Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6787 – 6795
Received 05 March 2021; Accepted 01 April 2021.

Positive effect of *Allium sativum* and *Citrus aurantifolium* plants on glucose level in diabetic rats using Alloxan

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Abstract

The current study was designated to investigate the effect of *Allium sativum* and *Citrus aurantifolium* plants (*C. aurantifolium*) extract on blood glucose and lipid profile as well as body weight in diabetic rats, thirty adult rats were divided into five groups (6rat for each). G1 :served as healthy control given tap water G2 :diabetic without treatment , G3: diabetic treated with garlic extract 150 mg\kg body weight, G4:diabetic treated with *C. aurantifolium* and G5: group treated with150 mg\kg mix extracts (garlic and *C. aurantifolium*).All treated animals were given orally 1 ml of extracts every day. The effects of aqueous extract of garlic and *C. aurantifolium* on some parameters were investigated in normal and diabetic rats such as fasting blood sugar(FBS), fasting serum insulin(F.serum insulin) ,ketone body , lipid profile (Cholesterol , Triglyceride, High density lipoprotein(HDL),and Low density lipoprotein LDL) , the results investigated a significant decrease in glucose levels in group treated with mix plants(159.73±2.67) as compared with garlic (176.10±2.69) and *C. aurantifolium* (205.45±4.09) after twenty days of treatment, also the results display a significant improvement in insulin level in groups which treated with garlic , *C. aurantifolium* and mix plants (4.61±1.22 ,3.69±1.03 and 4.21±1.50 mg\dl respectively) compared with untreated diabetic group (1.88±0. 60), the value of ketone body was decreased in all treated groups with garlic, *C. aurantifolium* and mix plants(5.73±1.98, 6.94±2.86 and4.90±1.84) respectively, the results report a significant decline in cholesterol level in groups treated with garlic ,*C. aurantifolium* and mix extract (91±3.98, 95±4.35 and 87±2.45)mg\dl respectively compared with the untreated diabetic group (108±3.08 mg\d). the level of Triglyceride reported a significant $p<0.05$ decrease in all groups treated with garlic ,*C. aurantifolium* and mix extract (89±3.96, 90±3.78 and 85±3.73) mg/dl respectively compared with untreated diabetic group (102±4.43) mg\dl . HDL level revealed significant $p<0.05$ improvement in groups treated with garlic ,*C. aurantifolium* and mix extract(38±2.94, 32±2.09 and 42±3.02) mg\dl compared with control and untreated diabetic groups (30±2.12 and 24±3.53) mg\dl , reduced level of LDL were assessed in groups treated with garlic ,*C. aurantifolium* and mix extract(40±3.59, 43±4.50 and30±3.42) mg\dl. There was a significant $p<0.05$ improvement in body weight in the group treated with mix plants extract (184 ±4.30 g) after 30 days as compared with these groups at the beginning of experiment (178 ±2.93) g.

Key word: plant extract, ketone body ,blood glucose

Introduction

Diabetes and its complications consider a major medical problem these complication include nephropathy, retinopathy, neuropathy, and cardiovascular morbidity [1]. Diabetes was also the main reason of the new cases of blindness and kidney failure in 2005 in the

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 6787 – 6795
Received 05 March 2021; Accepted 01 April 2021.

United States [2], almost 60 to 70 percent of patients with diabetes showed severe neurological injuries. Controlling diabetes and its complications is still a global problem and fully successful treatments are yet to be discovered[3]. According to latest studies plant products have demonstrated wide range of valuable therapeutic activities without causing any side effects [4]. The major concern in diabetes is increased oxidative stress. Therefore, dietary supplementation with antioxidants such as vitamins, and flavonoids has been used in attempts to prevent the occurrence of many diabetes complications by preventing oxidative damage and protect cells from damage caused by free radical species[5], thus this product have gained much attention due to their wide spectrum of therapeutic properties as verified by both *in vitro* and *in vivo* studies [6, 7]

Medical plants may have potential roles in the treatment of diabetes and becoming more popular because these spices show hypoglycemic and antioxidant activities, no side-effects and synergistic actions[8].Garlic (*Allium sativum*) is an aromatic herbaceous plant and one of the oldest and important herbs that have been used from ancient times as traditional medicine [9,10]. The plant extract have various biological activities and proved to be very important for human health due to its antioxidant, anticarcinogenic and antimutagenic effects [11.12].The main function of garlic on diabetes is in maintaining blood sugar level, this herb can decrease glucose level, the component such as allyl propyl disulfide and allicin in garlic can be used as antihypertension which reduce the blood pressure and plasma creatinine levels. Garlic also protects the kidneys from diabetes nephropathy[13.] Allicin have function in increasing liver metabolism, insulin secretion and controlling lipid peroxidation, it is also improving the antioxidant status of cells. Thus, garlic is beneficial for the body because it protects cells from the effects of oxidative stress due to hyperglycemia[14].

Lime (*C. aurantifolia*), also known as key lime is characterized by pulp poor, thick peel. it is used in the food and pharmaceutical industries and treatment of several diseases including fever, obesity and inflammation [15]. Chemical analysis of the extract revealed the presence of several flavonoids and limonoids [16], extract of lime has been found to inhibit pancreatic α-amylase activity which lead to reduce hyperglycemia and ameliorate diabetic complications [17,18]. In recent years actual clinical research investigate the beneficial effect of lime in regulating the balance and homeostasis of the body in a holistic fashion ,this plant exhibited many biological activities and pharmacological functions, such as antioxidation anti-inflammatory and free radical scavenging activity [19,20] .The aim of this current work was to estimate the effect of *Allium sativum* and *C. aurantifolium* plants extract on blood glucose and lipid profile as well as body weight in diabetic rats..

Materials and methods

1.prepartion of plant extract

About 50 g of dried garlic and 50 g of *C. aurantifolium* powder were mixed with 250 ml of the distilled water (for each powder) and kept on a water bath shaker for 24 h at 30 °C., a filter paper was used to collect filtrate which was used for further experiments.

2. Experimental design

Rats were obtained from biotechnology research center\Al-Nahrain university, thirty adult rats aged between 4-5 months ,animals were acclimatized for one week and they had free excess ad libitum to food and water.

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3. **Induction of diabetes**

The rats were allowed fasting for 12 hours and induced diabetic by as single dose of alloxan(Sigma) 100 mg\kg body weight , the level of blood sugar more than 250 mg\dl were selected for the study. The animals were randomly divided into five groups each containing six animals, as follow G1: served as control group given tap water, G2;diabetic without treatment ,G3: diabetic treated with garlic extract 150 mg\kg body weight,G4: diabetic treated with *C.aurantifolium* and G5: treated with150 mg\kg mix extracts (garlicand *C. aurantifolium*).All treated animals were given orally volume 1 ml \day of extracts for thirty days.

4.Biochemical analysis

Blood glucose was measured by glucometer (glucose enzymatic colorimetric test kit(Biocon Diagnostik,Germany).The T.chol concentration was estimated with the using commercially obtainable kit (bio-Merieux), the value of the cholesterol spectrophotometrically specified at wave length 500nm.The serum TG was assessed through the use of the enzymatic approach by using the Bio-Merieux kit. The TG serum concentration has been specified at 500nm.Level of the HDL-c and LDL were measured with the use of the enzymatic approach by using the (bio-Merieux) kit and specified spectrophotometrically at wave length 500nm. The ketone body was measured by using BioAssay\USA, EnzyChromTM Ketone Body Assay Kit (EKBD-100) and absorbance measured at wave length 340 nanometer.

5. Body Weight

Rats body weights were measured weekly through all the experimental period for all groups. Initial weight was registered at zero time, and then recorded the final weight at the end of the experiment after 30 days.

6. Statistical Analysis

The data of the experiment were calculated by using one-way analysis of difference and the group differences were calculated using Duncan multiple range test, data are presented as mean± SM, the different big letters investigate a significant difference ($P<0.05$).

Results

The obtained results in table 1 indicated the presence of Tannin, Saponine, Phenol, Flavonoids ,Terpenes, and Volatile oil

Table 1: Manual detection of some active compounds in the aqueous extracts of *Allium sativum* and *C. aurantifolium*

Phytochemicadl compoun	***Allium sativum***	***C. aurantifolium***
Tannin	+	+
Sap nine	+	-
Phenol	+	+
Flavonoids	+	+
Volatile oil	+	_
terpenes	+	+

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Received 05 March 2021; Accepted 01 April 2021.

As shown in table 2 the results of glucose levels significantly increased in untreated diabetic group(398.21±5.84) at the end of experiment compare with control group(89.33±3.65)and treated groups with garlic, *C.aurantifolium* and mix plants(176.10±2.69 ,205.45±4.09 and159.73±2.67) mg\dl respectively. On other hand the results showed a significant decreased in glucose levels in group treated with mix plants(159.73±2.67) as compared with garlic (76.10±2.69) and *C. aurantifolium* (205.45±4.09) after twenty days of treatment. Also the results display significant improvement in insulin level in groups which treated with garllic, *C.aurantifolium* and mix plants (4.61±1.22 ,3.69±1.03 and 4.21±1.50) mg\dl respectively compared with untreated diabetic group(1.88±0. 60).The value of ketone body was revealed significant increase in untreated diabetic group (12.65±3.04) while the value of ketone body was decreased in all treated gropes included garllic, *C.aurantifolium* and mix plants(5.73±1.98, 6.94±2.86 and4.90±1.84) respectively

Table2: The effect of *Allium sativum* and *C.aurantifolium* extracts on the level of glucose. insulin and Ketone body in diabetic rats.

Groups	FBS mg\dl means ±SE	F.s. insulin uU\ml means ±SE	FBS mg\dl means ±SE	F.s.insulin uU\ml means ±SE	FBS mg\dl means ±SE	F.s.insulin uU\ml means ±SE	ketone body Mmool means ±SE
Control	105.54 ±3.64 E	5.74±1.07 A	91.54± E	5.08±1.53 A	89.33±3.65 E	4.98±1.63 A	2.43±0.08 C
Untreated diabetic	383.22±5.69 B	383.22±5.69 B	368.06± A	2.09±0.65 C	398.21±5.84 A	1.88±0. 60 C	12.65±3.04 A
Diabetic + garlic 150 mg\kg	370.53±2.55 C	2.57±0.97 B	212.63± D	3.66±1.05 B	176.10±2.69 C	4.61±1.22 A	5.73±1.98 B
Diabetic +C. aurantifolium 150 mg\kg	345.37±4.67 D	2.34±0.78 B	265.31± B	3.32±1.09 B	205.45±4.09 B	3.69±1.03 B	6.94±2.86 B
Diabetic + garlic+C. aurantifolium 150 mg\kg	395.12±3.48 A	2.32±0.83 B	244.38± C	3.87±1.03 B	159.73±2.67 D	4.21±1.50 A	4.90±1.84 AB

Means having with the different letters in same column differed significantly

There was a significant $p<0.05$ increase in the level of serum cholesterol in untreated diabetic group (108±3.08) mg\dl compared with control group (85±2.90)mg\dl ,the results show a significant $p<0.05$ decline in cholesterol level in groups treated with garlic ,C. *aurantifolium* and mix extract (91±3.98, 95±4.35 and 87±2.45) mg\dl respectively compared with the untreated diabetic group (108±3.08) mg\d. The levels of Triglyceride obtained significant $p<0.05$ increase in untreated diabetic group(102±4.43) mg\dl compared with control group(82±2.65) mg\dl ,while results show significant $p<0.05$ decreased in Triglyceride in all groups treated with garlic ,*C. aurantifolium* and mix extract (989±3.96, 90±3.78 and 85±3.73) mg/dl respectively compared with untreated diabetic group102±4.43 mg\dl . The results of (HDL) revealed significant $p<0.05$ improvement in in groups treated with garlic ,*C. aurantifolium* and mix extract(38±2.94, 32±2.09 and 42±3.02) mg\dl compared with control and untreated diabetic groups(30±2.12 and 24±3.53) mg\dl .the results were revealed significant $p<0.05$ increased in (LDL) in untreated diabetic group(55±5.42)

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and reduced level of LDL in groups which treated with garlic ,*C. aurantifolium* and mix extract(40±3.59, 43±4.50 and30±3.42) mg\dl,as shown in table 3

Table3: Effect of *Allium sativum* and *C. aurantifolium* extracts on lipid profile.

Groups	Cholesterol mg\dl means ±SE	Triglyceride mg\dl means ±SE	HDL mg\dl means ±SE	LDL mg\dl means ±SE
Control	85±2.90 C	82±2.65 C	30±2.12 B	44±3.22 B
Untreated (diabetic)	108±3.08 A	102±4.43 A	24±3.53 C	55±5.42 A
Diabetic garlic 150 mg\kg	91±3.98 B	89±3.96 B	38±2.94 A	40±3.59 C
Diabetic C. aurantifolium+ 150 mg\kg	95±4.35 B	90±3.78 B	32±2.09 B	43±4.50 B
Diabetic C. aurantifolium+ garlic 150 mg\kg	87±2.45 C	85±3.73 C	42±3.02 A	30±3.42 D

Means having with the different letters in same column differed significantly

Body weight of each rat was investigated at the first day of experiment and the final body weights were recorded at the end of experiment after 30 days ,there was a significant <0.05 decrease in body weight in untreated diabetic groups156 ± 3.40 compared with the same animals groups at the beginning of experiment185 ± 4.85 ,also the results show no significant decrease in body weight for groups treated with garlic and C. aurantifolium (177±3.96 176±4.34respectively after 30 days of treatment compared with the same animals at the first day(179±4.76 ,181±3.99) g respectively. While body weight show a significant $p<0.05$ improvement in the group treated with mix plants extract 184 ±4.30 g after 30 days as compared with these group at the beginning of experiment (178 ±2.93 g,as recorded in table 4

Table4: Effect of *Allium sativum* and *C. aurantifolium* extracts on body weight.

Groups	Initial body weight\gm means ±SE	Final body weight\gm means ±SE
Control	182± 3.44 B	193 ± 5.88 A
Untreated diabetic	185 ± 4.85 A	156 ± 3.40 B
Diabetic + garlic 150 mg\kg	179±4.76 A	177±3.96 A
Diabetic+ C.aurantifolium 150 mg\kg	181±3.99 A	178±4.34 A
Diabetic + garlic+C. aurantifolium 150 mg\kg	178 ±2.93 B	184 ±4.30 A

Means having with the different letters in same row differed significantly

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Discussion

The result obtained from this study indicated the presence of Tannin, Sapnine, phenol, Volatile oil and Terpenes in the aqueous extracts of *Allium sativum* and *C. aurant*-ifolium (table 1) , The results presented in table2 showed a significant decreased in glucose levels in group treated with mix plants as compared with garlic and *C. aurantifolium* after twenty days of treatment, also the results display a significant improvement in insulin level in groups which treated with garlic, *C. aurantifolium* and mix plants compared with untreated diabetic group, these results might be related to that, Ethanolic extracts of garlic reported an antidiabetic activity against alloxan-induced diabetic mice by inducing the insulin secretion from parietal cells of the pancreas [20]. Another clinical work examined the antidiabetic effect of garlic pills administration in patients with type II diabetes and hyperlipidemia and they revealed that garlic pills inhibit the fasting blood sugar and cholesterol level [21]. Moreover garlic contain allicin , cysteine sulfoxide, and S-allyl cysteine sulfoxide and these compounds reduced the level of glucose by several mechanism that include, enhancing the secretion of insulin from beta cells, increasing the cell sensitivity to insulin and preventing the insulin activation caused by liver, the activity of allicin in reducing blood glucose in rats was similar to that investigated by insulin and glibenclamide. Garlic oil also was reported to decrease the serum alanine transferases ,amylase and aspartate in diabetic rats[22].The limonene effects include stimulation of insulin secretion ,regeneration of β-ells, amelioration of secondary complications of higher blood glucose such as hyperlipidaemia via inhibition of liver x receptors signaling pathway, modulation of transcription factors such as activation of peroxisome proliferator-activated receptors and modulation of rate limiting enzymes of carbohydrate metabolism [23,24] , garlic and citrus extract contain flavonoids which have anti-diabetic effect through their ability to modulate glucose metabolism or insulin sensitivity at different levels, increase glucose uptake and insulin secretion, and inhibit glucose production [25]

Also this results could be attributed to the antioxidant vitamins present in garlic and citrus extract . The mechanism of action could be explained through the ability of the antioxidant vitamins to scavenge free radicals preventing alloxan-induced oxidative stress and protecting the β cells. This will consequently increase insulin secretion and decrease elevated blood glucose levels and lead to decrease ketone body . Plant extracts are known to exert anti-diabetic activity through enhancing cellular glucose uptake and activation of insulin release from the pancreatic β-cells [26], the administration of *C. aurantifolia* oil D-limonene to hyperglycemic mice and rats caused a significant reduction in blood glucose, triacylglycerol and cholesterol level, this effect may be due to that D-limenone modulate the glycogen metabolism in hyperglycemic animals [27].thus our results investigated that both plant extract is good strategy for decreasing blood glucose when act synergicelly.

According to the results presented in table 3 there was a significant $p<0.05$ decreased in , cholesterol, Triglyceride,HDL,LDL level in groups treated with garlic ,*C. aurantifolium* and mix extract compared with the untreated diabetic group. Garlic can improve metabolic syndrome such as hypercholesterolemia and hypertension, the ability of garlic in reducing lipid peroxidation is through mechanism of reducing levels of malondialdehyde, this resulting a protection of heart blood vessels from damage due to oxidative stress [28].The mechanism for reducing blood cholesterol by garlic is related to that garlic contained vitamin C (ascorbic acid) which have the ability to destroy existing plaques by binding to lipoproteins

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Received 05 March 2021; Accepted 01 April 2021.

and expelling them from the body, increasing vessel elasticity blood by building collagen, prevent endothelial damage that normally initiates inflammatory responses, also garlic contain niacin (nicotinic acid) that can reduce cholesterol and LDL levels by inhibition of free fatty acid flow from adipose tissue and suppression the activity of the lipoprotein lipase enzyme, reduction fat mobilization and VLDL production in the liver. Furthermore garlic have the ability to inhibit enzyme 3- hydroxy-3-methylglutaril coenzyme (HMG-CoA) reductase by binding to the SH group which is a functional part of coenzyme, so that, there is direct inhibition of the enzyme and suppression of cholesterol synthesis [29]

Menichini et al. (2011) accredited the potential of citrus peel extract in plasma triglyceride reduction to the ability of citrus flavonoids to prevent conjugation between triglycerides and oleic acid ,thus leading to an overall decrease in cholesterol level. The citrus flavonoids decrease free fatty acids and increase fecal excretion of triglycerides, bioactive materials in citrus extract trigger the activation of receptor cells that incorporate excess triglycerides and LDL into the liver rather than circulating in the vascular system to form plaque [30],also the polyphenol compounds in the citrus extract are powerful plasma lipid lowering agents by increasing the antioxidant activity and by modulating hepatic HMG-CoA levels, possibly by binding bile acids and increasing the turnover rate of blood and liver cholesterol [31]. The present result investigated the beneficial and important effects of garlic and *C. aurantifolium* in the health sciences as it opens new felids in drug synthesis and treatment of diabetes.

Several studies may examine the effect of garlic extract on obesity by decreasing the synthesis of fatty acid [32,33], garlic contains multiple organosulfur compounds which have anti-obesity properties. Thiacremonone is sulfur compound isolated from garlic that has an effect on adipocyte cell which lead to decreasing body weight [34,35].The *C. aurantium* extract was demonstrated to enhance metabolic rate ,energy expenditure and to promote weight loss when given for six to 12 weeks [36], the extracts from peels citrus could prevent the development of obesity through the modulation of lipid and glucose metabolism. It is investigated that polyphenols considerably inhibited the fat accumulation, hyperlipidemia, high blood glucose levels and insulin resistance, weight gain which are different aspects of obesity [37], but our result indicated an improvement in body weight in groups treated with mix extract (table 4), this may be attributed to difference in study design and other mechanism that not fully understand.

Conclusion

From the results obtained in this present work, it could be safely concluded that both garlic and *C.aurantifolia* extract be useful in formulating strategies for therapeutic of hyperglycemia and diabetic complication.

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