0IJPSR (2018), Volume 9, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 May, 2017; received in revised form, 26 December, 2017; accepted, 06 January, 2018; published 01 February, 2018

EFFECT OF FRESH JUICE OF KHAT (*CATHA EDULIS*) ON BLOOD GLUCOSE LEVELS OF NORMOGLYCEMIC AND STREPTOZOCIN-INDUCED DIABETIC RATS

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Keywords:

Catha edulis, Fresh juice, Wistar rats, Blood glucose, Weight loss, Diabetes mellitus

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ABSTRACT: Khat is chewed traditionally in Ethiopia, Somalia, Yemen and Kenya. In Ethiopia, khat chewing is now becoming an everyday substance of abuse for the general population. Knowledge about the effects of khat chewing on blood glucose levels is very sparse. Therefore, the objective of this study was to investigate the effect of fresh juice of khat (*Catha edulis*) on blood glucose levels of normal and streptozocin-induced diabetic rats. Sixteen normal and 24 diabetic male wistar rats were studied. Diabetic rats were divided into three groups: group I were treated with 4.5 ml/kg of fresh juice of *Catha edulis* (N=8). Group II were treated with glibenclamide (5 mg/kg) (N=8), group III were treated with distilled water which served as controls. Normal rats were divided into two groups: group I were given 4.5 ml/kg of fresh juice of *Catha edulis* (N=8) and group II were given distilled water as a control. The rats in each group was orally administered with single dose of fresh juice, glibenclamide or distilled water daily and blood glucose was measured at 0, 2 and 4 h on day 1, thereafter fasting blood glucose was measured in daily basis for first two weeks and once weekly on every 5th day in the following four weeks. Oral administration of a fresh juice of *Catha edulis* in diabetic and normal rats reduced the fasting blood glucose level from 223.7 ± 27.6 and 115.4 ± 2.48 mg/dl at baseline to 106 ± 18.2 and 79.6 ± 3.41 mg/dl, respectively at the end of study ($p<0.05$). Administration of fresh juice of *Catha edulis* in diabetic and normal rats respectively decreased blood glucose levels from 282.4 ± 45.5 and 95.2±6.2 mg/dl at baseline to 164.5 ± 31.6 ($p <0.05$) and 67.6 ± 6.8 mg/dl ($p <0.05$) at 4 h. It also decreased body weight in diabetic and normal rats from 304.81 ± 14.46 and 214 ± 17.84 g at baseline to 237.37 ± 12.28 ($p <0.05$) and 160.8 ± 15.49 g ($p <0.05$) at 4th wk., respectively. In summary, oral administration of a fresh juice of *Catha edulis* exerts a hypoglycemic effect and weight reduction in normal and streptozocin-induced diabetic rats. Further studies to isolate different active components of *Catha edulis* and to elucidate the exact mechanism of action are recommended.

INTRODUCTION: The habit of khat (*Catha edulis*) chewing has prevailed for centuries among populations in the horn of Africa and the Arabian Peninsula. Khat is grown in Yemen and many parts of East Africa, especially Ethiopia and Kenya.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(2).784-89

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(2).784-89

The plant belongs to the family Celastracea. Fresh leaves of khat are customarily chewed to attain a state of stimulation [1, 7, 8, 10, 11, 15]. Several studies show that khat chewing controls the levels of glucose in the blood and khat has a therapeutic role in the management of high blood glucose [3, 12, 13, 24].

While some studies show that in healthy non-diabetics, khat does not affect fasting or post-prandial serum glucose levels, others have suggested a decrease in serum glucose [22]. Chewing of fresh leaves of Khat is a common practice in many parts

of Africa for their stimulant effect and have been claimed to lower blood glucose levels in diabetic patients [17]. The effect of khat chewing on the blood glucose levels was compared to the effects of two anti-diabetic drugs in diabetic patients and it was found that the rate of blood glucose decrease in khat chewers was significantly higher than the effect of the two anti-diabetic drugs. Khat chewers had a 61.22 % reduction of blood glucose levels within 4 hours of khat chewing. It is justifiable to postulate that its hypoglycemic potential is due to anti-diabetic effects of trace elements like magnesium, chromium, manganese, zinc, iron, vanadium, copper, nickel, lead and strontium contained in it [19, 25].

The hypoglycemic action of the extract could be attributed to the presence of flavonoids, flavones, flavonols, saponins and trace elements, which have been shown to have hypoglycaemic properties. The aqueous extract of *Catha edulis* lowered blood glucose levels to normal and as effective as insulin in the third and fourth hours. Furthermore, the extract of *Catha edulis* may have achieved hypoglycaemic activity by decreasing the rate of carbohydrate absorption into the portal hepatic circulation. Tannins and the inorganic ions present in khat may possibly contribute to the delayed absorption of glucose.

Moreover, the *Catha edulis* induced delay of gastric emptying may also play a role in reducing blood glucose levels after food intake [2, 9]. Effects of khat chewing on appetite may also indirectly influence blood glucose levels and body weight. The study showed that chewing khat significantly decreased subjective feelings of hunger and increased the sensation of fullness but had no effect on ghrelin and peptide YY levels [18]. High plasma levels of the anorectic hormone, leptin, have been found 4 h after a heavy khat chewing session (400 g). This hormone may then contribute to the decreased appetite and body weight observed in khat chewers [6, 14, 16]. Other study showed that different khat extracts or cathinone produces changes in terms of weight, fat mass, appetite, lipid biochemistry and hormonal levels. While some studies showed that in healthy non-diabetics, khat did not affect fasting or post-prandial blood glucose levels, others have suggested a decrease in blood glucose levels [4, 5, 16, 20].

Therefore, the main aim of the present study was to investigate the effect of fresh juice of *Catha edulis* on the blood glucose levels of normoglycemic and streptozocin (STZ)-induced diabetic rats.

MATERIALS AND METHODS

Collections and Preparation of Plant Materials: The fresh khat (stem tips and leaves) weighing 3 kg was purchased from Merkato in Addis Ababa in February, 2011. A voucher specimen of *Catha edulis* has been deposited in Arat Killo Herbarium, College of Natural Science, Addis Ababa University. Then Arat Killo Herbarium authenticated the botanical identity of the plant.

Procedures for Preparation of Fresh juice of *Catha edulis* (FJCE): Three kg of fresh khat (leaves and stem tips) was washed in distilled water and crushed by blender machine within one month study. The crushed khat was dissolved in 3 liters of distilled water by stirring it thoroughly and then filtered by using clean white cloth. The fresh juice was prepared on daily basis and placed in refrigerator at -8 °C.

Experimental Animals: The experimental animals used in this study were 40 male wistar rats aged between 14-16 weeks and weighing between 200-320gm. The animals were purchased from Ethiopian Health and Nutrition Research Institute (EHNRI) for the study. They were given one week of acclimatization period before the start of experiment in the animal house, Black Lion Hospital, Faculty of Medicine, Addis Ababa University. They were fed standard rat pellets and water. The rats were housed in plastic cages at a controlled ambient temperature of 22 ± 2 °C and 50 ± 10% relative humidity, with 12 hour light/12 hour dark cycles. The experimental procedures were carried out in strict compliance with Animal Ethics Committee's rules and regulations followed in Addis Ababa University. The proposal was approved by Ethics committee in the Department of Physiology and the College of Health Sciences.

Induction of Diabetes in Rats: Diabetes was induced by a single intraperitoneal injection of streptozocin (STZ) (50 mg/kg BW) which was prepared in 1.47 gm of sodium citrate buffered in 0.01 M citric acid (0.96gm) (pH 4.5) in a volume of 1 mL kg^{-1} b.w [21]. After 2-3 days of STZ

administration, rats with fasting blood glucose levels of 140 mg/ dL or above were considered as diabetic rats.

Diabetic Animals: Twenty four male wistar rats were randomly grouped into three; each group consisted of 8 rats/cages. Group I diabetic rats were treated with single dose of fresh juice of *Catha edulis* (4.5 ml/kg). Group II diabetic rats were treated with single dose of glibenclamide (5mg/kg). Group III diabetic rats were treated with vehicle (2 mL distilled water) and were used as control. The rats in each group was orally administered with single dose of fresh juice, glibenclamide and distilled water daily and plasma glucose was measured at 0, 2 and 4 h on day 1, thereafter fasting blood glucose was measured in daily basis for first two weeks and once weekly on every 5th day in the following four weeks. Administration was conducted using gavage without damaging their trachea by careful handling of rats' neck and tail by crossing their front legs.

Normoglycemic Animals: Sixteen normal male Wistar rats were randomly grouped into two; each group consists of eight rats/cages. Group I rats were treated with single dose of a fresh juice of *Catha edulis* (4.5 ml/kg) and group II were treated with vehicle (2 mL distilled water) and were used as control. The rats in each group was orally administered with single dose of fresh juice and distilled water and plasma glucose was measured at 0, 2 and 4 h on day 1, thereafter fasting plasma glucose was measured in daily basis for first two weeks and once weekly on every 5th day in the following four weeks.

Blood Sugar Determination: A drop of blood was obtained from the tails of the rats by snipping (mincing) the tips with sterile scissors, which had first been sterilized by swabbing with 70% ethanol. Bleeding was then enhanced by gently "milking" the tail from the body towards the tip. After taking a drop of blood, the tips of the tail were again sterilized by swabbing with 70% ethanol.

The blood glucose level was determined by using Senso Card Glucometer (D45-8001-x, Electronika, Kft. Hungary). Blood glucose test strips (77 Electro -nika Kft. H-1116 Budapset, Hungary) compatible with the glucometer were appropriately inserted in the glucometer and blood from the tail of the rats was placed on the glucometer strip. The blood glucose level was read on glucometer screen in mg/dL.

Statistical Analysis: Blood glucose levels were expressed in mg/dl as mean ± SEM. The statistical analysis of data was done using paired sample t test and one way analysis of variance (ANOVA), followed by Dunnett's test and Post hoc comparisons between the experimental and control groups were made using the software" SPSS16 Statistical software package." P value less than 0.05 was considered to be significant.

RESULTS: The effects of fresh juice of *Catha edulis* on blood glucose levels of STZ-induced diabetic and normal rats was shown in **Fig. 1**. The administration of fresh juice of *Catha edulis* in diabetic and control rats respectively decreased blood glucose levels from 282.4 ± 45.5 and 95.2 ± 6.2 mg/dl at baseline to 164.5 ± 31.6 ($p < 0.01$) and 67.6 ± 6.8 mg/dl ($p < 0.05$) (41.8 and 29% reduction respectively) at 4 h. There was also a significant decrease in blood glucose levels from 358.7 ± 63.8 mg/dl at baseline to 148.3 ± 37.3 mg/dl (58.7%) ($p<0.01$) in diabetic rats treated with glibenclamide. There was no significant changes of plasma glucose levels with distilled water in both diabetic and control rats.

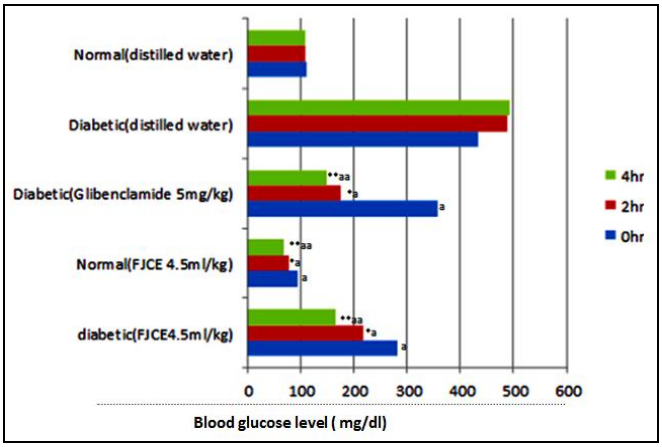

FIG. 1: EFFECTS OF FRESH JUICE OF *CATHA EDULIS* ON FASTING BLOOD GLUCOSE LEVELS OF DIABETIC AND NORMAL RATS

FJCE- fresh juice of *Catha edulis*, Values are mean± SEM, * P<0.05, **P<0.01 when compared with 0hr (before treatment) of the same group. [a] P<0.05 and [aa] p<0.01 when compared with the corresponding value of control group.

The effects of fresh juice of *Catha edulis* on blood glucose levels of diabetic and normal rats were shown in **Table 1**. Treatment with fresh juice of

Catha edulis decreased fasting blood glucose levels significantly from baseline through 4th week ($p<0.05$) in diabetic and control rats and there was a significant decrease in the fasting blood glucose levels from baseline through 4th week with glibenclamide in diabetic rats. No significant difference of fasting blood glucose levels were observed with distilled water in both diabetic and control rats.

As shown in **Table 2**, treatment with fresh juice of *Catha edulis* significantly decreased body weight from baseline through the 4th week ($p<0.05$) and there was significant decrease in the body weight in diabetic rats treated with glibenclamide as well. However, the reduction of body weight was more significantly greater in a fresh juice treated group when compared with group treated with glibenclamide (($p<0.05$)).

TABLE 1: EFFECTS OF FRESH JUICE OF *CATHA EDULIS* ON FASTING BLOOD GLUCOSE LEVELS OF DIABETIC AND NORMAL RATS

Treatment and dose	Fasting blood glucose level (mg/dl)				
	Day 0	1st week	2nd week	3rd week	4th week
FJCE (4.5ml/kg)					
Diabetic rats	223.7 ± 27.6	130.3 ± 22.8^{**a}	98.4 ± 6.5^{**aa}	107.14 ± 20.8^{**aa}	106 ± 18.2^{**aa}
Normal rats	115.4 ± 2.48	103.4 ± 3.5*	90 ± 3.39^{**aa}	83.4 ± 2.44^{**aa}	79.6 ± 3.41^{**aa}
Glibenclamide (5mg/kg)					
Diabetic rats	354.6 ± 50.5	194.4 ± 6.8^{**a}	184.4 ± 50^{**aa}	222.8 ± 61.2^{*aa}	117 ± 10.4^{**aa}
Normal rats	NA	NA	NA	NA	NA
Distilled water					
Diabetic rats	506.8 ± 18.5	509.2 ± 18.1	508.1 ± 25	516.3 ± 24.5	495.7 ± 28.6
Normal rats	107.6 ± 3.82	103.2 ± 5.45	118.8 ± 2.13	117.4 ± 2.89	115 ± 2.30

FJCE- fresh juice of *Catha edulis*, Values are mean± SEM, * P<0.05, **P<0.01 when compared with 0hr (before treatment) of the same group. ^{a} P<0.05 and ^{aa} p<0.01 when compared with the corresponding value of control group.

TABLE 2: EFFECTS OF FRESH JUICE OF *CATHA EDULIS* ON THE BODY WEIGHT OF STZ-INDUCED DIABETIC AND NORMAL RATS

Treatment and dose	Body weight (gm)				
	Day 0	1st week	2nd week	3rd week	4th week
FJCE (4.5ml/kg)					
Diabetic rats	304.81 ± 14.46	267.37 ± 14.47*	243.8 ± 12.33*	247.18 ± 12.69**	237.37 ±12.28**aa
Normal rats	214 ± 17.84	189 ± 17.56*a	182 ± 16.47**aa	175.4 ± 15.8**aa	160.8 ± 15.49**aa
Glibenclamide (5mg/kg)					
Diabetic rats	306.8 ± 25.89	264.2 ± 17.58*	260.1 ± 13.77*a	254.8 ± 18.56**aa	244.2 ± 25.89*aa
Normal rats	NA	NA	NA	NA	NA
Distilled water					
Diabetic rats	263.42 ± 5.85	266.94 ± 4.32	271.25 ± 4.84	276.78 ± 3.90	276.52 ± 3.53
Normal rats	266.8 ± 7.21	271.6 ± 7.83	273.6 ± 6.51	281.4 ± 4.23	276.7 ± 4.82

FJCE- fresh juice of *Catha edulis*, Values are mean± SEM, * P<0.05, **P<0.01 when compared with 0hr (before treatment) of the same group. ^{a} P<0.05 and ^{aa} p<0.01 when compared with the corresponding value of control group.

Treatment of fresh juice of *Catha edulis* also significantly decreased body weight in normal rats whereas it was not observed with distilled water.

DISCUSSION: Diabetes mellitus is a major public health problem in the world. The number of patients with diabetes is increasing due to population growth, aging, urbanization and increasing prevalence of obesity and physical inactivity. Besides exercise, weight control and medical nutrition therapy, oral glucose-lowering drugs and insulin injection are the conventional therapies for the disease. These conventional therapies have adverse side effects, are expensive and require expertise. There is a new trend in the world to turn back to natural substances as alternatives to synthetic drugs either due to cost or the side effects of drugs [1, 7, 8, 10, 11, 15].

The results of this study are in agreement with the previous-study on intraperitoneal injection of aqueous extract (150 mg/kg) of *Catha edulis* in alloxan-induced diabetic mice where it lowered blood glucose levels as effectively as insulin in the third and fourth hours after administration [3, 12, 13, 24]. The rapid plasma glucose reduction of *Catha edulis* in diabetic and normal rats may be mediated by the decreased rate of carbohydrate absorption into the

portal hepatic circulation. The delayed gastric emptying effect of tannins and the inorganic ions presented in khat may contribute to the delayed absorption of glucose from gastrointestinal tract [19, 25]. This is in accordance with the previous findings which showed that healthy khat chewers had a 61.22% reduction of blood glucose levels within 4 hours of khat chewing [2, 9]. This study showed that *Catha edulis* can reduce fasting blood glucose levels and the effect is sustainable. It also indicates that the glucose-lowering effect of *Catha edulis* is as effective as glibenclamide in diabetic rats.

Weight reduction effect of *Catha edulis* is significant. It was observed that high plasma levels of the anorectic hormone, leptin, was elevated 4 h after a heavy khat chewing (400 g) and this hormone may then contribute to the hyperthermia, decreased appetite and body weight reduction observed in khat chewers [2].

The anorexigenic effect of khat may be secondary to central mechanisms mediated *via* cathinone, one of khat leaves' extract. Indeed, khat leaves have been used in the control of obesity, and cathinone has been reported to be responsible for the increase in metabolic rate and oxygen consumption in rats [6, 14, 23]. The cause of weight loss in diabetic rats treated with glibenclamide is not known. Whether weight loss from *Catha edulis* per se can contribute to its glucose-lowering effect is uncertain and need further investigation.

CONCLUSION: The present study showed that fresh juice of *Catha edulis* possessed a significant hypoglycemic and weight reduction properties in normal and STZ - induced diabetic rats, which suggests the presence of biologically active components which may be worth of further investigation and elucidation. Therefore, the following activities for future research are recommended: Detailed phytochemical screening and isolation of active ingredient is required to identify the exact chemical compounds responsible for the hypoglycemic activity observed in fresh juice of *Catha edulis*. Another study should be carried out in human to evaluate the effect of *Catha edulis* on blood glucose levels.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Debecho DA, Kinfe YA, Dugul TT and Melka DS: Effect of fresh juice of khat (*Catha edulis*) on blood glucose levels of normoglycemic and streptozocin-induced diabetic rats. Int J Pharm Sci & Res 2018; 9(2):784-89. doi: 10.13040/IJPSR.0975-8232.9(2).784-89.