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Original Article

DOSAGE RESPONSE OF *PIMPINELLA TIRUPATIENSIS* TUBEROUS ROOT EXTRACT ON HYPERGLYCEMIC CONDITION IN STZ- INDUCED DIABETIC RATS WITH REFERENCES TO SHORT AND LONG TERM TREATMENT

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ABSTRACT

Objectives: To evaluate the antidiabetic effect of three extractions [*n*-Hexane (*n*-HE), ethyl alcohol (EAE) and aqueous extract (AE)] of *Pimpinella tirupatiensis* (*Pt*) tuberous root on the fasting blood glucose (FBG) level of rats during streptozotocin (STZ) induced diabetes.

Methods: Experimental diabetes was induced by intra peritoneal injection of STZ (40 mg/kg b.w.). FBG level was determined at 0 hour (before extract administration), 1st, 3rd 5th and 7th hour (after extract administration) by using electronic glucometer (accucheck).

Results: We observed, AE showed a maximum efficacy with a dosage of 750 mg/ kg b.w. at 5th hour which is about 49% reduction in FBG level over zero time values. Hence, we have selected 750 mg dose of AE of *Pt* to investigate the long term effect on down regulation of blood glucose level. Oral administration of AE (750 mg/kg b.w./day) for 30 days showed a significant antihyperglycemic effect in diabetic rats. However, no significant changes were noticed in blood glucose level in normal rats treated with AE alone. It seems AE considerably reduced the blood glucose concentration in a similar manner to that of reference drug *glibenclamide* (20 mg/kg b.w.) in diabetic rats.

Conclusion: These results suggest that *Pimpinella tirupatiensis* aqueous extract is beneficial in the control of diabetes by reduction of blood glucose levels.

Keywords: *Pimpinella tirupatiensis,* Diabetes mellitus, Fasting blood glucose level.

INTRODUCTION

Diabetes is a disorder of carbohydrate, fat and protein metabolism attributed to diminished production of insulin or mounting resistance to its action. Chronic hyperglycemia during diabetes causes glycation of body proteins that in turn leads to secondary complications affecting eyes, kidneys, nerves and arteries [1]. The World Health Organization (WHO) predicts about 300 million people would have diabetes mellitus by the year 2025 [2]. There is an increasing demand from patients for the natural products with antidiabetic activity due to side effects associated with the use of insulin and oral hypoglycemic agents [3, 4]. The available literature pertaining to medicinal plants showed that there are more than 400 plant species which have hypoglycemic activity [5, 6] and in recent time several laboratories are involved in isolating new herbal hypoglycemic agents. There are several plants with antidiabetic potentiality whose antidiabetic effect is yet to be established. *Pimpinella tirupatiensis (pt)* is one among them. It is an endemic species and restricted to Seshachalam hills, Eastern Ghats of India. The vernacular name of *Pt* is *Adavi kothimeera* which belongs to Apiaceae (Umbelliferae) family. Though, there is no scientific evidence for the antidiabetic properties of *Pt,* the tribal population of Tirumala region (in Andhra Pradesh, India) has been using this plant in the management of diabetes mellitus as folk medicine. The main objective of the present investigation was to ascertain the scientific basis for the use of this plant in the management of diabetes, in streptozotocin induced type 2 diabetic rats.

MATERIALS AND METHODS

Animals

Wistar strain male albino rats, aged 3 months (200-250g) were used for the present study. The rats were maintained on the standard pellet diet and provided access to water *ad libitum*. They were housed in clean, dry polypropylene cages and maintained in a well ventilated animal house with 12 h light- 12 h dark cycle. All the experiments were carried out between 8 and 10 am in order to avoid circadian rhythm induced changes.

The experiments were carried out in accordance with guidelines and protocol approved by the Institutional Animal Ethics Committee (Regd. No. 438/01/a/CPCSEA/ dt.17.07.2001) in its resolution number 09 (iii)/a/CPCSCA/IAEC/07-08/SVU/Zool/KSR-SRR/dated 26/6/08.

Chemicals

Streptozotocin and *glibenclamide* were obtained from Sigma Company (St. Louis, MO, USA),

Induction of diabetes

Diabetes was induced in healthy male wistar strain albino rats aged about 3 months, with body weights ranging from 200 – 250 g, by a single intra peritoneal injection of freshly prepared STZ (40 mg/kg b.w.) Dissolved in ice cold 0.1M citrate buffer (pH 4.5) after allowing the rats for overnight fasting for 12-15 hours as per the method followed by Rakietenet al [7]. 8 hrs after STZ administration the rats were kept for the next 24 hours on given 15% glucose solution to prevent hypoglycemia, as STZ is capable of producing fatal hypoglycemia due to destruction of β cells which in turn results into massive pancreatic insulin release. Diabetes was assessed by determining the fasting blood glucose after 48 hrs of injection of STZ. The blood glucose levels in STZ rats were increased markedly to higher levels than normal. After a week, when the condition of diabetes was stabilized, rats with marked hyperglycemia (blood glucose level ≥ 250 mg) were selected. Blood was collected from the tail vein of rats.

Collection of plant tuberous roots

Pt was collected from Tirumala Hills of Chittoor district, Andhra Pradesh, India and the plant material was taxonomically identified and authenticated by the concerned herbarium officer, Dept of Botany, S.V. University Andhra Pradesh. Voucher specimen was deposited in the campus. *Pt* tuberous roots were dried and powdered. The powder was stored in airtight containers and was used for the extraction of the bioactive compounds in different solvents.

Preparation of extracts

Pt tuberous root powder was soaked in individual solvents (water or 95% ethanol or n-hexane) in different glass jars for 2 days at room temperature and the solvent was filtered. This was repeated three to four times until the extract gave no coloration. The extracts were distilled and concentrated under reduced pressure in the Rotary Evaporator (Model no-HS-2005V) and finally freeze dried by lyophilizer (Lyodel). These extracts were used for further studies. The yield of the aqueous, ethanolic and *n*-hexane extracts was 8.5, 5.9 and 2.1% respectively (w: w in terms of dried starting material) (8).

Acute toxicity studies

The acute toxicity study for the aqueous extract was performed using Wistar strain male albino rats according to OECD Guideline 423. Four groups of three rats each were used for the study. Group I served as control and received normal saline (0.9%). Group II received the single oral dose of n-HE (1000 mg/kg), Group III received the single oral dose of EAE (1000 mg/kg) Group IV received the single oral dose of AE (1000 mg/kg). The animals were observed for toxic effects at short intervals of time for 24h and then daily for 14 days.

Short term effect of single administration of different extracts of *Pt* on FBG level in normal and diabetic rats

In this experiment a total of 78 albino rats were taken which were divided into 2 batches each batch containing 39 animals. Batch I rats were induced with diabetes by the single administration of STZ whereas, batch II rats were considered as normal.

The diabetic rats of batch I were divided into 13 groups, each group containing 3 animals. Group I (DC) served as diabetic control received 0.9% normal saline orally. Group II (EAE-250), Group III (EAE-500), Group IV (EAE-750) and Group V (EAE-1000) diabetic rats were treated orally with ethyl alcohol extract (EAE) of *Pt* with a dose of 250 mg, 500 mg, 750 mg and 1000 mg/kg b.w. respectively. Group VI (*n*-HE-250), Group VII (*n*-HE-500), Group VIII (*n*-HE-750) and Group IX (*n*-HE-1000) diabetic rats were treated orally with *n*-Hexane extract (*n*-HE) of *Pt* with a dose of 250 mg, 500 mg, 750 mg and 1000 mg/kg b.w. respectively. Where as, Group X (AE-250), Group XI (AE-500), Group XII (AE-750) and Group XIII (AE-1000) diabetic rats were treated orally with aqueous extract (AE) of *Pt* with a dose of 250 mg, 500 mg, 750 mg and 1000 mg/kg b.w. respectively

Batch II normal rats were also divided in to 13 groups on the similar lines as described earlier. But the only difference was batch II animals were normal where as batch I animals are diabetic rats.

The antidiabetic effect of the *Pt* extracts was assessed in normal and diabetic rats after a single administration by measuring FBG level at 0 hour (before drug administration), 1, 3, 5 and 7 hour intervals (after drug administration).

Long term effect of daily administration of AE of *Pt* on FBG level and body weight changes in diabetic and normal rats

5 groups of animals, containing 6 animals in each group were divided as follows: Group I normal control (NC). Group II diabetic control (DC), Group III (D+AE) diabetic animals treated orally with 750 mg/kg/day of *Pt* aqueous extract for 30 days, Group IV (N+AE) normal animals treated orally with 750 mg/kg/day of *pt* aqueous extract for 30 days and group V (D+GLB) diabetic animals treated with 20 mg/kg/day of Glibenclamide for 30 days.

Blood samples were collected from the tail vein and blood glucose levels were estimated on Zero day (Initial) and 30th day (Final). Blood glucose levels were determined by using electronic glucometer (Accucheck). Body weight changes were measured by the digital balance on Zero day and 30th day.

Statistical analysis

The data obtained was expressed as mean values with their SE. In order to carry out statistical analysis, the data was analyzed by using SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and M.S. Office, excel software. In our study, the comparison is with respective groups and zero time values, hence one way analysis of variance technique was applied to observe the significance between the groups and hours. The post – Hoc test Duncan's multiple range test and Dunnet test was also performed to know the significant difference among the groups and hours. Entire statistical analysis was carried out at $p< 0.05$, 0.01and 0.001 levels.

RESULTS

Acute toxicity studies

In acute toxicity study, n-HE, EAE, AE treated animals did not show any change in their behavioral pattern. There was no significant difference in the body weights and food consumption when compared to the vehicle treated group. Also, no gross pathological changes were seen. Thus, it was concluded that n-HE, EAE, AE were safe at 1000 mg/kg.

FBG levels were estimated with different doses (250mg, 500mg, 750mg and 1000 mg) and at time intervals of 1, 3, 5 and 7 hours with three extractions of *Pt* in hyperglycemic and normal rats.

Short term effect of single administration of *Pimpinella tirupatiensis* different extracts on FBG levels in diabetic rats.

The short term effect of three extracts of *Pt* on the FBG level of diabetic rats is shown in the table 1. A single administration of AE of 250 mg, 500 mg, 750 mg and 1000 mg/kg b.w. Showed a maximum reduction in FBG level at 5th hour which is about 8.6, 31.5, 49.7 and 16.9% respectively over zero time values. A single administration of EAE of 250 mg, 500 mg, 750 mg and 1000 mg/kg b.w. Showed a reduction in FBG level at 5th hour which is about 6.4, 8.81, 27.2 and 17.6% respectively over zero time values. *n*-HE with any dose showed a non significant reduction in FBG level at all time intervals in diabetic rats.

Short term effect of single administration of *Pimpinella tirupatiensis* different extracts on FBG levels in normal rats.

The short term effect of three extracts of *Pt* on FBG level of normal rats is shown in the table 2. All these three extracts of *Pt* with selected doses did not show any significant hypoglycemic effect on FBG level in normal rats

Long term effect of daily administration of *Pimpinella tirupatiensis* aqueous extract on FBG level and body weights of diabetic and normal rats

The Blood glucose levels were estimated on Zero day and on 30th day. The long term effect of daily administration of 750 mg of AE on FBG level and body weight changes of diabetic and normal rats is shown in table 3 and 4.

The FBG level of diabetic control (DC) rats was significantly (<0.01) higher than those of saline control rats. Administration of STZ led to significant elevation of FBG which was maintained over a period. AE with a dosage of 750 mg/kg b.w. produced maximum glucose lowering effect in diabetic rats. Treatment with *glibenclamide* (an oral hypoglycemic agent, sulfonyl urea) with a dosage of 20 mg/kg b.w. resulted in lowering of FBG level in diabetic rats. Thus, the antihyperglycemic efficacy of the AE (45.6%) was near to the effect of *glibenclamide* (50.4%) a well known hypoglycemic drug. After completion of treatment period, a marked decrease in body weight was observed in the diabetic group of rats when compared with saline control group rats.

Oral administration of AE to diabetic rats resulted in a notable increase in body weight when compared to that of diabetic control group. The gain in the body weight of AE treated diabetic rats was near to the body weights of *glibenclamide* treated diabetic animals. AE could not bring any hypoglycemic effect in normal treated rats. The body weights are more or less similar in all groups before treatment with AE. The body weights of control rats treated with AE showed no significant changes when compared to the saline control rats.

DISCUSSION

The present study was conducted to evaluate the antidiabetic activity of different extracts from *Pimpinella tirupatiensis*, considered as antidiabetic plant by the local folklore without scientific evidence for the first time identified by our research team

to secure a berth in the exploration of antidiabetic plants. We observed different extracts from *Pimpinella tirupatiensis* did not exhibit any sign of toxicity.

In the present study, among all the selected doses of extractions of *Pt*, the dosage of 750 mg/kg/ b.w. of AE produced maximum antihyperglycemic activity bringing down the blood glucose levels to almost normal. The percentage of fall of blood glucose levels is 49% in diabetic rats after treatment of 5 hours with the dose mentioned above. In STZ rats, the AE caused a significant reduction in blood glucose levels within 1 hour, while maximal reduction was reached at 5th hour.

After 5 hours, a decrease in the reduction of FBG level was observed. The AE and EAE of *Pt* caused a significant reduction in FBG level with a dosage of 250 mg/kg/b.w. while maximal reduction was reached for 750 mg/kg/b.w.

Table 1: Short term effect of different doses of EAE, *n*- HE and AE of *Pimpinella tirupatiensis* on fasting blood glucose levels in STZ - induced diabetic rats

Time (h)	Fasting Blood Glucose Levels(mg/dl)												
	DC	EAE-250mg	EAE-500mg	EAE-750mg	EAE-1000mg	n-HE-250mg	n-HE-500mg	n-HE-750mg	n-HE-1000mg	AE-250mg	AE-500mg	AE-750mg	AE-1000mg
0 h	326.6±6	320±5.7	325.3±6.2	330±5.7	314±5.8	340±3.4	345±2.8	345±5.7	329.3±2.3	319±2	333.3±7.7	324.3±7	329.3±1.7
1 h	321.3±2.9 (1.6)	310±2.8 (3.2)	322.6±2.6 (0.82)	320±5.7 (3)	305±2.8 (-2.86)	335±2.8 (1.4)	340±2.3 (1.4)	345±6 (1.48)	325±2.8 (1.3)	314.6±5.2 (1.3)	303±2.8* (7.5)	294±2** (9.3)	311.6±0.8* (5.3)
3 h	316.6±3.3 (3.0)	308±1.5 (0.7)	304.3±0.8* (4.91)	293.3±6.6* (11.1)	282±1* (10.19)	328±6.9 (3.5)	334.3±2.9 (3.1)	340±3 (2.84)	321.6±2.3 (2.3)	305±2.8 (4.3)	280.3±8.9** (15.9)	248±2*** (23.5)	298.6±4.6** (9.3)
5 h	318±4.04 (2.6)	299.3±2.3** (6.4)	296±4.4** (8.81)	240±10*** (27.2)	258.6±4.9** (17.6)	323±6 (5)	331.3±5 (3.96)	335±2.8 (4.2)	319.6±4.5 (2.9)	291.3±5.7** (8.6)	228.3±5.8** (31.5)	163±3.7*** (49.7)	273.6±6.3*** (16.9)
7 h	323.3±2.8 (1)	307±1.1 (4.0)	310±2.3 (4.71)	260±11.5*** (21.2)	265±14.3** (15.6)	330±5.1 (2.9)	333.3±2.4 (3.38)	336±2.3 (4)	321.3±5 (2.4)	304±3 (4.7)	241.6±12.5*** (27.5)	181±2.4*** (44.1)	304.3±3.7** (7.5)

Values are expressed Mean ± SE, Values in Parenthesis denote percent change over respective zero time values, Statistically significant difference to the corresponding zero time value; * P≤0.05,**P≤0.01,***p≤ 0.001,

Table 2: Short term effect of different doses of EAE, *n*- HE and AE of *Pimpinella tirupatiensis* on fasting blood glucose levels in normal rats

Time (h)	Fasting Blood Glucose Levels(mg/dl)												
	NC	EAE-250mg	EAE-500mg	EAE-750mg	EAE-1000mg	n-HE-250mg	n-HE-500mg	n-HE-750mg	n-HE-1000mg	AE-250mg	AE-500mg	AE-750mg	AE-1000mg
0 h	87±1.2	84.8±0.72	85±4.04	89.3±2.60	86.66±1.58	83±1.52	83.3±0.88	88.6±1.45	85.6±0.16	93±2.3	88±3.78	86.3±1.33	88.3±1.45
1 h	85.5±0.76 (2.27)	84.3±0.81 (0.58)	86.3±0.88 (1.56)	87.3±1.45 (2.33)	84.5±0.86 (2.49)	83±2.51 (0.1)	82.6±0.88 (0.80)	90±0.57 (1.51)	85.5±0.28 (0.18)	91.3±0.88 (1.79)	85±1.73 (3.40)	85.33±2.02 (1.15)	86.6±1.20 (1.89)
3 h	85.8±0.72 (1.34)	82.6±0.66 (2.55)	83.5±2.29 (1.76)	89.6±1.20 (0.36)	86.1±4.47 (0.57)	85.6±0.66 (3.20)	84.5±1.25 (1.46)	89.3±0.66 (0.75)	84.5±0.28 (1.35)	93.6±0.66 (0.70)	87±0.57 (1.13)	83.6±2.02 (3.09)	86±0.57 (2.63)
5 h	86.3±0.72 (0.77)	84.3±1.2 (0.58)	81.6±2.66 (3.92)	87.6±3.52 (1.86)	85.1±1.96 (1.73)	85.6±1.52 (3.20)	82±1 (1.59)	88.3±1.85 (0.40)	84.6±0.44 (1.23)	95.3±1.66 (2.50)	86.6±1.20 (1.52)	86.6±3.33 (0.38)	85.6±2.02 (3.2)
7 h	85.6±1.36 (1.54)	82±1.52 (3.33)	82.6±1.78 (2.75)	89.6±0.88 (0.36)	87.5±1 (0.96)	84±0.7 (1.2)	81±1.33 (2.49)	89±2.08 (0.38)	84.5±0.57 (1.35)	96.6±1.66 (3.8)	87.3±0.80 (0.79)	85±0.57 (1.54)	87.6±0.87 (0.75)

Values are expressed Mean ± SE, Values in Parenthesis denote percent change over respective zero time values, Statistically significant difference to the corresponding zero time value; P ≤0.05,

Table 3: Initial and Final FBG Levels (mg/dl) (Before treatment) of Normal Control (NC), Diabetic Control (DC), AE treated Diabetic (D+AE), AE treated Normal (N+AE) and *Glibenclamid*e treated Diabetic (D+GLB) rats

Groups	Mean ±SE	
	Initial FBG levels	Final FBG levels
NC	83^{a}±0.57	84^{a}±0.57 (1.2)
DC	297.5^{b}±3.81	370.8^{b}±5.06(24.6)
D+AE	305^{b}±4.08	165.8^{c}±5.38(45.6)
N+AE	81.5^{a}±0.42	82.5^{a}±0.76(1.22)
D+GLB	303.8^{b} ±3.83	150^{c}±5.32 (50.4)

Values in the table are represented as Mean ± SE., Values in Parenthesis denote percent change over respective Initial values, Means not sharing a common superscript differ significantly at P<0.01 compared to Normal control rats.

Table 4: Initial and Final Body weights (grams) (Before treatment) of Normal Control (NC), Diabetic Control (DC), AE treated Diabetic (D+AE), AE treated Normal (N+AE) and *Glibenclamid*e treated Diabetic (D+GLB)

Groups	Mean ±SE	
	Initial Body weights	Final Body weights
NC	230^{a}±1.29	254.1^{a}±3.96 (10.4)
DC	216.6^{b} ±1.05	124.1^{b}±3.51(42.7)
D+EA	215.8^{b}±2.38	205^{c}±2.71(5)
N+EA	233.3^{a}±2.47	259.1^{a}±3(11.1)
D+GLB	212.5^{b}±4.23	210^{c}±2.38(1.17)

Values in the table are represented as Mean ± SE., Values in Parenthesis denote percent change over respective Initial values, Means not sharing a common superscript differ significantly at P<0.01 compared to Normal control rats

The ability of lowering blood glucose activity of *Pt* at a dose higher than 750 mg /kg/ b.w. could be due to reduced or no effect of the components present in the extracts Kameswara Rao et al [9] reported that ethanolic fraction of *Pterocarpus santalinus* at doses higher than 0.25g/kg/b.w. decreased reduction in FBG level in diabetic rats. The EAE also produced significant antihyperglycemic activity (a maximum of 27.2%) when given with a dose of 750 mg/kg/b.w. in diabetic rats. But n- HE of *Pt* did not produce any blood glucose lowering activity in diabetic and normal rats. The antihyperglycemic activity of *Pt* may be due to its stimulating effect on the remnant beta cells or improvement in insulin action at cellular level or it could also be due to its insulin like effect.

In this study we found that *Pimpinella tirupatiensis* decreased blood glucose levels in STZ diabetic rats but not in normal rats. We observed AE showed the maximum antihyperglycemic efficacy than the other extracts. Jaspreet Virdi et al [10] reported that aqueous extract of *Momordica charantia* showed the maximum antihyperglycemic efficacy when compared to chloroform and methanol extract. Treatment with *Aporosa lindleyana* aqueous and ethanol extracts decreased the blood glucose levels in STZ-induced diabetic rats [11].

Antidiabetic plants exert their activity through a variety of mechanisms such as improving insulin sensitivity, augmenting glucose-dependent insulin secretion and stimulating the regeneration of islets of langerhans in pancreas of STZ-induced diabetic rats [12]. In the present study the antihyperglycemic efficacy of the AE (45.6%) was near to the effect of glibenclamide (50.4%) a well known hypoglycemic drug. The blood glucose lowering activity of glibenclamide is an indication of the presence of some remnant β-cells, as glibenclamide is known to stimulate insulin secretion from β-cells. The aqueous extract of *Pimpinella tirupatiensis* may has stimulating effect on the production of insulin from remnant β cells. It may also exert its blood glucose lowering activity by enhancing the utilization of glucose in hepatic and peripheral tissues through the action of bioactive principles on the up regulation of key enzymes involved in the carbohydrate metabolism. The mechanism of this antihyperglycemic effect of the extract is not elucidated in this study. A possible mechanism of action is that, the extract might have stimulated residual pancreatic mechanism, probably increasing peripheral utilization of glucose [13]. Similar reports are available on the oral administration of aqueous extract of leaves of *Gymnema sylvestre* which normalized blood sugar levels of diabetic animals through β-cell regeneration [14]. The significant and consistent antihyperglycemic effect of aqueous extract of *Pimpinella tirupatiensis* in induced diabetic rats indicates that this effect can be mediated by stimulation of glucose utilization by peripheral tissues.

AE and EAE of *Pimpinella tirupatiensis* did not produce any hypoglycemic activity in normal rats, whereas the same extracts showed the maximum antihyperglycemic activity (49.7 and 27.2%) in diabetic rats after 7 h of treatment. Our results are similar to the reports of Chakravarthy *et al* [15, 16] who reported the hypoglycemic activity with *Pterocarpus marsupeum* only in diabetic rats but not in normal rats. KameswaraRao *et al* [9] reported that ethanolic, aqueous and hexane extracts of *Pterocarpus santalinus* showed significant reduction in FBG level in diabetic rats but not in normal rats. Tchamadeu *et al* (17) reported a single administration of the DCMM stem bark extract of *Mammea africana* did not decrease blood glucose level in normal rats, but induced a significant fall in diabetic rats at the 5th hour. The normal rats being in homeostasis, this plant extract could cause very negligible suppression of normal regulatory mechanisms involved in carbohydrate metabolism. Water extract of *S. fruticosa* did not show a clear hypoglycemic effect in normoglycemic rats. With the exception of the slight decrease in the blood glucose level between the second and the third hour this decrease seemed to be restored within the fourth hour, probably by the release of counter-regulation of hormones (mainly by glucagon) [18]. From the above results we can conclude that the aqueous extract of the *Pimpinella tirupatiensis* tuberous root with a dose of 750 mg/kg b.w. has beneficial effect in reducing the blood glucose level of diabetic rats. This effect may be due to the presence of flavanoids, tannins, polyphenolic compounds, alkaloids and other constituents present in the root which could synergistically or independently improve the glucose disposal.

CONCLUSION

From this study we understand that *Pimpinella tirupatiensis* tuberous root has effective blood glucose lowering activity and can be useful in the management of diabetes. Further experiments are needed to identify the active antihyperglycemic components and to determine the mechanism of action.

CONFLICT OF INTERESTS

Declared None

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