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Comparative evaluation of antidiabetic antihypertensive activity of *Cynodon dactylon* L. and *Phyllanthus niruri* L in ratswith simultaneous type 2 diabetic and hypertension

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ABSTRACT

In recent years, the use and search for drugs and dietary supplements derived from plants have accelerated in the treatment of diabetes and hypertension because of the hazardous adverse effects of the current therapy. A comparison was made between the antidiabetic-antihypertensive activities of aqueous extracts of leaves of Cynodon dactylon and Phyllanthus niruriin rats with simultaneous type 2 diabetic and hypertension. The aq. extracts of leaves of Cynodon dactylon (200mg/kg/day)and Phyllanthus niruri (600mg/kg/day) was administered orally in Diabetic Control (DC), SHR and Diabetic-SHR (D-SHR). Body weight of animals were measured weekly throughout the study (28 days). Blood glucose level and total cholesterol level was measured at day 0 after induction of diabetes and at day 28. Arterial blood pressure of all the groups was measured at day 14 and day 28 by tail cuff method. Serum glutamic oxaloacetic transaminase (SGOT) levels in all the groups were measured at the end of experiment. No loss in the weight of animal was observed in the group treated with the aqueous herbal extracts. The study showed that herbal extracts prevented attenuation of the blood glucose and total cholesterol levels; significant decrease in mean arterial blood pressure (MABP) and decrease in SGOT level. The findings of the study support the traditional use of C. dactylon and P. niruri for the treatment of diabetes and arterial hypertension, and indicate that they may have a beneficial effect in patients with co-existing diabetic hypertension.

Key words: Diabetic hypertension, *Cynodon dactylon*, *Phyllanthus niruri*, Spontaneously hypertensive rats, Streptozotocin,

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INTRODUCTION

Diabetes mellitus (DM) and hypertension (HTN) have emerged as major medical and public health issues worldwide, and both are important risk factors for coronary artery disease (CAD), heart failure, and cerebrovascular disease. DM is increasing in epidemic proportions globally [1]. DM exerts a significant burden resulting in increased morbidity and mortality, decreased life expectancy, and reduced quality of life, as well as individual and national income losses. Additionally, HTN affects about one billion people worldwide [2] and it is estimated that by 2025, up to 1.56 billion adults worldwide will be hypertensive [3]. Raised blood pressure (BP) is estimated to cause 7.5 million deaths.

DM and HTN are also known to coexist in patients [4]. Indeed, there is a strong correlation between changing lifestyle factors and increase in both DM and HTN. The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy. For all these considerations, therapeutic interventions should target all the risk factors, including blood glucose levels and arterial hypertension. In this context, many studies have demonstrated the ability of phytotherapy to significantly decrease plasma glucose level and blood pressure, in addition to the conventional hypoglycemic agents and hypotensive drugs used in the treatment of T2DM and arterial hypertension.

Since from ages, plants have been the main source of medicines for human beings. Plants contain various phytochemicals which can play an important role in reducing occurrence of several diseases by boosting up various organ functions. Numerous traditional healing herbs and their parts have been shown to have medicinal value and can be used to prevent, alleviate or cure several human diseases [5]. It is estimated that 70–80 % of people worldwide rely chiefly on traditional, largely herbal medicine to meet their primary healthcare needs [6,7].

Cynodon dactylon (L.) (Family: Poaceae) is a perennial grass, possess various medicinal properties such as antimicrobial and antiviral activity [8]. Furthermore, the aqueous extract of this plant has anti- inflammatory [9], diuretic [10], and anti-emetic [11] activity. It has been reported to possess anti-arrhythmic [12], cardioprotective [13], antioxidant [9], immunomodulatory [14], anti-anaphylactic and mast cell stabilizing [15] activity. *Cynodon dactylon* has been used as an Indian traditional medicine for asthma [16]. Leaf, root and rhizome of the plant have been used in folk medicine in various countries as anticystitis [17], antihysteria, antipsychotic [18] antigonorrheal infection [19]. The phytochemical studies on *Cynodon dactylon* revealed the presence of flavonoids, glycosides, saponins, tannins, carbohydrates and essential oil [20.21]

Phyllanthus niruri L., (Family: Phyllanthaceae) is a little shrub found both in tropical and subtropical countries. Several species from this genus are used worldwide in folk medicine for diverse therapeutic purposes [22].Various active constituents to which the biological activity of *P. niruri* has been attributed include lignans, tannins, coumarins, terpenes, flavonoids, alkaloids, saponins and phenylpropanoids. These active constituents along with common lipids, sterols and flavonols are mainly found in the leaves, stem and roots of the plant [23].These all phytochemicals present in *P. niruri* exert different pharmacological actions, for example, a) hepatoprotective [23, 24] and anti-viral properties by lignans [25] b) anti-microbial activity by terpenes [26] c) anti-oxidant[27], antileishmanial [28], andanti-inflammatory activities by flavonoids [29], d)antispasmodic activity,[30] smooth muscle relaxation effect by alkaloid[31]e) aldosereductase inhibitory (ARI) activity [32] by glycosides (quercitrinand geraniin).

It is desirable to explore the action of herbal medicines for safe and effective management of diabetes hypertension, a) As the diabetes and hypertension has become a global burden and long term management with available pharmacological therapy is gradually getting costlier, sometime ineffective as well as associated with number of side effects, b) As patients have to consume separate medicine for these two diseases though both diseases are existed in same individual i.e. diabetes hypertensive patients.

Here we report antidiabetic antihypertensive activity of the water extract from leaves of *Cynodon dactylon* and *Phyllanthus niruri* with a view to provide scientific evidence of modern lines in Streptozotocin induced diabetes in SHR to evaluate and compare their antidiabetic and antihypertensive activity. The effects produced by these extracts on arterial blood pressure, blood glucose level, and total cholesterol and SGOT level were evaluated.

MATERIALS AND METHODS

Plant material

The fresh aerial parts of leaves of *Cynodon dactylon* and *Phyllanthus niruri* were collected from outskirt of Palghar, Maharashtra, India and authenticated by Agharkar Research Institute, Pune, India. The animal usage protocol was approved by the IAEC of National Toxicology Centre through Protocol No.38/1415.

Preparation of the aqueous extract

Aerial parts of leaves of *C. dactylon* and *P. niruri* were dried under shade and coarsely powdered. Powdered material was subjected to continuous hot percolation (soxhlation) with distilled water. After the exhaustive

extraction, the solvent was removed under reduced pressure (Buchi RV-100) using rotary flash evaporator then finally dried in desiccator.

Animals used

The Male Wistar rats weighing 200-250 grams were procured from in-house animal facility of National Toxicology Centre, Pune. They were housed under standard conditions of temperature and relative humidity with 12 hr light/dark cycle. Animals were fed on standard commercial pellet diet and water *ad libitum*.

Induction of diabetes

Male Wistar rats were kept on fasting overnight and Streptozotocin (Sigma-Aldrich Ltd, Mumbai), 55 mg/kg, in 0.1M citrate buffer, pH 4.5 was administered intraperitoneally (i.p.) for the induction of diabetes [22]. The animals were bled through the retro orbital plexus and blood was collected in heparinised tube. The plasma glucose was measured in a biochemical analyzer by GOD/POD method. The rats that developed more than 250 mg/dl of plasma glucose [23] on the 3rd day of induction were selected for the study.

Animal experimentation

In the present study the animals were distributed into 12groups containing six animals each (n=6) in the following manner:

Group I (NC): Normal Control (0.1 M citrate buffer (pH 4.5)).
Group II (NC-AECD): Normal Control + aq. extract of *C. dactylon* (200mg/kg/day, p.o.,)
Group III (NC-AEPN): Normal Control + aq. extract of *P. niruri* (600mg/kg/day, p.o.,)
Group IV (DC): Diabetic Control (STZ injected rats)
Group V: D+AECD (Diabetic rats + aq. extract of *C. dactylon* 200mg/kg/day, p.o.,).
Group VI: D+AEPN (Diabetic rats + aq. extract of *P. niruri* 600mg/kg/day, p.o.,).
Group VII: SHR
Group VIII: SHR+AECD (Hypertensive rats + aq. extract of *C. dactylon* 200mg/kg/day, p.o.)
Group IX: SHR+AEPN (Hypertensive rats + aq. extract of *P. niruri* 600mg/kg/day, p.o.,).
Group X: D+SHR (Diabetic Hypertensive rats)
Group XI: D+SHR+ AECD (Diabetic Hypertensive + aq. extract of *C. dactylon* 200mg/kg/day, p.o.)
Group XII: D+SHR+ AEPN (Diabetic Hypertensive rats + aq. extract of *P. niruri* 600mg/kg/day, p.o.)

The treatment with plant extract (1 ml) was given daily for 28 days using gastric cannula. No detectable irritation or restlessness and noticeable adverse effect (i.e., respiratory distress, abnormal locomotion or catalepsy) was observed after extract administration. Throughout the experimental period, the body weight was monitored.The study was conducted for 28 days to evaluate the potential of the extracts to lower blood glucose level and mean arterial blood pressure.

Biochemical examination

During 28 days study, blood was withdrawn at an interval of 7 days from the retro orbital plexus under anaesthesia of the fasted animals. Blood glucose levels were then estimated by GOD/POD method in an auto analyzer using the commercial enzyme estimation kit (Coral Biosystems, India) besides this, parameters like total cholesterol, SGOT were monitored by using commercial kit (Coral Biosystems, India).

Blood pressure measurement

Animals were anesthetized with Ketamine/Xylazine (1:1). Mean arterial blood pressure (MABP) was recorded by tail-cuff method (ADInstruments ML125 NIBP PowerLab), at 14th day and 28th day upto end of the study and expressed as mm Hg.

Statistical analysis

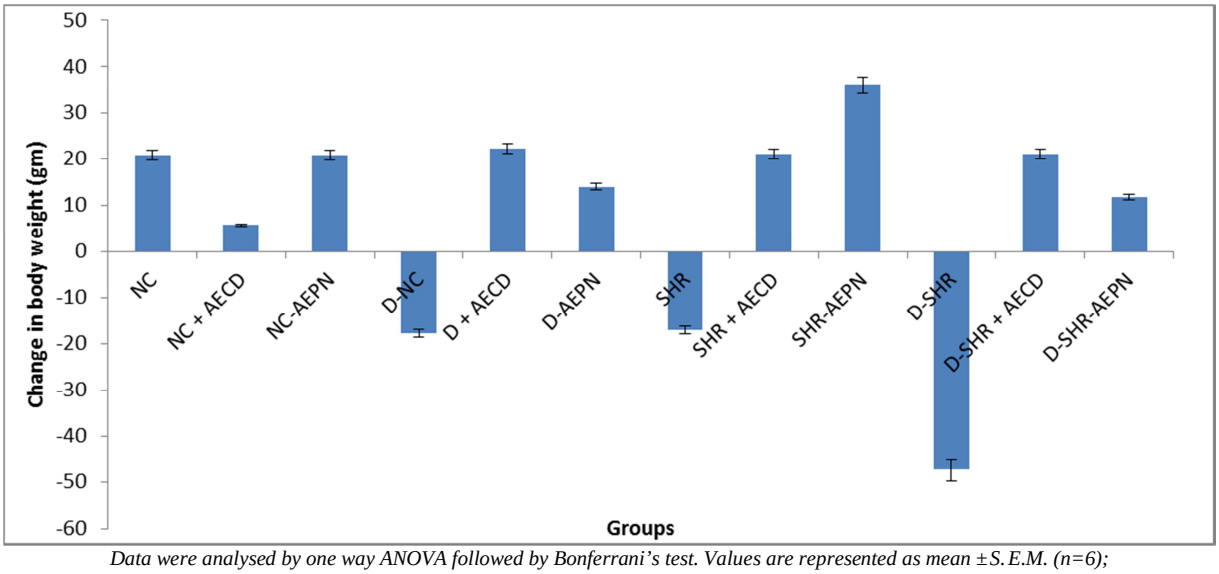
Data were expressed as mean ± SEM of six observations. Statistical analysis was done using one-way analysis of variance followed by post-hoc test, Bonferrani's test by using Graph pad Prism 5 version. Statistical significance was considered at $p< 0.05$.

RESULTS

Effect on body weight

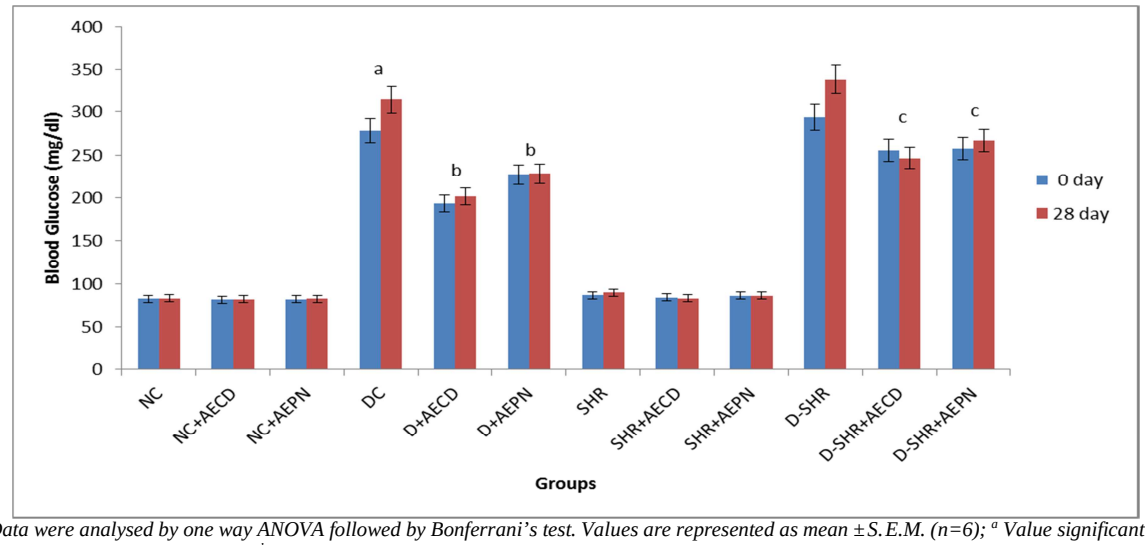
The control animals showed a linear proportion of growth in terms of weight whereas the untreated diabetic, SHR and Diabetic SHR rats were found to have significant weight loss. However, Administration of two extracts for 28 days were able to correct this aberration significantly (p<0.05). The results of all the extracts tested are presented in Fig1.

Fig.1- Effect of aqueous extract of *C. dactylon and P. niruri* on body weight of rats



Data were analysed by one way ANOVA followed by Bonferrani's test. Values are represented as mean ±S.E.M. (n=6);

Fig. 2- Effect of aqueous extract of *C. dactylon* and *P. niruri* on blood glucose



Data were analysed by one way ANOVA followed by Bonferrani's test. Values are represented as mean ±S.E.M. (n=6); [a] Value significantly different from NC,(p< 0.05); [b] Value significantly different from DC, (p< 0.05); [c] Value significantly different from D-SHR, (p< 0.05);

Effects on blood glucose

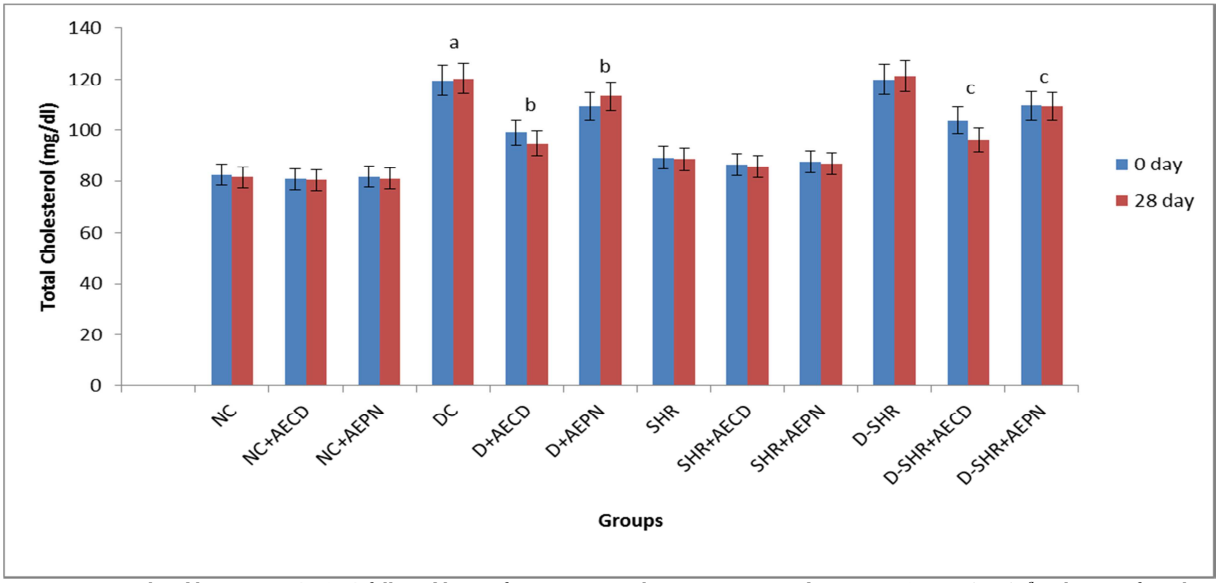
Streptozotocin induced diabetic rats showed a 73.60% rise in the plasma glucose levels as compared to normal control group. Treating those hyperglycemic rats with aqueous extract of *C. dactylon* (200 mg/kg) and *P. niruri* (600 mg/kg) resulted in significant reduction in the plasma glucose level (p< 0.05) which came at par with the normal control animals at the end of 28 days study. On the other hand the diabetic control animals which received no

treatment continued to show high plasma glucose throughout the study (Fig.2).Plasma glucose levels observed at 0 and 28 days after treatment with aq. extract of *C. dactylon* and *P. niruri* in hypertensive rats was almost similar to that of pretreatment levels.

Effects on total cholesterol

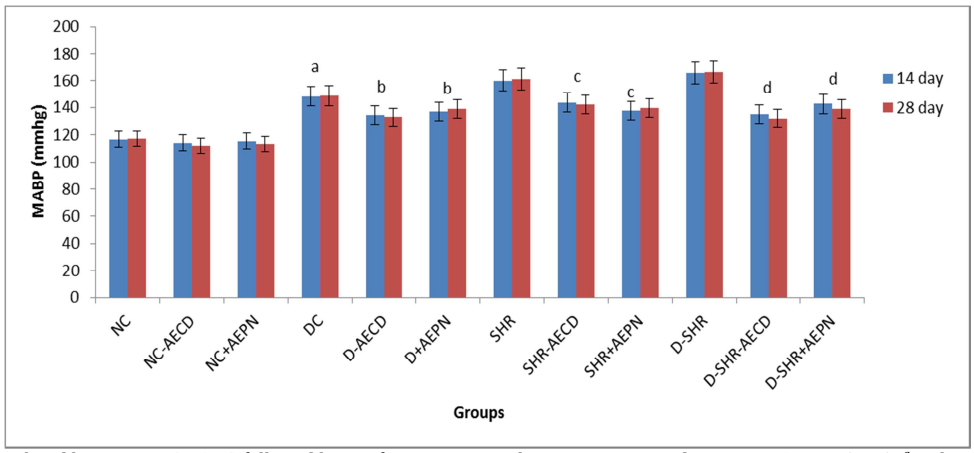
Total cholesterol level were found to be significantly (p<0.05) increased in the vehicle treated diabetic group in comparison with the control group. Treatment with two extracts for a 28 days significantly attenuated (p<0.05) the elevated total cholesterol level in comparison with the vehicle treated diabetic rats given in Fig.3. Total cholesterol levels observed at 0 and 28 days after treatment with aq. extract of *C. dactylon* and *P. niruri* in hypertensive rats was almost similar to that of pretreatment levels.

Fig.3- Effect of aqueous extract of *C. dactylon* and *P. niruri* on total cholesterol



Data were analysed by one way ANOVA followed by Bonferrani's test. Values are represented as mean ±S.E.M. (n=6); [a] Value significantly different from NC,(p< 0.05); [b] Value significantly different from DC, (p< 0.05); [c] Value significantly different from D-SHR, (p< 0.05);

Fig.4- Effect of aqueous extract of *C. dactylon* and *P. niruri* on mean arterial blood pressure



Data were analysed by one way ANOVA followed by Bonferrani's test. Values are represented as mean ±S.E.M. (n=6); [a] Value significantly different from NC, (p< 0.05); [b] Value significantly different from DC, (p< 0.05); [c] Value significantly different from SHR, (p< 0.05); [d] Value significantly different from D-SHR, (p< 0.05); after 14 days and 28 days treatment.

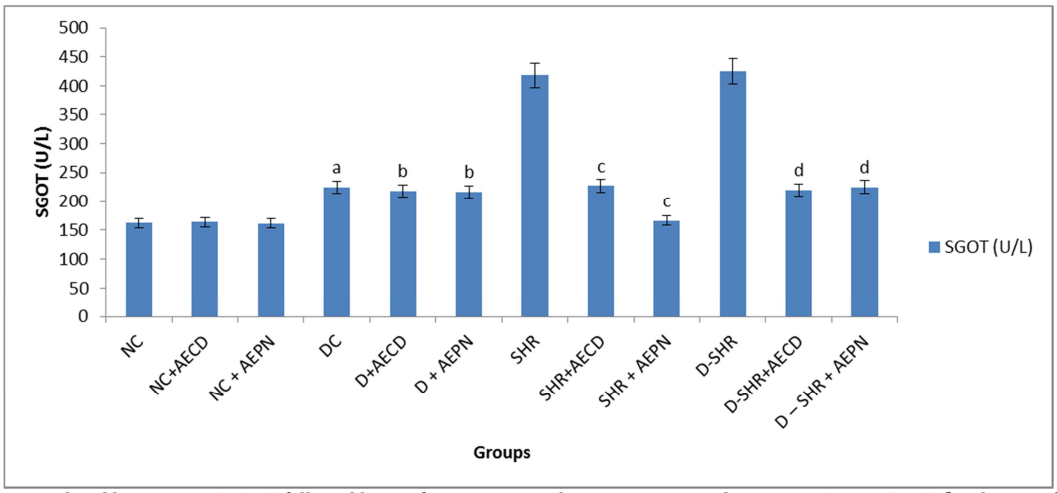
Effects on blood pressure

In present study, mean arterial blood pressure of SHR reaches upto 161.2 ± 2.120mmHg. Concomitant administration of aq. extract of *C. dactylon* (200 mg/kg) and aq. extract of *P. niruri* (600mg/kg) for 28 days decreases blood pressure as depicted in Fig.4. Mean arterial blood pressure reaches upto 166.5 ± 1.875 mmHg in SHR treated with Streptozotocin. Administration of aq. extract of herbal drugs for 28 days prevented the increase in mean arterial blood pressure in diabetic hypertensive group (D+SHR) as shown in Fig. 4.

Effects on SGOT

The effect of repeated oral administration of aq. extract of *C. dactylon* (200 mg/kg) and *P. niruri* (600mg/kg) for 28 days on SGOT in severe diabetic, SHR and D - SHR is presented in Fig.5. Serum glutamic oxaloacetic (SGOT) level decreased dynamically in D-SHR-AECD and D-SHR-AEPN, ($p< 0.05$) after challenge with herbal extracts for 28 days. SGOT level reached peak during the study in SHR and D-SHR groups.

Fig.5- Effect of aqueous extract of *C. dactylon* and *P. niruri*on SGOT at day 28



Data were analysed by one way ANOVA followed by Bonferrani's test. Values are represented as mean ±S.E.M. (n=6); [a] Value significantly different from NC, ($p< 0.05$); [b] Value significantly different from DC, ($p< 0.05$); [c] Value significantly different from SHR, ($p< 0.05$); [d] Value significantly different from D-SHR, ($p< 0.05$);

DISCUSSION

It is desirable to explore the action of herbal medicines for safe and effective management of Diabetes Hypertension as a cost effective complementary therapies.

In the present study, the aqueous extracts of *Cynodon dactylon* and *Phyllanthus niruri* were investigated for its antidiabetic-antihypertensive activity in diabetic hypertensive rats. The STZ-treated spontaneously hypertensive rat (SHR) has been extensively used an example of animal model where hypertension and diabetes occur simultaneously [33,34]. STZ-treated SHR (D-SHR) develop a hyperglycaemic syndrome, associated with other biochemical and morphological changes that to some extent approach insulin-dependent diabetes mellitus combined with hypertension [34]. Advantages of animal studies in the examination of alternative medicines and their efficacy include the ability to define experimental conditions more tightly and to undertake more detailed studies of the biologic effects of the agents being used. The mechanisms by which Streptozotocin brings about its diabetic state include selective destruction of pancreatic insulin secreting β- cells, which make cells less active and lead to poor glucose utilization by tissues [35].

In the present study, the administration of STZ to normal and spontaneously hypertensive rats effectively induced diabetes as reflected by glucoseurea, hyperglycemia and loss in body weight. The two plants extracts treatment showed as significant antihyperglycemic effects. But none of these extracts could produce any hypoglycemic effect in normal rats. The experimental results indicated that the aq. extracts of *Cynodon dactylon* and *Phyllanthus niruri*exhibited a potent blood glucose lowering property in diabetic rats and diabetic hypertensive rats (D-SHR). The capacity of plant extracts to decrease the elevated blood glucose level near to normal glycogenic level is an

essential trigger for the liver to revert to its normal homeostasis during experimental diabetes. These results suggested that one of the possible mechanisms by which *C. dactylon* and *P. niruri* extracts bring about their antihyperglycemic action is due to inhibition of hepatic glycogen degradation.

Induction of diabetes with STZ is associated with the characteristic loss of body weight, which is due to increased muscle wasting and due to loss of tissue proteins [36]. Diabetic rats and diabetic hypertensive rats (D-SHR) treated with the plant extracts showed significant gain in body weight as compared to the diabetic control, which may be due to its protective effect in controlling muscle wasting (i.e. reversal of gluconeogenesis and glycogenolysis) and may also be due to the improvement in insulin secretion and glycogenic control. Insulin deficiency leads to various metabolic aberrations, namely increase blood glucose, decreased protein content and increased levels of cholesterol and triglyceride [37].

Results from present study have shown that MABP was significantly elevated in DC by about 30 % compared to non-diabetic control group whereas it was very slightly increased in D-SHR by about 3 % compared to non-diabetic SHR. The increase in MABP following induction of diabetes in rats was in good agreement with a previous study [38]. Common observations in the clinic are diabetes patients generally have higher MABP than non-diabetic patients [39], but it is not clear why not in diabetic SHR. It may reflect the presence of a compensatory response that opposes elevation of MABP in the underlying state of hypertension following induction of diabetes but clearly needs further study.

Diabetic hypertensive rats treated with aqueous extract of *C. dactylon* and *P. niruri* exhibited significant decrease in MABP compared with diabetic control, SHR and D-SHR.Significant($p< 0.05$) decrease in mean arterial blood pressure by about 10.7% in diabetic rats, 12% in SHR, 22% in diabetic SHR respectively after 28 days treatment with aqueous extract of *C. dactylon* (200mg/kg of body weight) was observed. MABP was significantly decreased ($p< 0.05$) by about 13.47 % in aqueous extract of *P. niruri* (600 mg/kg body weight) treated group compared with SHR group, 20.85 % in aqueous extract of *P. niruri* treated group compared with D-SHR group [40]. Decline in mean arterial blood pressure in diabetic rats treated with aqueous extract of *P. niruri* was not significant.

SGOT is an enzyme found mainly in heart muscle, liver cells, skeletal muscle and kidneys. Injury to these tissues results in the release of the enzyme in blood stream. Elevated levels are found in myocardial infarction, cardiac operations, hepatitis, cirrhosis, acute pancreatitis, acute renal diseases, and primary muscle diseases. In present study, administrations of aqueous extracts of *C. dactylon* and *P. niruri* shows significant ($p< 0.05$) decrease in SGOT level in diabetic and hypertensive animals. This result signifies that aqueous extracts of *C. dactylon* and *P. niruri* protects theorgans from injury or damage due to high blood pressure or myocardial infarction, cardiac operations, primary muscle diseases.

Altogether the results obtained *in vivo* indicated that oral treatment with aqueous extracts of *C. dactylon* and *P. niruri* decrease blood pressure of diabetic and hypertensive rats. The hypotension can be correlated to as indicated by prevention of abnormal vascular reactivity to constrictor and dilator stimuli in the vasculature,reduced MABP. One important observation was the aqueous extracts of plants did not interfere with the animal growth throughout the study. This is a positive sign of biosafety of the extract to treat diabetic hypertension without affecting the normal body functions.

The presences of glycoside, flavonoid, saponins, tannin, sterol and carbohydrate in aqueous extracts of*C. dactylon* and *P. niruri*, which are known to be bioactive for the management of hypertension and diabetes, may be responsible for its action. It is well known that certain flavonoids exhibit hypoglycaemic activity and is also known for their ability of beta cell regeneration of pancreas. Sterols have also shown to decrease blood sugar in experimental animal models. The cardiac glycosides have also been proved for its cardio-protective and cardio tonic activity thus, the significant antihypertensive effect of aqueous extracts of *C. dactylon* and *P. niruri* may be due to the presence of more than one antihypertensive principle and their synergistic properties.

To evaluate fast and short-lasting effect of the isolated compounds, new pharmacodynamic and pharmacokinetic studies of the plant chemical constituents should be developed in contrast with the delayed onset of the hypotension and the slow washout after oral administration.

CONCLUSION

The present study was conducted to evaluate the antidiabetic antihypertensive activity of two herbal extracts in ratswith simultaneous type 2 diabetic and hypertension. After completion of the study protocol, it was found that with test, the serum level of glucose and total cholesterol improved significantly (p<0.05) as compared to diabetic control, and in comparative evaluation the two plants found to be safe as they did not shown any sign of acute toxicity. Meant arterial blood pressure was significantly reduced (p<0.05) in groups treated with herbal plant extracts compared with control. The aqueous extract of *Cynodon dactylon* was found to be more efficacious as compare to aqueous extract of *Phyllanthus niruri*. Hence, the data of present study provide impetus for further molecular and mechanistic studies on the therapeutic action of *Cynodon dactylon* and *Phyllanthus niruri* extracts, before they can be considerable as a possible replacement or adjuvant in the management of diabetes hypertension. Further investigations on identification of the active principles and their mode of action are needed to explore the molecular mechanisms involved in the observed effects.

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REFERENCES

[1] H. King, R. E. Aubert, W. H. Herman, *Diabetes Care*,**1998**, vol. 21, no. 9, pp. 1414-1431.
[2] A. V. Chobanian, G. L. Bakris, H. R. Black et al., *The Journal of the American Medical Association*,**2003,** vol. 289, no. 19, pp. 2560–2572,
[3] P. M. Kearney, M. Whelton, K. Reynolds, P. Muntner, P. K. Whelton, J. He, **2005**, *The Lancet*, vol. 365, no. 9455, pp. 217–223.
[4] R. M. Lago, P. P. Singh, and R. W. Nesto, *Nature Clinical Practice Endocrinology & Metabolism*, **2007**, vol. 3, no. 10, p. 667.
[5] Dhar U, RawalRS, Samant SS, Airi S, Upreti J, *Current Sci.*,**1999**, 76: 36–40.
[6] Farnsworth NR, Soejarto DD,Cambridge University Press, Cambridge. **1991**; pp 25–51.
[7] Pei Shengji, *Pharma. Botany*,**2001**; 39:74–79.
[8] Dhar, M.L.,Dhawan, M.,Melhrotra,C.L.,**1968**, *Indian.J.Exp.Biol*.6,232–247.
[9] Sindhu, G.,Ratheesh, M.,Shyni,G.L.,Helen,A.,**2009**, *Immunopharmacol. Immunotoxicol*, 31,647–653,
[10] Sadki, C.,Hacht, B.,Souliman,A.,Atmani,F., *J. Ethnopharmacol*,**2010**,128, 352–356,
[11] Ahmed, S., Reza, M.S.,Jabbar, A., *Fitoterapia*, **1994**, 65,463–464.
[12] Najafi, M.,Nazemiyeh,H.,Ghavimi,H.,Gharakhani,A.,Garjani,A.,.*DARUJ.Pharmaceut.Sci*.**2008**, 16,233–238.
[13] Garjani,A.,Afrooziyan,A.,Nazemiyeh,H.,Najafi,M.,Kharazmkia,A., Maleki-Dizaji ,N.,. *BMC. Complement. Altern. Med.* **2009**, 9, 28,
[14] Mangathayaru,K.,Umadevi,M.,Reddy,C.U., *J. Ethnopharmacol*, **2009**, 123,181–184,
[15] Savali, A.S.,Biradar,P.R.,Jirankali,M.C., *Int.J.Pharm.Pharmaceut.Sci*.**2010**, 2, 69–73.
[16] Kirtikar, K.K.,Basu,B.D.,.IndianMedicinalPlants,LalitMohan,India **1980,** seconded. Publication, p.2650.
[17] UnciniManganelli RE, Tomei PE, *J Ethnopharmacol*,**1999**; 65: 181–202.
[18] Auddy B, Ferreira M, Blasina F, *J Ethnopharmacol*,**2003**; 84: 131-138.
[19] Yesilada E, Sezik E, Honda G, Takaishi Y, Takeda, Y, Tanaka T. *J Ethnopharmacol*,**1999**; 64: 195–210.
[20] Council of Scientific and Industrial Research, The Wealth of India (Raw Materials): 2nd supplement series. Vol.I. CSIR, New Delhi, **1948**,pp.331–332.
[21] Evans,W.C., Trease, G.E., Evans, D., TreaseandEvansPharmacognosy, Elsevier India Pvt. Limited, fifteenth ed. Elsevier. **2002**, ADivision of Reed, pp. 204–205.
[22] Chopra, R. N., Nayar, S. L., Chopra, I. C. *Glosssary of Indian medicinal plants*.Catholic Press, Ranchi, CSIR, New Delhi,**1986**; India.
[23] Chang, C. C., Lien, Y. C., Liu, K. C., Lee, S. S. *Phytochemistry*.**2003**;63: 825–833.
[24] Yan F, Zhang Q, Jiao L, Han T, Zhang H, Qin L, Khalid R. *Phytomedicine*.**2009**; 16: 805-813.
[25] Gnabre JN, Itob Y, Mab Y, Huanga RC . *J Chromatogr*.**1996**;*719*: 353-364.
[26] Popova MP, Chinou IB, Marekov IN, Bankova VS. *Phytochemistry*.**2009**; 70: 1262-1271.

[27] Hayashi Y, Matsushima M, Nakamura T, Shibasaki M, Hashimoto N, Imaizumi K, Shimokata K, Hasegawa Y, Kawabe T . *Biochem Biophl Res Co.*,**2012**; 417: 169- 174.
[28] Muzitano MF, Cruz EA, De Almeida AP, Da Silva SA, Kaiser CR, Guette C, Rossi-Bergmann B, Costa SS. *Planta Med*.**2006**; 72: 81-83.
[29] Guardia T, Rotelli AE, Juarez AO, Pelzer LE. *Farmaco*.**2001**; 56: 683-687.
[30] Calixto JB, Santos RSA, Filho CV, Yune SRA. *Gen Pharmacol*.**1995**; 26: 1499-1506.
[31] Kitisin, T., Reinli, K., Block, G. Sirriaj.*Hosp. Gaz*. **1952**; 4: 641–649.
[32] Ueno, H., Horie, S., Nishi, Y., Shogawa, H., Kawasaki, M., Suzuki, S., Hayashi, T., Arisawa, M., Shimizu, M., Yoshizaki, M. *J. Nat. Prod.* **1988**;51: 357–359.
[33] Jerald EE, Joshi SB, Jain DC. *Indian J Pharmacol*.**2008**; 40: 256-260.
[34] Paul T, Das B, Apte KG, Banerjee S, Saxena RC. *J Diabetes Metab*.**2012**; 3: 226.
[35] Lenzen S. *Diabetologia* **2008**; 51: 216-226.
[36] Li WL, Zeng HC, Bukuru J and De Kimpe N. *J. of Ethnopharmacology*, **2006**; 92:1-21.
[37] Tenpe CR and Yeole PG. *International Journal of Pharm Tech Research*,**2009**;1(1):43-49.
[38] Haidara, M.A., Mikhailidis, D.P., Rateb, M.A., Ahmed, Z.A., Yassin, H.Z., Ibrahim, I.M., Rashed, L.A J *Diabetes Complications*.**2009**; 23(2): 130.
[39] Kumagai, S., Kai, Y., Hanada, H., Uezono, K., Sasaki, H. *Metabolism*.**2002**; 51, 1247–1252.
[40] Bharati D, Rawat S, Sharma P, Srivastava B; *Ann Clin Exp. Hypertension*, **2015**, 3(3): 1031.