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THERAPEUTIC EFFECTS OF ALLICIN AGAINST THE DIABETES MELLITUS INDUCED BY STREPTOZOTOCIN IN MALE RATS

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Abstract

This study aimed to see how allicin (45mg/kg BW) affected diabetic Mellitus in male rats (DM). Forty male rats were utilized, and they were split into four groups at random for 42 days. T2 was treated with 45 mg/kg B.W of allicin dissolved in 1 ml of D.W daily and injected with a single dose of sodium citrate buffer (0.5ml Intra-Peritoneal IP), DM was induced in T1 and T2 by injection of a single dose of streptozotocin 50 mg/kg B.W IP, T1 was assigned as a positive control, T3 received 45 mg/kg B.W. of allicin dissolved in 1 ml D.W. every day, and a single dose of sodium citrate buffer was injected (0.5ml IP). When diabetic rats treated with allicin in T2 were compared to diabetic rats in T1, the findings indicated a significant increase (P0.05) in body weight growth, insulin, total protein, and albumin, better lipid profile, and reduced glucose concentration. Histological investigations revealed that the island of Langerhans had atrophy and necrosis in the exocrine tissue in the T1 group, whereas the T2 group had a large island of Langerhans. The findings in the T3 group marked hyperplasia of the island of Langerhans. The 45mg/kg, B.W. of allicin, has a hypoglycemic effect and elevates the expression level of insulin and pancreas tissue protection effect when used orally in adult rats at the given dose for forty-two days.

Keywords: Allicin therapy, Diabetes mellitus, Insulin, Lipid profile determination, Streptozotocin poisoning

Introduction

Diabetes mellitus is a group of metabolic illnesses characterized by hyperglycemia induced by insulin production, action, or both. Diabetes causes long-term damage, dysfunction, and failure of multiple organs, including the eyes, kidneys, nerves, heart, and blood vessels (Cho et al., 2018; Ugbaja et al., 2021). Because of the side effects that come with oral hypoglycemic drugs used to treat diabetes, there is a growing interest in herbal therapies (Rao et al., 2010; Kumar et al., 2020). As a result, traditional herbal treatments produced from plants are commonly used and serve an important role in diabetes control (Pere M. and Cerar A. 2011). Because allicin has the ability to lower blood sugar, it's an effective dietary approach for diabetes management. Garlic lowered blood glucose levels in STZ-induced (Patumraj et al., 2000; Wang et al., 2017) and alloxan-induced DM rats and mice (Kumar and Reddy 1999; Iftikhar et al., 2020). Further to that, allicin has been shown to reduce diabetes conditions in rats at nearly the same levels as glibenclamide and insulin (Shoshi and Akter H. 2016). When diabetic rats were given garlic oil, the activities of serum acid and alkaline phosphatases, serum alanine and aspartate transferases, and serum amylase all decreased significantly (Ohaeri 2001). At 250 mg Kg1 body weight, allicin was around 60% as effective as tolbutamide against alloxan-induced diabetes (Banerjee and Maulik 2002).

Allicin performs physiological activities in microbial, plant, and human cells (Borlinghaus et al., 2014). Allicin's pharmacokinetics have been investigated largely in terms of absorption and metabolism (Vazquez-Prieto and Miatello 2010). Because of its high membrane permeability, it may be swiftly absorbed in somatic cells without causing damage to the phospholipid bilayer. After absorption, it is

quickly metabolized in the body to produce acetone, allyl methyl sulfide (AMS), and other metabolites, with AMS being the most active. According to several studies, allicin is quickly absorbed after consumption (Lawson and Wang 2005; Najafi and Masoumi 2018).

STZ is a DNA methylating agent and a small molecule antibiotic. This chemical showed substantial methylation of the liver, kidney, and pancreatic cells in rat cells, as well as selectivity for these cells over the aglycone analog N-methyl-N-more nitrosourea's broad methylating action. STZ has been used to cause diabetes in animals and to treat human pancreatic malignancies due to its specific action in the pancreas (Konda *et al.,* 2020). The anomalies in -cell function are reflected in these alterations in blood glucose and insulin concentrations. STZ reduces insulin production and secretion and affects glucose oxidation (Zangeneh *et al.,* 2018; Xinglong et al., 2020). (Bayramoglu *et al.,* 2014).

In diabetes research, STZ is the most significant diabetogenic molecule. STZ is a hazardous glucose analog that binds to the GLUT2 glucose transporter and accumulates in pancreatic cells (Tekula *et al.,* 2018). STZ is broken down into its glucose and methyl nitrosourea moiety once it is taken in by the cells. Because of its alkylating capabilities, it changes biological macromolecules, breaks DNA, and kills cells, resulting in insulin-dependent diabetes. STZ's ability to suppress glucose-induced insulin release is further explained by its targeting of mitochondrial DNA, which impairs the signaling function of cell mitochondrial metabolism (El-Borady *et al.,* 2020; Xinglong et al., 2020).

Material and methods

Experimental Animals

In this investigation, forty adult male rats with an average weight of 190-250 gm and a lifespan of 120 days were employed. The animals were kept in well-ventilated wire-plastic cages with diameters of 40-60cm and raised under regulated circumstances of 12 hours of light and 12 hours of darkness at a temperature of (232). Standard laboratory food and water were provided. Before the trial, the animals were given two weeks to acclimate in the animal home. Before the experiment began, three rats were used to induce diabetes after a fasted night by injecting a single dose of Streptozotocin (50mg/kg BW IP) and measuring glucose using blood test strips according to Stedman (2006)'s method, which was utilized with an Accu-Chek Active meter. All animals were sedated with a combination of Ketamine + xylazine (Alfasan, WOERDEN-HOLAND) (90mg and 10mg/kg IP) (Lei et al., 2001) and sacrificed to extract the pancreas and preserved in formalin 10% for histological investigations to prove induction of diabetes.

The animals were randomly allocated into four equal groups as follows: T1 group received D.W 1ml daily for 42 days and was injected with a single dose of citrate buffer (0.5 ml IP) ph 4.5, whereas the control group received a single dose of STZ (50mg/kg BW IP) (Gupta and Gupta 2009) After a fasted night, STZ was dissolved in citrate buffer ph4.5 and administered in D.W1ml for forty days, after which rats were given water containing 5% glucose instead of drinking water after five hours from STZ injection to overcome the high insulin released by all rats injected with STZ, T2 group injected with a single dose of STZ (50mg/kg BW IP) to overcome the high insulin released by all rats injected with STZ (Gupta and Gupta 2009) and after five days then treated with allicin orally (45mg/kg/BW) dissolved in 1ml D.W for forty-two days and T3 group administration with allicin (45mg/kg BW) (Huang et al., 2017) daily dissolved in 1 ml of D.W for forty-two days and injected with a single dose of citrate buffer (0.5 ml IP).

Methods

Preparation of allicin

Allicin was purchased from Bioactive Mega Company in the United States and was dissolved in distal water at room temperature in a dark container every day for drenching.

Preparation of STZ for IP Injection

The appropriate amount of STZ was obtained from (medchemxpress company/USA) and freshly dissolved in citrate buffer based on the weight of the animals and the dose of STZ (50mg/kg, BW). STZ was newly made (20 minutes before injection), and the container was covered with aluminum foil to prevent the buffer from direct light exposure (Akbarzadeh et al., 2007).

Preparation of Sodium Citrate Buffer:

1 molar sodium citrate buffer was made by combining 2.1 grams of citric acid and 2.94 grams of sodium citrate (BDH, England) in 50 ml of distilled water, adjusting the pH to 4.5 using NaOH (BDH, England), and then completing the volume to 100 ml (Rajurkar et al., 2011).

Induction of Diabetes

In overnight starved rats, a single IP injection of STZ at a dose of 50 mg/kg body weight was utilized to induce diabetes mellitus.Before injection, STZ was newly produced by dissolving it in citrate buffer (pH 4.5). (Gupta and Gupta 2009). Then, five hours after STZ injection, instead of drinking water, provide water containing 5% glucose to all rats treated with STZ to counteract the elevated insulin release. The use of an Accu-Chek Active meter was used to track hyperglycemia in rats for five days (Nagpur, Maharashtra, India). Diabetic rats were defined as male rats with blood glucose levels more than 250 mg/dl. (Zhang et al., 2006) and utilized to test the anti-hyperglycaemic activity of allicin.

Blood samples collection:

After 24 hours after the previous dose of allicin and after an overnight fast, all animals were sedated with a combination of ketamine and xylazine (90mg/kg/B.W,10mg/kg/B.W IP) according to the technique of (Stedman 2006) that was utilized with Accu-Chek Active meter. Then a blood sample was taken directly from the heart to obtain serum from the animals, which was stored at -20 until used for insulin hormone assessment (Ray Biotech, USA) and biochemical tests such as serum glucose (Comatest linear, Spain), serum albumin, serum total protein, serum total cholesterol, serum triglyceride, serum HDL-c, and serum HDL-c, Serum VLDL-c, Serum LDL-c concentrations (Biolabo SA, France) and remove the pancreas and reserved in formalin 10%, for histological studies.

Data Analysis:

After statistical examination of the data using the computer program SPSS, Version 23, one-way analysis of variance (ANOVA), the difference was determined to be significant at P 0.05. (Zar 1984).

Results and Discussions

1. Body Weight

Table 1 presented the findings of body weight growth during 42 days in the trial, which revealed substantial disparities. When compared to the other groups, statistical analysis revealed a substantial reduction (P> 0.05) in the T1 group, which included diabetic non-treated male rats. T2 group gained much more weight than T1, whereas T3 group gained significantly more weight than the control group.

Table 1: Body Weight (g) Gain of Diabetic Male Rats Treated by Allicin

Group	Week					
	First	Second	Third	Fourth	Fifth	Sixth
C	183.5±3 a	189.2±1.77 b	197.8±1.23 c	205.9±1.5 d	211.3±1.24 e	217.8±3.62 e
T1	183.8±3.3 7 a	182.1±3.02 B	178.5±2.22 x	173.3±1.24 c	170.7±1.49 d	167.6±3.92 f
T2	184.4±2.5 1 a	185.4±2.43 b	186.6±2.26 x	188.6±2.42 e	188.9±2.52 f	192.3±2.53 v
T3	182.4±3.0 7 a	191.6±2.75 B	203.6±1.46 c	214.6±1.01 n	222.7±2.18 i	231.6±2.19 s
$L.S.D_{0.05}$				8.27		

Numbers represent the mean ± standard error.

Significant differences between groups (P<0.05) are denoted by different letters. Control group administration of D.W 1ml and injected with single dose of citrate buffer (0.5 ml IP), T1 group injected with STZ (50mg/kg B.W IP) and administration D.W 1ml, T2 group received of single dose of STZ (50mg/kg B.W IP) and after five day then treated with allicin orally (45mg/kg/B.W dissolved in 1ml D.W), T3 group administration of allicin (45mg/kg BW) once daily dissolved in1ml D.W and received a single dose of citrate buffer (0.5 ml IP).

2. Glucose and Insulin Serum Levels

Table 2 showed the concentrations of glucose and insulin in induced diabetic rats treated with allicin. The results revealed a significant reduction in blood glucose levels for the animals treated with allicin when compared to the diabetic animal group while remaining significantly higher than the control animal group, whereas insulin levels significantly increased when compared to the diabetic rats. The T3 group showed a substantial rise in insulin levels when compared to the control group.

Table 2: Concentration of Serum glucose and insulin in diabetic male rats treated by allicin

Tests	Groups				
	C	T1	T2	T3	$LSD_{0.05}$
Glucose (mg/dl)	114.98±2.07 a	535.18±11.58 b	221.03±11.26 c	100.78±1.75 a	24.347
Insulin conc. (µIU/ml)	23.61±0.61 a	6.82±0.29 b	17.32 ±0.5 c	27.76 ±1.51 d	2.918

Numbers represent the mean ± standard error. Significant differences between groups (P<0.05) are denoted by different letters. Control group administration of D.W 1ml and injected with single dose of citrate buffer (0.5 ml IP), T1 group injected with STZ (50mg/kg B.W IP) and administration D.W 1ml, T2 group received of single dose of STZ (50mg/kg B.W IP) and after five day then treated with allicin orally (45mg/kg/B.W dissolved in 1ml D.W), T3 group administration of allicin (45mg/kg BW) once daily dissolved in1ml D.W and received a single dose of citrate buffer (0.5 ml IP).

3. Lipid Profile Serum Levels

Table 3 exhibited a significant rise in the levels of cholesterol, triglycerides, VLDL-c, and LDL-c serum in T1 (Diabetic rats) compared with the control group (P<0.05), but a significant decrease in the level of HDL-c serum in T1. Orally ingested of allicin to diabetic rats (T2) decreased the level of cholesterol, triglyceride, VLDL-c, and LDL-c compared to T1 (diabetic rats) (P<0.05), while increasing the level of HDL-c, with no significant difference among T2 and control group in the level of cholesterol, triglyceride, HDL-c, VLDL-c, and LDL-c serum Although there is a substantial drop in cholesterol, triglyceride, VLDL-c, and LDL-c levels between the control and T3 groups, there is an increase in HDL-c levels in the T3 group compared to the control group.

Table 3: Level of serum lipid profile in diabetic male rats treated by allicin

	Parameter				
Group	Cholesterol mg/dl	triglyceride mg/dl	HDL mg/dl	LDL mg/dl	VLDL mg/dl
C	93.46±1.5 a	83.88±0.98 a	29.91±1.2 a	46.76±1.17 a	16.77±0.9 a
T1	180.13±5.9 b	143.74±4.6 b	20.47±0.8 b	130.84±4.7 b	28.64±0.2 b
T2	95.08±1.22 a	85.63±1.07 a	27.47±0.1 a	50.46±0.98 a	17.1±0.21 a
T3	81.47±1.13 d	72.87±0.99 d	38.71±.02 d	28.18±1.2 d	14.57±0.9 d
$LSD_{0.05}$	9.267	6.579	2.761	7.565	1.197

Numbers represent the mean ± standard error.

Significant differences between groups (P<0.05) are denoted by different letters. Control group administration of D.W 1ml and injected with single dose of citrate buffer (0.5 ml IP), T1 group injected with STZ (50mg/kg B.W IP) and administration D.W 1ml, T2 group received of single dose of STZ (50mg/kg B.W IP) and after five day then treated with allicin orally (45mg/kg/B.W dissolved in 1ml D.W), T3 group administration of allicin (45mg/kg BW) once daily dissolved in1ml D.W and received a single dose of citrate buffer (0.5 ml IP).

4. Total Protein and Albumin

Table 4 showed total protein and albumin levels in induced diabetic rats treated with allicin. The results indicated a significant increase (P<0.05) in blood total protein and albumin levels for the animal treated with allicin when compared to the diabetic animal group, since there is a significant (P<0.05) difference in serum total protein levels between T3 and the control group, with T3 group higher than the control group.

Table 4: Total protein and albumin of dabetic male rats treated by allicin

Tests	**Group**				
	C	**T1**	**T2**	**T3**	**$LSD_{0.05}$**
Total protein (g/dl)	6.3±0.1 A	3.58±0.23 B	5.13±0.19 C	6.89±0.11 D	0.514

Albumin (g/dl)	3.66±0.11 A	2.53±0.11 B	3.3±0.09 C	3.94±0.05 A	0.294

Numbers represent the mean ± standard error.

Significant differences between groups (P0.05) are denoted by different letters. Control group administration of D.W 1ml and injected with single dose of citrate buffer (0.5 ml IP), T1 group injected with STZ (50mg/kg B.W IP) and administration D.W 1ml, T2 group received of single dose of STZ (50mg/kg B.W IP) and after five day then treated with allicin orally (45mg/kg/B.W dissolved in 1ml D.W), T3 group administration of allicin (45mg/kg BW) once daily dissolved in1ml D.W and received a single dose of citrate buffer (0.5 ml IP).

Histopathological Changes in Pancreases of Diabetic Male Rats Treated by allicin

Appear our figure pancreatic tissue is composing of normal island of Langerhans with normal blood vessel also there is thin trabiculae separated normal exocrine tissue (Figure 1). Appear our figure pancreatic tissue rats that sacrifice after five day that give STZ (50mg/kg B.W IP) to improve happened of diabetes there is marked necrosis in exocrine tissue and in the island of Langerhans with atrophy of the island of Langerhans also there is thickening of blood vessels with wide trabiculae between exocrine tissue (Figure 2).

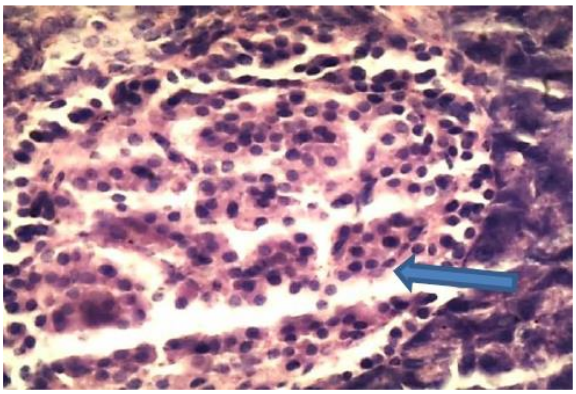

Figure 1: Control group pancreas of rat it drenched with D.W 1 ml for forty two days and injected with sodium citrate buffer (0.5 ml IP). Higher magnification there is normal island of Langerhans (blue arrow) which showed with normal blood vessel (blue arrow) also there is than trabiculae separated normal exocrine tissue 40X H&E.

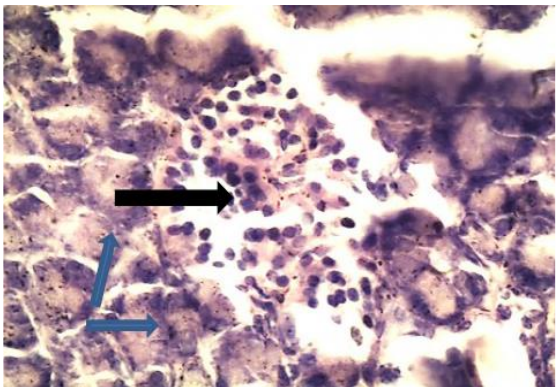

Figure 2: T1 diagnosis pancreas of rat injected with STZ (50 mg/kg BW IP) single dose there is marked necrosis in exocrine tissue (blue arrow) and in the island of langerhans with atrophy of the island of Langerhans (black arrow) 40xH&E.

Appear our figure pancreatic tissue in the T2 group give STZ (50mg/kg BW IP) and after five day drenching with allicin (45mg/kg B.W) for forty two days there is wide island of Langerhans with normal exocrine tissue also there is presence of thin trabiculae between exocrine tissue also there is mild thickening in the wall of blood vessel with presence of adipose tissue in exocrine tissue (Figure 3). Appear our figure pancreatic tissue in T3 group drenching with allicin (45mg/kg BW) for forty two days there is marked hyperplasia of island of Langerhans with proliferation of adipose tissue within exocrine tissue also there is normal blood vessels (Figure 4).

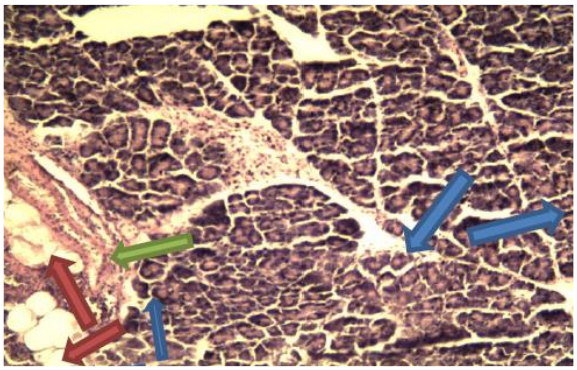

Figure 3: T2 pancreas of rat injected with STZ (50 mg/kg BW ip) single dose and after five days drenched with allicin (45 mg/kg BW) for forty two days. There is wide island of Langerhans (black arrow) with normal exocrine tissue (blue arrow) also there is presence of thin trabiculae between exocrine tissue Also there is mild thickening in the wall of blood vessel (green arrow) with presence of adipose tissue in exocrine tissue (red arrow) 10X H&E.

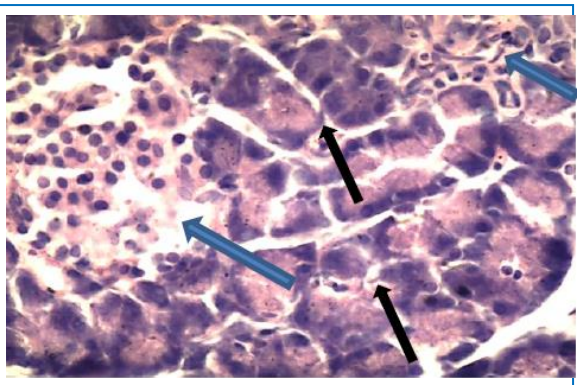

Figure 4: T3 pancreas of rat it drenched with allicin (45 mg/kg BW) for forty two daysand injected with sodium citrate buffer(0.5 ml IP) single dose There is marked hyperplasia of island of Langerhans (black arrow) with proliferation of adipose tissue (blue arrow) within exocrine tissue also presence of marked trabiculae (green arrow) separated normal exocrine tissue also there is normal blood vessels (red arrow). 40X H&E.

Discussion

After 42 days of therapy with allicin, diabetic rats gained weight despite consuming less food and water. This might be linked to improved hyperglycemic control and allicin's antihyperlipidemic effects in diabetic rats. Allicin treatment was shown to be effective and resulted in a significant increase in body weight in diabetic rats (Liu et al., 2012; Xin'e et al., 2019). When compared to control animals, the T1 group had higher food consumption and lower body weight, indicating polyphagia and weight loss through tissue protein breakdown. Dehydration might be to blame for the diabetic rats' weight loss and catabolism of fat and proteins (Dubey et al., 2012).

In this study, the structural and molecular effects of allicin on diabetes and -cell damage in STZ-induced diabetic male rats were studied. The outcomes of this study demonstrated that oral administration of allicin (45mg/kg BW) for 42 days had a significant hypoglycemic effect in STZ-induced diabetic male rats. Allicin is an anti-diabetic compound (Osman et al., 2012; DAFRIANI et al., 2020). Garlic has been demonstrated to influence insulin synthesis from -cells, the release of bound insulin, and insulin sensitivity improvement (Szkudelski and Szkudelska 2015; Kaur et al., 2016).By interacting with endogenous thiol-containing molecules including cysteine, glutathione, and serum albumin, allicin-derived organosulphur compounds protect insulin against –SH inactivation(Eidi A., Eidi M. and Esmaeili 2006; Shoshi and Akter H. 2016). Diabetic rats had higher levels of cholesterol, triglycerides, VLDL-c, and LDL-c, as well as lower levels of HDL. Furthermore, increased non-enzymatic glycation, lipid peroxidation, and the cholesterol/phospholipid ratio suggest that diabetes alters the lipid composition of cell membranes (Masjedia, Golb and Dabiric 2013; Lee et al., 2019).

Sprague–Dawley rats fed a high fructose diet with allicin had considerably lower triglyceride levels (Abdel-Daim et al., 2017).

Female Sprague–Dawley rats fed garlic powder containing 0.6 percent allicin had decreased cholesterol and triglyceride levels, according to another study (Al-Qattan et al., 2000). The levels of cholesterol and LDL were observed to be lower in hyperlipidemic rabbits after eight weeks of oral treatment of allicin at a dosage of 3 mg/kg daily (Dubey et al., 2012). Garlic's hypocholesterolemic impact might be due to allicin's ability to inhibit hepatic cholesterol synthesis by forming sulfide bridges between 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-COA) reductase and the disulfides found in garlic (Matsutomo et al., 2017; Najafi and Masoumi 2018).Our findings are in agreement with those of (Masjedia, Golb, and Dabiric 2013; Liu and Yeh 2001), who found a decrease in blood cholesterol and triglyceride levels that were lower than normal in rats given garlic juice for three weeks prior to STZ injection (1 mL garlic juice/100 g BW/day) (Masjedia, Golb and Dabiric 2013; Lee et al., 2019).

In diabetic rats, serum total protein and albumin were substantially lower than in control rats. Insulin shortage caused a decrease in ribosomal protein synthesis, which resulted in a drop in serum total protein. The drop in serum albumin was another another sign of liver injury. Our findings are in line with those of (Alhazza 2007), who discovered that diabetic rats had considerably lower blood total protein and albumin levels. The capacity of allicin to efficiently scavenge oxygen free radicals is connected to its antioxidant action. According to Zhang and Shi (2002), allicin may effectively remove •O2- and •OH radicals, with a significant dose-dependent relationship. The antioxidant activity of garlic and garlic extracts has been demonstrated. Our results are supported with those of (Metwally 2009), who noticed that total protein in serum was considerably higher in fish fed any source of garlic than in other control groups, and to those of (HUSSEIN, ABD-EL-MAKSOUD, and AZAB 2001), who discovered that serum total protein levels were elevated in male albino rats after administration of garlic oil. The increase in total protein level may be linked to the increase in immunoglobulin level and total globulin concentration in hyperlipidemic rats given garlic oil (Yuvashree, Ganesh and Viswanathan 2020).

STZ-induced -cell death mostly affects big pancreatic islets in the pancreatic core, according to the findings. We also discovered that hyperglycemic STZ-treated animals have a substantial pool of surviving -cells, although GLUT2 islet shape is downregulated throughout the pancreas. These results are in line with previous findings (Attia 2009; Hahn et al., 2020).

Allicin's antioxidative activity provided protection to the Langerhans island and the cell. The antioxidant capabilities of allicin, which reduced lipid peroxidation, may be responsible for these beneficial benefits. Allicin's antioxidant properties might be another explanation for its positive effect on diabetes (Najafi and Masoumi 2018), postponing diabetic adverse effects. The majority of cells in Langerhans Island were protected by allicin. Allicin appears to mitigate the majority of STZ's harmful effects on pancreatic islets. This might be a compensatory strategy to adjust to metabolic changes by dividing to supply the energy needed for insulin synthesis and release, as well as increasing the production of antioxidant enzymes to protect -cells from oxidative stress. The results of this study accord with those of (Osman et al., 2012; Kalhotra et al., 2020), who found that injecting alllicin (8 mg/kg.B.W IP) into diabetic rats preserved the majority of cells in the islets of Langerhans. Allicin drenching (45mg/kg BW) showed marked hyperplasia of island of Langerhans with proliferation of adipose tissue within exocrine tissue present study agree with (Najafi and

Masoumi 2018; Masjedia, Golb and Dabiric 2013), drenching of garlic to rat for forty two days showed increase number and diameter of island of Langerhans.

Conclusion

Can be concluded that 45mg/kg, B.W, of allicin, has a hypoglycemic effect and elevating the expression level ofinsulinand pancreas tissue protect effect when used orally in adult rats at the given dose and for forty two days, therapeutic effects of allicin induce skeletal muscle cell proliferation, improved body weight and showed antihyperlipidemic effect that demonstrates the antidiabetic effect and its possible mechanism of action.

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AUTHOR'S CONTRIBUTION

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References

Abdel-Daim, M.M.; Kilany, O.E.; Khalifa, H.A.; Ahmed, A.A.M (2017). Allicin ameliorates doxorubicin-induced cardiotoxicity in rats via suppression of oxidative stress, inflammation and apoptosis. Cancer Chemother Pharmacol. Oct;80(4):745-753.

Akbarzadeh, A.; Norouzian, D.; Mehrabi, M.R.; Jamshidi, S. and Lame, R (2007). Induction of diabetes by Streptozotocin in rats. Indian J Clin Biochem. Sep;22(2):60-4.

Alhazza,I.M (2007). Antioxidant and hypolipidemic effects of olive oil in normal and diabetic male rats. Saudi Journalof Biological Sciences;, 14(1): 69-74.

Ali, M., Al-Qattan, K.,Al-Enezi, F., Khanafe, R. and Mustafa, T (2000). Effect of allicin from garlic powder on serum lipid and blood pressure in rats fed high cholesterol diet. Prostaglandins Leukot Essent Fatty Acids. Apr;62(4):253-9.

Anjana Rao , Yongqiang Zhang, Sabina Muend, Rajini Rao (2010). Mechanism of antifungal activity of terpenoid phenols resembles calcium stress and inhibition of the TOR pathway. Antimicrob Agents Chemother. 2010 Dec; 54(12):5062-9.

Asra Iftikhar, Bilal Aslam, Maryam Iftikhar, Wafa Majeed, Mehwish Batool, Bushra Zahoor, Naseem Amna, Hareem Gohar, Iqra Latif (2020). "Effect of Caesalpinia bonduc Polyphenol Extract on Alloxan-Induced Diabetic Rats in Attenuating Hyperglycemia by Upregulating Insulin Secretion and Inhibiting JNK Signaling Pathway", Oxidative Medicine and Cellular Longevity, 2020 Mar 17;:9020219.

Attia, A.A. (2009). Histological and electron microscopic studies of the effect of beta carotene on the pancreas of streptozotocin (STZ)-induced diabetic rats. Pak J Biol Sci. 2009 Feb 15;12(4):301-14.

Banerjee SK, Maulik SK.. (2002). Effect of garlic on cardiovascular disorders: a review. Nutr J. Nov 19;1:4.

Bayramoglu G, Senturk H, Bayramoglu A, Uyanoglu M, Colak S, Ozmen A, Kolankaya D Cytotechnology. 2014 Mar;66 (2):251-7.

Cho, N. H. *et al.*, (2018). IDF diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res. Clin. Pract.*Apr; 138, 271–28.

DAFRIANI, Putri et al., (2020). Garlic: an alternative in reducing blood glucose on diabetic patients. International Journal Of Community Medicine And Public Health, [S.l.], v. 7, n. 6, p. 2078-2081.

Dubey, H., Singh, A., Patole, A. M., Tenpe, C. R., & Ghule, B. V (2012). Allicin, a SUR2 opener: Possible mechanism for the treatment of diabetic hypertension in rats. Brazilian Journal of Pharmacognosy, 22(5), 1053–1059.

Eidi, A., Eidi, M., Esmaeili, E (2006). Antidiabetic effect of garlic (Allium sativum L.) in normal and streptozotocin-induced diabetic rats. Phytomedicine. Nov;13 (9-10):624-9.

El-Borady OM, Othman MS, Atallah HH, Abdel Moneim AE. (2020). Hypoglycemic potential of selenium nanoparticles capped with polyvinyl-pyrrolidone in streptozotocin-induced experimental diabetes in rats. Heliyon. May 30 ;6 (5):e04045.

Fatemeh Masjedia, Ali Golb and Shahriar Dabiric (2013). Preventive Effect of Garlic (Allium sativum L.) on Serum Biochemical Factors and Histopathology of Pancreas and Liver in Streptozotocin- Induced Diabetic Rats. Iran J Pharm Res. Summer;12 (3):325-38.

Gupta R, Gupta RS (2009). Effect of Pterocarpus marsupium in streptozotocin induced hyperglycaemic state in rats: comparison with glibenclamide. Diabetol Croat., 38: 39-45.

Hahn M, van Krieken PP, Nord C, Alanentalo T, Morini F, Xiong Y, Eriksson M, Mayer J, Kostromina E, Ruas JL, Sharpe J, Pereira T, Berggren PO, Ilegems E, Ahlgren U (2020). Topologically selective islet vulnerability and self-sustained downregulation of markers for β-cell maturity in streptozotocin-induced diabetes. Commun Biol. Sep 30;3(1):541.

Hong Huang, Ying Jiang, Genxiang Mao, Fang Yuan,a Hexin Zheng, Yuan Ruana and TianfengWua (2017). Protective effects of allicin on streptozotocin-induced diabetic nephropathy in rats. J Sci Food Agric. Mar; 97(4):1359-1366.

HUSSEIN SA., ABD-EL-MAKSOUD H., AZAB ME (2001). Certain biochemical effect of garlic oil on normal and experimentally induced hyperlipidemia in male albino rats. In: INTERNATIONAL SCIENTIFIC CONFERENCE, 2, Mansoura. Mansoura: Mansoura University, 2001. p.103-29.

Jan Borlinghaus , Frank Albrecht , Martin C H Gruhlke , Ifeanyi D Nwachukwu , Alan J Slusarenko (2014). Allicin: chemistry and biological properties. Molecules. Aug 19;19 (8):12591-618.

Kalhotra, P.; Chittepu, V.C.S.R.; Osorio-Revilla, G.; Gallardo-Velazquez, T (2020). Phytochemicals in Garlic Extract Inhibit Therapeutic Enzyme DPP-4 and Induce Skeletal Muscle Cell Proliferation: A Possible Mechanism of Action to Benefit the Treatment of Diabetes Mellitus. Biomolecules. Feb 14;10 (2):305.

Kaur G, Padiya R, Adela R, Putcha UK, Reddy GS, Reddy BR, Kumar KP, Chakravarty S and Banerjee SK (2016). Garlic and Resveratrol Attenuate Diabetic Complications, Loss of β-Cells, Pancreatic and Hepatic Oxidative Stress in Streptozotocin-Induced Diabetic Rats. Front. Pharmacol, 7:360.

Konda, P.Y., Nagalapuram, R., Venkateswarlu, J.K.M. et al., (2020). Pathophysiology of STZ-induced pancreatic β cell injury and dysfunction: traditional role of Boswellia ovalifoliolata Bal. & Henry on diabetes and dyslipidemia. Comp Clin Pathol., 29, 609–619.

Kumar, G.R., and Reddy, K.B (1999). Reduced nociceptive responses in mice with alloxan induced hyperglycemia after garlic (Allium sativum L.) treatment. Indian J. Exp. Biol., 37:662–666.

Lawson LD, Wang ZJ (2005). Allicin and allicin-derived garlic compounds increase breath acetone through allyl methyl sulfide: use in measuring allicin bioavailability. J Agric Food Chem. Mar 23;53(6):1974-83.

Lee, C.G.; Rhee, D.K.; Kim, B.O.; Um, S.H.; Pyo, S (2019). Allicin induces beige-like adipocytes via KLF15 signal cascade. J Nutr Biochem. Feb;64:13-24.

Lei H, Grinberg O, Nwaigwe CI, Hou HG, Williams H, Swartz HM, Dunn JF (2001). The effects of ketamine-xylazine anesthesia on cerebral blood flow and oxygenation observed using nuclear magnetic resonance perfusion imaging and electron paramagnetic resonance oximetry. Brain Res. Sep 21;913(2):174-9.

Liu Y, Qi H, Wang Y, Wu M, Cao Y, Huang W, Li L, Ji Z, Sun H (2012). Allicin protects against myocardial apoptosis and fibrosis in streptozotocin-induced diabetic rats. Phytomedicine. Jun 15;19(8-9):693-8.

Liu, L. and Yeh, Y. Y (2001). Water soluble organosulphur compounds of garlic inhibit fatty acid and triglyceride synthesis in cultured rat hepatocytes. Lipids. Apr;36(4):395-400.

M.A.A. Metwally (2009). Effects of Garlic (Allium sativum) on Some Antioxidant Activities in Tilapia Nilotica (Oreochromis niloticus). World Journal of Fish and Marine Sciences 1, (1): 56-64.

Martina Perše and Anton Cerar (2011). Morphological and molecular alterations in 1,2 dimethylhydrazine and azoxymethane induced colon carcinogenesis in rats. J Biomed Biotechnol. ;2011:473964.

Matsutomo, T., Ushijima, M., Kodera, Y et al., (2017). Metabolomic study on the antihypertensive effect of S -1-propenylcysteine in spontaneously hypertensive rats using liquid chromatography coupled with quadrupole-orbitrap mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2017, Mar 1;1046:147-155.

Md. Shefat Jahan Shoshi1 , Hasina Akter (2016). Effects of Garlic (Allium sativum) on Blood Glucose Level in Type 2 Diabetes Mellitus Patients Treated with Metformin. Journal of Enam Medical College. Vol 7 No 3: 151−155.

Muhamed Osman, Ariza Adnan, Nor Salmah Bakar and Fatma ALashkham (2012). Allicin Has SignificantI Effect on Autoimmune Anti-islet Cell Antibodies in Type 1 Diabetic Rats. Pol J Pathol. Dec;63(4):248-54.

Najafi, N., Masoumi, S. (2018). The Effect of Garlic (Allium Sativum) Supplementation in Patients with Type 2 Diabetes Mellitus: A Systematic Review. International Journal of Nutrition Sciences; 3(1): 7-11.

Ohaeri, O.C. (2001). Effect of garlic oil on the levels of various enzyme in the serum and tissue ofstreptozotocin diabetic rats. Biosci Rep. Feb;21(1):19-24.

Patumraj, S., Tewit, S., Amatyakul, S., Jariyapongskul, A. Maneesri, S., Kesantikul,V., and Shepro, D. (2000). Comparative effects of garlic and Aspirin on diabetic cardiovascular complication. Drug Deliv., 7:91–96.

Rajurkar SP, Presant CA, Bosserman LD, McNatt WJ.J (2011). A copay foundation assistance support program for patients receiving intravenous cancer therapy. J Oncol Pract. Mar;7(2):100-2.

Shubham Kumar , Anu Mittal , Dinesh Babu , Amit Mittal (2020). Herbal medicines for diabetes management and its secondary complications. . Curr Diabetes Rev. 2020 Nov 3.

Stedman, T. L. (2006). Stedman's medical dictionary. Philadelphia: Lippincott Williams & Wilkins.

Tekula S, Khurana A, Anchi P, Godugu C. (2018). With a ferin-a attenuates multiple low doses of Streptozotocin (MLD-STZ) induced type 1 diabetes. Biomed Pharmacother. Oct;106:1428-1440.

Tomasz Szkudelski, Katarzyna Szkudelska (2015). Resveratrol and diabetes: from animal to human studies, Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, Volume 1852, Issue 6, Pages 1145-1154.

Ugbaja, R.N., Fatokun, T.P., Akinloye, D.I. et al., (2021). Propolis ethanol extract abrogates hyperglycemia, lipotoxicity, and lowered hepatic poly (ADP-ribose) polymerase protein level in male albino rats. J Diabetes Metab Disord.

Vazquez-Prieto MA, Miatello RM. (2010). Organosulfur compounds and cardiovascular dsease. Mol Aspects Med. Dec; 31(6):540-5.

Wang J, Zhang X, Lan H, Wang W. (2017). Effect of garlic supplement in the management of type 2 diabetes mellitus (T2DM): a meta-analysis of randomized controlled trials. Food Nutr Res. Sep 27;61(1):1377571.

Xin'e Shi , Xiaomin Zhou, Xinyi Chu, Jie Wang, Baocai Xie, Jing Ge, Yuan Guo, Xiao Li and Gongshe Yang (2019). Allicin Improves Metabolism in High-Fat Diet-Induced Obese Mice by Modulating the Gut Microbiota. Nutrients, 11, 2909.

Xinglong Liu, Wencong Liu, Chuanbo Ding, Yingchun Zhao, Xueyan Chen, Sadia Khatoon, Yinan Zheng, Zhiqiang Cheng, Guangsheng Xi (2020). "Antidiabetic Effects of Arginyl-Fructosyl-Glucose, a Nonsaponin Fraction from Ginseng Processing in Streptozotocin-Induced Type 2 Diabetic Mice through Regulating the PI3K/AKT/GSK-3β and Bcl-2/Bax Signaling Pathways", Evid Based Complement Alternat Med. Jul 2;2020:3707904.

Yuvashree, M., Ganesh, R.N. & Viswanathan, P (2020). Potential application of nanoemulsified garlic oil blend in mitigating the progression of type 2 diabetes-mediated nephropathy in Wistar rats. 3 Biotech. Jun;10(6):272.

Zangeneh, M.M., Goodarzi, N., Zangeneh, A. et al., (2018). Amelioration of renal structural changes in STZ-induced diabetic mice with ethanolic extract of Allium saralicum R.M. Fritsch. Comp Clin Pathol., 27, 861–867.

Zar J.H.,(1984): Biostatisticial analysis. 2thedn. Prencice-Hall, Englewood Cliffs, N.J., pp. 196-198.

Zhang J L and Shi Z X (2002). An experimental study of scavenging oxygen free radicals with garlicin. Journal of China-Japan Friendship Hospital. 16(5-6): 298-300.

Zhang, J.; Huang, Y.; Hou, T., and Wang, Y 2006). Hyperglycemic effect of Artemisia sphaerocephala Krasch seed polysaccharide in Alloxan diabetic rats. Swiss Med Wkly. Aug 19;136(33-34):529-32.