.20^{b}	56.6±0.20^{a}	43.3±0.30^{a}
		(14.37%)	(18.45%)	(26.03%)	(39.74%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **GLU**: Glucose in 1 % of Tween 80 in normal saline (negative control); **BPI**: Butanol/water extract of *Phragmanthera incana* leaves; **GLI**: Glibenclamide.

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Table 12: Anti-diabetic activity of the crude extracts of *Phragmanthera incana* on streptozotocin-induced diabetic rats

Extract/Drug	Blood glucose levels as a percentage of T_o (% reduction in blood glucose relative to negative control T_t)					
(mg/kg)	Day 1	Day 4	Day 7	Day 10	Day 14	Day 21
NS	100	95.36±3.37^{b}	94.26±4.45^{d}	99.34±3.00^{e}	100.26±2.81^{e}	103.21±3.82^{d}
HPI (400)	100	58.71±6.87^{a}	34.46±4.26^{a}	24.03±0.89^{a}	16.56±1.55^{a}	14.10±0.91^{a}
		(38.43%)	(63.44%)	(75.81%)	(83.48%)	(86.34%)
CPI (400)	100	99.50±10.46^{b}	88.42±10.61^{d}	74.54±9.74^{d}	43.02±3.62^{b}	31.31±3.40^{b,c}
		(-4.34%)	(6.20%)	(24.96%)	(57.09%)	(69.66%)
EPI (400)	100	92.18±4.64^{b}	68.77±5.33^{c}	40.89±1.80^{b}	38.13±1.88^{b}	25.89±0.88^{b}
		(3.33%)	(27.04%)	(58.84%)	(61.97%)	(74.92%)
MPI (200)	100	94.64±1.48^{b}	84.65±4.55^{d}	72.00±0.53^{d}	64.26±3.70^{d}	38.02±1.16^{c}
		(0.76%)	(10.20%)	(27.52%)	(35.91%)	(63.16%)
BPI (200)	100	90.05±8.08^{b}	78.49±7.07^{d}	61.89±5.71^{c}	51.05±2.88^{c}	35.37±1.88^{c}
		(5.57%)	(16.73%)	(37.70%)	(49.08%)	(65.73%)
GLI (5)	100	80.23±5.94^{b}	51.54±7.42^{b}	27.86±1.60^{a}	22.46±2.38^{a}	17.00±1.91^{a}
		(15.87%)	(45.32%)	(71.95%)	(77.60%)	(83.53%)

Data show the mean ± SEM blood glucose levels at the different time points expressed as percentages of levels at 0 h (T_o), n = 5. Values in parentheses represent the percentage reductions in blood glucose levels relative to negative control for each time point. Values with different superscripts within columns are significantly different ($p < 0.05$, one-way analysis of variance followed by the Student–Newman–Keuls' test). **NS**: Diabetic rats with 1 % of Tween 80 in normal saline (negative control); **HPI**: Hexane extract of *Phragmanthera incana* leaves; **CPI**: Chloroform extract of *Phragmanthera incana* leaves; **EPI**: Ethyl acetate extract of *Phragmanthera incana* leaves **MPI**: Methanol extract of *Phragmanthera incana* leaves; **BPI**: Butanol/water extract of *Phragmanthera incana* leaves; : Diabetic rats with extract of *Phragmanthera incana*; **GLI**: Glibenclamide.

antihyperglycaemic effect of the extracts (Tables 7-11). There was no reduction in the hyperglycaemic condition of the diabetic negative control group of rats that received only the vehicle which showed that the diabetic state that was induced in the rats by the drug was permanent (Table 12).

Among all the extracts, only HPI 400 gave a significantly ($p<0.05$) better blood glucose level reduction on days 4 and 7 than glibenclamide (5 mg/kg) which indicated early onset of antidiabetic activity of the extract. In addition, HPI 400 gave a comparable effect to the positive control on days 10-21 of the study showing its better effectiveness as an antidiabetic agent than the other extracts (Table 12). Interestingly, HPI 400 with the highest activity in this study was also the most active extract in the glucose loaded experiment (Table 7) confirming n–hexane as the best solvent of extraction. The antidiabetic effect of EPI 400 became pronounced on day 10 while that of CPI 400 on day 14 but they both gave comparable activity on days 14-21.

Both MPI 200 and BPI 200 gave moderate antidiabetic effect observable from day 10 to 21 that was significantly lower than other extracts and glibenclamide (Table 12). Also, MPI and BPI gave similar activity in glucose-induced hyperglycaemic rats model with additional extrapancreatic effect (Tables 10 and 11). This result suggested that the extracts, MPI and BPI contained the same constituents that may be working majorly through extrapancreatic mechanism such as inhibition of α-amylase and α-glucosidase or prevention of glucose uptake from the stomach. Furthermore, EPI with higher antihyperglycaemic activity than CPI in glucose loaded rats model (Tables 8 and 9) was also more active in STZ model (Table 12) confirming the antidiabetic effect of the extracts. Low antidiabetic activity exhibited by CPI and EPI in this model may indicate that the constituents in the extract may be working through another mechanism and not majorly by insulin stimulation.

Conclusion

The study concluded that all the leaf extracts of *Phragmanthera incana* from the different organic solvents possessed antidiabetic activity to various degrees in both glucose and streptozotocin-induced hyperglycaemic rats. The *n*-hexane extract (HPI), with the highest antihyperglycaemic effect in the two models used in the study confirmed that the extract contained the highest concentration of the active constituents and hence, *n*-hexane was the best solvent for extraction.

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Competing interest

There is absolutely no conflict of interest among authors.

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