*Original research paper

EFFECTS OF *CAPSICUM FRUTESCENS* SUPPLEMENTED DIET (C.F.S.D) ON FASTING BLOOD GLUCOSE LEVEL AND BIOCHEMICAL PARAMETERS IN ALLOXAN INDUCED DIABETIC WISTAR RATS.

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ABSTRACT

Aim of the study: Assessment of the effects of *Capsicum frutescens* supplemented diet (C.F.S.D) on biochemical parameters in alloxan induced diabetic Wistar rats.

Experimental Design: Forty male Wistar rats weighing between 130 to 150g were divided into four groups. Group 1 served as a normal control and received normal feed. Group 2 (Diabetic control) received normal feed. Group 3 (Diabetic test 1) received normal feed + 1% C.F. Group 4 (Diabetic test 2) received normal feed + 2% C.F. The feeding trial lasted for three weeks. At the end of the experiments, the animals were sacrificed, blood samples were collected and the serum was further subjected to biochemical analysis using biochemical analyzer (Reflotron Plus). Indexes investigated include; AST, ALT, ALP, GGT, Creatinine, Uric acid, total cholesterol, high density lipoprotein cholesterol (HDL-c) and fasting blood sugar level.

Results: Serum AST, ALT, ALP, GGT, Creatinine, Uric acid, total cholesterol and fasting blood sugar level were increased while serum high density lipoprotein cholesterol (HDL-c) was decreased in diabetic control (group 2), when compared with normal control (group 1). The incorporation of *Capsicum frutescens* in the diet at 1% and 2 % doses significantly ($P<0.05$) reduced the fasting blood glucose level as well as the serum level of AST, ALT, ALP, GGT, Creatinine, Uric acid, total cholesterol when compared with diabetic control. Serum HDL was also significantly increased when compared with diabetic control (Table 1). Decrease in body

weight in diabetic control group and increased in body weight of 1% and 2% C.F.S.D groups were also observed (Table 2).

Conclusion: The observed improvement in the biochemical parameters of alloxan induced oxidative stressed Wistar rats by 1% and 2% *Capsicum frutescens* supplemented diet suggests *Capsicum frutescens* to possess, cardio-protective and anti-diabetic properties. This could be attributed to its Phytochemical constituents.

Recommendation: The incorporation of *Capsicum frutescens* in the diet of patients susceptible to oxidative imbalance such as diabetes mellitus is worthy of recommendation.

INTRODUCTION

Diabetes mellitus (DM) has been described as a multifactorial disease that is characterized by hyperglycemia and lipoprotein disorders (Scoppola, *et al.*, 2001), increased basal metabolic rate (Avesani, *et. al.,* 2001), defect in reactive oxygen species scavenging enzymes, as well as altered intermediary metabolism of major food substances (Avesani, *et al.*, 2001). Diabetes is a major degenerative disease in the world today (Ogbonnia, *et al.*, 2008), affecting at least 15 million people and having complications which include hypertension, atherosclerosis and microcirculatory disorders.

At least 80% of Africans rely on plant medicine for their healthcare (Sofowora, 1993). Today, medicinal plants are increasingly being used in most parts of the world as: hypolipidemic (Ugochukwu, *et al.*, 2003); antihypertensive (Ojewole and Adewole, 2007); treatment for skin diseases (Ajose, 2007) and hypoglycemic (Eddouks, *et al.*, 2003).

For the past 25 years, epidemiological studies have revealed a diminished risk of chronic diseases in populations consuming diets fortified with fruits and vegetables, (Pryor, *et al.*, 2000). It has been suggested that antioxidants found in large quantities in fruits and vegetables may be responsible for this protective effect, (Halliwell, 2004). In the past three decades, it has been experimentally documented that several common spices can also exert health beneficial physiological effects, (Srinivasan and Chandrasekhara, 1992; Srinivasan, 2005). These physiological effects of spices in most instances have been traced to the bioactive chemicals in them. Among these physiological effects of spices documented are hypolipidemic and antioxidant properties with beneficial health implications, (Manjunatha and Srinivasan, 2008).

One of such phytomedicine is *Capsicum frutescens*, a short lived evergreen shrub that usually grows from 1 to 1.5m in height and 1 to 3cm in basal stem diameter. It is commonly recognized by its fruit, the large red, orange, or yellow chili peppers that the plant produces. *Capsicum frutescens* fruits grow as long pods, and when ripe they develop their characteristic warm coloring. Its species likely originated in south or Central America. It spread quickly throughout the subtropical regions in the area and still grows wild today. The plant grows in tropical climates, because it needs a warm, humid climate to survive. It had been reportedly used in the treatment of various ailments such as Diabetes, Blood pressure [high/ low], Bronchitis, Burning feet, Arthritis, among others, (Dewitt, *et al.*, 1998).

A number of studies have shown multiple pharmacological effects of Capsicum on a variety of physiological systems such as cardiovascular system, gastro-intestinal tract, metabolic rate, and pain relief, (Chaiyata, 2003).

Previous research had shown the Chemo-Protective effect of spices among which are; *Turmeric*, *Capsicum frutescens*, *Cloves* and *Cardamom* on Correcting Iron Overload-Induced Liver Injury, Oxidative Stress and Serum Lipid Profile in Rat Model. The incorporation of chili (*Capsicum frutescens*) in the diet at 2 % significantly restored the enzyme activities of the liver AST, ALT, and ALP to normal level. The mean values of lipid profile, the MDA and serum total bilirubin were also reduced, (Eman, *et al.*, 2010).

The active substance in *Capsicum frutescens* that gives the hot and spicy flavor was identified as capsaicin, (Chaiyata, 2003). Red chili (RC) (*Capsicum frutescens)* is widely used as a spice for flavoring foods, particularly in South- East Asian and Latin-American countries. Pungent capsaicinoids (capsaicin, dihydrocapsaincin), antioxidant vitamins (ascorbic acid, vitamin E), carotenoids (β-carotene, β- cryptoxanthine) and several organic acids and minerals are the major active ingredients of *Capsicum frutescens,* (Antonious, *et al*., 2006). Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. Capsaicin and several related compounds are called capsaicinoids and are produced as a secondary metabolite probably as deterrents against certain herbivores and fungi. The burning and painful sensations associated with capsaicin result from its chemical interaction with sensory neurons. Capsaicin, as a member

of the vanilloid family, binds to a receptor called the vanilloid receptor subtype 1 (VR1), (Story and Crus-Orengo, 2007).

Diabetes mellitus which arise as a result of insulin insufficiency is associated with altered activity of various biochemical parameters such as alkaline phosphatase (ALP), alanine transaminase (ALT), aspertate transaminase (AST), serum electrolyte, lipid profile, among other biochemical parameters, (Siddiqui, 2005; Grossi, *et al*., 1998).

Because the liver plays a critical role in the maintenance of carbohydrate homeostasis, glucoregulation, and insulin degradation, it is not surprising that its functions may be affected as a result of diabetes mellitus.

However, scientific information on the effects of *Capsicum frutescens* supplemented diet on biochemical parameters of alloxan induced diabetic Wistar rats is lacking. It is against this background that this study was designed.

MATERIALS AND METHODS

Chemicals and equipments:

All chemical used in the research were procured as follows:

Red Chili (*Capsicum frutescens*), purchased from Abraka market in Ethiope East local government area, Delta State. Alloxan monohydrate (Sigma, alpha Aesar, 25g. A15324, CAS:2244-11-3. Cotton wool, Hand gloves, Dissecting kit, Centrifuge, Pipettes, Growers mash ,Beakers, Electronic weighing balance, Syringes and needles, Marker pen, Oncall Redii Glucometer and Reflorton plus$^{(R)}$ reflectance photometer (Roch Diagnostic GmbH, D-68298).

COLLECTION AND IDENTIFICATION OF *CAPSICUM FRUTESCENS*

Capsicum frutescens was purchased from Abraka market in Ethiope East Local Government of Delta sate and was authenticated by Dr. (Mrs). N.E. Edema in the department of Botany, Faculty of Science, Delta State University, Abraka. It was then blended for use in the experiment.

PREPARATION OF PEPPER SUPLEMENTED DIET

1% and 2% *Capsicum frutescence* supplemented diet were prepared weighing 1g and 2g of powdered Capsicum frutescence and mixing them with 99g and 98g of animal feed (growers mash) respectively.

HANDLING OF EXPERIMENTAL ANIMALS

Forty (40) Male Wister rats weighing 130-150g were procured from the International institute of tropical agriculture, (IITA), Ibadan Nigeria. They were acclimatized for 14-days at in the animal house unit in the Department of Pharmacology, Faculty of Basic Medical Science, Delta State University Abraka before commencement of the experiment. The rats were kept in well ventilated wooden cages. They were exposed to 12 hours of natural daylight and darkness and fed standard rat feed and water *ad libitum*. Procedures followed in raising the experimental animals were in accordance with the ethical standards of the Institutional Animals Ethics Committee (IAEC).

Induction of diabetes

Thirty (30) animals were food deprived for 24hours (but with free access to water) and later rendered diabetic by a single intraperitonial dose of alloxan monohydrate (150mg/kg) prepared in stock of 1500mg/50ml and a concentration of 30mg/ml. Three days after induction of diabetes, rats with fasting blood glucose concentration above 200mg/dl were confirmed diabetic and were randomly selected for the study. Diabetic state was maintained for three days for well establishment of diabetes.

EXPERIMENTAL PROCEDURE

Rats with evidence of diabetes mellitus were randomized into different groups alongside with non diabetic rats as follows;

Group 1: Non diabetic rats received normal diet (normal control)

Group 2: Diabetic rats received normal diet (diabetic control)

Group 3: Diabetic rats received 1% *Capsicum frutescens* supplemented diet (test 1 group)

Group 4: diabetic rats received 2% *Capsicum frutescens* supplemented diet (test 2 group).

Animal feed was formulated with 1% and 2% *Capsicum frutescens* and treatment was done twice daily for twenty one days. Rats' initial body weight prior to commencement of treatment was recorded. Inclusion criteria in this study were; non diabetic that were not induced with diabetes (which served as positive control), and animals with evidence of diabetes. Exclusion criteria include those animals that died during the maintenance of diabetes. Thus higher numbers of animals were allocated to groups 1, 2 and 3.

BLOOD COLLECTION AND BIOCHEMICAL ASSAY

After twenty one days of treatment, all overnight fasted rats were anaesthetized using chloroform and then sacrificed. Blood samples collected by cardiac puncture were delivered into lithium heparin bottles. The tubes were then centrifuged at 4000rpm for ten minutes to obtain clear serum which were later subjected to biochemical evaluation for ALT, AST, ALP, GGT, URIC ACID, CREATININE, HDL, and TOTAL CHOLESTEROL using Reflotron plus kit.

Fasting blood glucose level was determined with the aid of glucose analyzer machine (Oncall-Redii glucometer) by collecting blood samples from tail vains of overnight fasted animals. Values were expressed in mg/dl.

STATISTICAL ANALYSIS

The result of this study were expressed as mean $\pm$ SEM, and were analyzed by one way analyses of variance (ANOVA) using statistical package for social science (SPSS, 16). Difference between the means were tested with post Hoc- Turkey's test for multiple comparison and significance was considered when $p < 0.05$. Student's dependent t-test was used to analyze the significant difference between body weight before treatment and after treatment.

RESULT

Table 1:

Effects of *Capsicum frutescens* supplemented diet on biochemical parameters of alloxan induced diabetis in Wistar rats.

	Group 1: Normal control	Group 2: Diabetic control	Group 3: Diabetic +1% C.F.S.D	Group 4: Diabetic + 2% C.F.S.D.
Creatinine (IU/L)	0.42 ± 0.03	0.94 ± 0.17[a]	0.47 ± 0.3[b]	0.54 ± 0.07[b]
Uric acid (IU/L)	5.49 ± 0.2	7.87 ± 0.85[a]	5.03 ± 0.2[b]	6.3 ± 0.7[b]
GGT (IU/L)	223.4 ± 7.5	275.0 ± 10.7[a]	221.8 ± 6.4[b]	224.8 ± 6.0[b]
AST (IU/L)	278.4 ± 19.6	325.2 ± 26.1	247.2 ± 10.8[b]	251.8 ± 12.3
ALP (IU/L)	251 ± 6.81*	316.4 ± 37.7*	302.6 ± 27.6*	243.8 ± 4.53*
ALT (IU/L)	61.7 ± 1.03*	128.2 ± 32.97*	98.98 ± 8.74*	87.86 ± 8.54*
HDL (mg/dl)	47.98 ± 1.8 [ns]	43.1 ± 2.8 [ns]	46.8 ± 1.6 [ns]	46.0 ± 1.4[ns]
T. Cholesterol (mg/dl)	65.6 ± 5.6	79.2 ± 4.4	78.6 ± 3.3[b]	61.5 ± 3.4[abc]
Blood glucose Pre-treatment (mg/dl)	88.8 ± 6.22	380.2 ± 16.6	363.8 ± 24.3 [d]	382.2 ± 14.7[d]
Blood glucose Post-treatment (mg/dl)	94.8 ± 6.18 (6.8%)	370.0 ± 19.81[a] (-2.63%)	182.8 ± 16.82[bd] (-49.8%)	146.6 ± 14.8[bd] (-61.6%)

Values are expressed as mean ± S.E.M, n=10. *P<0.05

Table 2:

Effects of Capsicum frutescens (C.F.) supplemented diet on body weight of alloxan induced diabetic rats.

	Body weight before treatment Week 0 (g)	**Body weight after treatment Week 3 (g)**
Group 1 (Normal control)	131 ± 9.8	195 ± 17.2 (48.9%)
Group 2 (Diabetic control)	140 ± 9.6	120 ± 7.9 (-16.7%)
Group 3 (Diabetic, 1% C.F.S.D)	125 ± 6.7	134 ± 19.2 (7.2%)
Group 4 (Diabetic, 2% C.F.S.D)	140 ± 7.2	152 ± 16.9 (8.5%)

Values are expressed as mean ± SEM, n =10,*P<0.05

Table 1 above depicts the effects of *Capsicum frutescens* on biochemical parameters of alloxan induced diabetic Wistar rats.

From the result of serum creatinine, group 2 (0.94 ± 0.17) significantly increased serum creatinine level when compared with group 1 (0.42 ± 0.03). Group 3 (0.40 ± 0.3) and group 4 (0.54 ± 0.07) significantly reduced (P<0.05) serum creatinine level when compared with group 2.

From the result of serum uric acid, group 2 (7.87 ± 0.85) significantly increased serum uric acid level when compared with group 1(5.49 ± 0.2). Group 3 (5.03 ± 0.2) significantly reduced serum uric acid level when compared with group 2. Group 4 (6.3 ± 0.7) reduced serum creatinine level when compared with group 1, but did not attain statistical significance (P>0.05).

From the result of serum gama glutamyl transferase (GGT), group 2 (275.0 ± 10.7) significantly (P<0.05) increased serum GGT level when compared with group 1 (223.4 ± 7.5). Groups 3 (221.8 ± 6.4) and 4 (224.8 ± 6.0) significantly (P<0.05) reduced serum GGT level when compared with group 2.

From the result of serum aspertate transaminase (AST) group 2(325.2 ± 26.1) increased serum AST level but did not attain statistical significant (P>0.05) when compared with group 1 (278.4 ± 19.6). However, group 3 (247.2 ± 10.8) significantly (P=0.030) reduced serum AST level when compared with group 2. Group 4 (251.8 ± 12.3) reduced the serum level of AST when compared with group 2, but was not statistically significant (P>0.05).

From the result of serum alkaline phosphatase (ALP), there was an overall significant difference (P<0.05) as determined by one way ANOVA. However Turkey's post hoc test did not reveal any significant difference between groups. However, there was an increase in group 2 (316.4 ± 37.7) serum ALP level when compared to other groups. Group 1 (327.6 ± 27.6) was increased among other groups while group 4 (243.8 ± 4.53) reduced its level and group 3 (327.6 ± 27.6) increased its level its level.

From the result of serum alanine transaminase (ALT), a significant difference was observed as determined by one way ANOVA. Turkey's post hoc test did not reveal any statistical significant. However, serum ALT mean value was highest in group 2 (128.2 ± 32.97) followed by group 3(98.98 ± 8.74), next to group 4 (87.86 ± 8.54) and least in group 1 (61.7 ± 1.03).

From the result of serum high density lipoprotein cholesterol (HDL) there was no significant difference as determined by one way analyses of variance (ANOVA), (P>0.05). However, serum HDL level was highest in group 1 (47.98 ± 1.8) followed by group 3 (46.8 ± 1.6) next to group 4 (46.0 ± 1.4) and least in group 2 (43.1 ± 2.8).

From the result of serum total cholesterol level, there was a significant difference as determined by one way ANOVA. Post hoc Turkey's test showed that the group 3 (101.6 ± 3.3) significantly increased serum total cholesterol level when compared with group 2 (79.2 ± 4.4). Group 4 (61.5 ± 3.4) significantly ($P<0.05$) reduced serum total cholesterol level when compared with group 2 and 3 (101.6 ± 3.3).

From the result of blood glucose level, one way ANOVA revealed an overall significant difference ($P<0.05$) among group means. Turkeys post hoc test showed that group 2 (370.0 ± 19.81) significantly increased FBGL when compared with group 1 (94.8 ± 6.18). Groups 3 (182.8 ± 16.82) and 4 (146.6 ± 14.8) significantly decreased FBGL when compared with group 2(370.0 ± 19.81). There was no significant difference ($P>0.05$) when initial and final FBGL of groups 1 and 2 were compared. However, group 3 and 4 significantly reduced FBGL after treatment when compared with initial value.

From table 2 above, body weight of normal rats (group 1) was significantly ($P<0.05$) increased after treatment period. Body weight of diabetic control rats (group 2) was significantly ($P<0.05$) decreased after treatment. Body weight of 1% C.F.S.D treated rats (group 3) was increased after treatment. Body weight of 2% C.F.S.D treated rats (group 4) was increased after treatment. Percentage change in body weight (between before treatment and after treatment) were expressed in percentage.

DISCUSSION

The present study was undertaken to investigate the effect of *Capsicum frutescens* supplemented diet on biochemical parameters in alloxan induced diabetic Wistar rats. The action of capsaicin is mediated by TPRV1 (vanilloid receptor), which belongs to an ion channel group. VR1 when activated permits cations to pass through the cell membrane and into the cell resulting in depolarization of the neuron stimulating it to signal the brain. By binding to the VR1 receptor, the capsaicin molecule produces the same sensation that excessive heat or abrasive damage would cause, explaining why the spiciness of capsaicin is described as a burning sensation. The inflammation resulting from exposure to Capsaicin is believed to be the result of the body's

reaction to nerve excitement rather than just chemical burn or any direct tissue damage when chili peppers are the source of exposure.

Alloxan is a well- known diabetogenic agent widely used to induce Type 11 diabetes in animals (Viana, *et al.,* 2004). Alloxan is a urea derivative which causes selective necrosis of the pancreatic islet β-cells. Alloxan and its reduction product dialuric acid establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide. The action of reactive oxygen species with a simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of beta cells, (Szkudelski, 2001). Alloxan which has been reported to destroy the beta cells of the pancreas causing reduction in insulin secretion thereby increasing blood glucose level and decreasing in body weight gain (Al kalifa *et al*., 2009). From results of the present study, the diabetic rats induced with alloxan showed these changes by decreasing body weight from (140 ± 9.6), before treatment to (120 ± 7.9), after treatment [Table 2]. Body weight of 1% and 2% *Capsicum frutescens* supplemented diet treated groups were increased more than rats in group 2. This could be traced to the recovery effects of *Capsicum frutescens* against weight loss associated with diabetes mellitus caused by alloxan monohydrate.

Alloxan induced diabetic is characterized by Increase in blood glucose (hyperglyceamia) above normal level (normorglyceamia), (Al kalifa, *et al*., 2009). Increased in fasting blood glucose level (FBGL) in group 2 could be attributed to the diabetogenic effect of alloxan. Significant reduction in FBGL in 1% (group 3) and 2% (group 4) C.F.S.D treated groups may be attributed to the presence of hypoglyceamic agents in *Capsicum frutescens*. Studies had shown that *Capsicum frutescens* is used to treat diabetes mellitus by traditional healers in Jamaica, (Tolan, *et. al*., 2004). Pharmacokinetic and the effect of Capsaicin in *Capsicum Frutescens* on decreasing Plasma Glucose Level in a crossover study of 12 healthy volunteers by performing the OGTT while receiving placebo or 5 grams of capsicum had been documented (Kamon, *et al.*, 2009).
In this study polydipsia and excess voiding of urine observed in group 2 rats (diabetic control) was most predominant when compared with groups 1, 3 and 4. In diabetes, the obligatory renal water loss combined with the hyperosmolarity tends to deplete intracellular water, triggering the osmoreceptor of the thirst centre of the brain and polydipsia which leads

to increase in water intake, (UKPDS, 1998). Reduce diauresis and excessive taste observed in groups 3 and 4 could be attributed to the effects of *Capsicum frutesence* in the diet of such rats.

Impaired carbohydrate utilization in the diabetic also leads to accelerated lipolysis, which results in elevated plasma triglycerides levels (hyperlipidaemia), (Granner, *et. al.,* 1996). The observed abnormalities of triglyceride and HDL metabolism are in accordance with reports on early manifestation of insulin resistance, the precursor to diabetes (Frederickson and Lee, 1965; Lyons, 1992). From the result of the study, 2% C.F.S.D treated group elicited reduction in serum level of total cholesterol than 1% treated group. The physiological effects of most spices had been documented to exhibit hypolipidemic and antioxidant properties with beneficial health implication, (Manjunatha and Srinivasan, 2008).

Individuals with type 2 diabetes had also been reported to have a higher incidence of liver function test abnormalities than non diabetic individuals. Mild chronic elevations of transaminases often reflect underlying insulin resistance. Diabetes mellitus can arise as a result of insulin insufficiency, which is associated with altered activity of various liver enzymes, (Siddiqui, 2005). Grossi, *et al*., (1998) had also reported that values of serum ALP can be raised in diabetic patients. The liver releases alanine aminotransferase (ALT) and an elevation in plasma concentrations are an indicator of liver damage, (Claudia, *et al*., 2006**).** The levels of aspertate aminotransferase (AST), alanine amino transaminase (ALT) and alkaline phosphatase (ALP) had been reported to be increased in alloxan-induced diabetic rats, (Akah, *et a*l., 2009). Increased in serum liver enzymes parameters in diabetic control group observed in the present investigation corroborates these findings. Reduction in liver enzyme levels in group 3 (1%, C.F.S.D.) and 4 (2% C.F.S.D.) clearly indicates the therapeutic role of *Capsicum frutescens* against increased in serum liver enzyme parameters correlated with alloxan induced diabetes. In previous research, *Capsicum frutescens* had been documented to protect against iron overload liver injury by reducing plasma liver parameters level to normal, (Eman, *et al.*, 2010).

There was a significant increase in serum creatinine level of group 2. An increase in plasma creatinine levels may be a sign of impaired renal function which is associated with diabetes. The elevation in the plasma creatinine concentration indirectly suggests kidney damage specifically the renal filtration mechanism, (Wasan, *et al*., 2001). Significant reduction observed in the serum

creatinine levels of the diabetic rats treated with 1% and 2% C.F.S.D in this study suggests protective effect by *Capsicum frutescens* against kidney disorders associated with diabetes mellitus.

Another characteristic feature of severe diabetic is an elevated excretion of urea whose concentration may be five times higher than the normal value (Lehninger, 1998). As corroborated by this study, serum uric acid level of group 2 (Diabetic control) was significantly increased when compared with group 1 (Normal control). The significant reduction in serum uric acid level observed in the group 3 conferred protections against elevated uric acid associated with diabetes mellitus. The significant reduction could be attributed to the main active principles present in *Capsicum frutescens*.

CONCLUSION AND RECOMMENDATION

From the above study increased in serum liver enzymes (AST, ALT, ALP, GGT) levels, increased in serum uric acid, creatinine, total cholesterol, fasting blood glucose level and reduced high density lipoprotein (HDL) cholesterol associated with alloxan induced diabetes mellitus were reversed after treatment with 1% and 2% C.F.S.D. Such remarkable changes observed in this study could be traced to the active ingredients [capsaicin, dihydrocapsaincin, antioxidant vitamins (ascorbic acid, vitamin E), carotenoids (β-carotene, β- cryptoxanthine) and several organic acids and minerals present in *Capsicum frutescens.* Its therefore recommended that *Capsicum frutescens* be added to diet especially of diabetic patients.

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