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GENE EXPRESSION ALTERATION IN *B*-CELL REGENERATION IN STZ-INDUCED DIABETIC MALE RAT TREATMENT WITH N-BUTANOL CUMIN EXTRACT

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Abstract

The present research measured the impact of Cumin (*Cuminum cyminum* Linn.) on diabetes mellitus caused by streptozotocin (60 mg/kg b.w., i.p.). Blood glucose level around 200 mg/dl of rats have been used as a diabetic. Male rats of type Wister were used and divided into five groups classify into 8 rats for each group: 1st group: with administration of water were used as normal control; 2nd group: diabetes was induced by a single subcutaneous injection of streptozotocin 60 mg/kg body weight and used as diabetic control; n-butanol cumin extract into (50, 100, 200 mg/kg, b.w.) were administered to groups III, IV, V, respectively. Cumin therapy in both doses contributes to a substantial decrease of the glucose rates, Our study provides important knowledge about the role of N-butanol cumin by showing InsI gene expression. Male mature rats were organized about 5.6 times (0.162 ± 0.064) in diabetic rats (V) compared to rats with male rats (0.029 ± 0.018). While Reg3a was significantly regulated 4.3 times (1.63 ± 0.61) inches from rats with diabetes (V) compared to male diabetics (II) in rats (0.34 ± 0.26) but in group (III, IV) in the InsI gene . (0.102 ± 0.043,0.154 ± 0.054) Our quantitative data, in particular, did not show the desired result compared to group (V). Likewise, (1.23 ± 0.58,1.46 ± 0.42) with the gene expression of Reg3a in group (III, IV), respectively, no required recurrence of a good level compared to group (V) was shown. The InsI and Reg3a genes also partially support increased insulin level and low blood glucose. These results confirm that the treatment of N-butanol cumin leads to an increase in the level of tissue regeneration of the pancreas, especially since beta cells are present in Langerhans Island which can be attributed to the possible role of being a complete component of cumin The findings obtained clearly show the role of oxidative stress in diabetes induction. The cumin prophylactic effect as a nutritional supplement is suggested in this study because of its role in reducing blood glucose and regeneration of the Reg3a gene responsible for regeneration of B-cells in the pancreas.

Key Words: Cumin, Streptozotocin (STZ), Diabetes mellilus, Reg3a gene.

Introduction

Diabetes mellitus is a complex, multifactorial disease triggered by a progressive pancreatic malfunction or insulin-releasing b-cell dysfunction. It contributes to persistent biochemical hyperglycemia and neural problems, causing long-term multi-organ damage including nephropathy, retinopathy and enteropathy. There are reportedly about 382 million people live with diabetes worldwide, or the figure is expected to increase to 592 million by 2035 (Association, 2002). Type 1 diabetes (T1D) is an inflammatory disease caused by a bcell death of cytotoxic T-cells. The development of the most severe type 2 diabetes (T2D) at adulthood is typically documented in contrast to T1D. Low blood pressure: Genetic predispositionREG3A (protein derived from islets 3 alpha, also known as the protein associated with pancreatitis or PAP) is a C-type lectin protein that is excreted by acini during acute pancreatitis. Recently, we have measured inactivation of the whole pancreas with the Pdx1-Cre-mediated IGF-I gene [in pancreatic-specific IGF-I gene-deficient (PID) rats], resulting in reduced ²-cell mass and strong defense against type 1 and type 2 diabetes. Given that the phenotype is unlikely to be a direct product of IGF-I deficiency, this analysis has been intended to explore potential proislet activation Factors in PID Rats use DNA-laden microarray genome. Cumin (*Cuminum cyminum* Linn.), a genus of

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Umbelliferae, a low annual herbaceous plant. Cumin is a rising spice globally, particularly in Latin America, North Africa and in Asia. This knows the Egyptians 5,000 years ago and a major ancient pharmacy has been established in Egypt (Maggen *et al.,* 2020) (Thomas, n.d.). Fruit is the medicinal component of cumin, cumin has various applications for over a thousand years (Thomas, n.d.), such as medication and spice. Cumin is used as a stimulant, antispasmodic, carminative, especially in the veterinary and antimicrobial practices. Cumin is used extensively in the treatment of In herbal medicine and for cumin, flatulence, bowel issues and diarrhea (Singh & Upadhyay, 1991) often tend to relieve and improve milk production in lactating women (Kaur & Sharma, 2012) and cold and fever (Kandiannan *et al.,* 2002). Cumin also contains vitamins including a vitamin C and contains amino acids, fats, nutrients, tannin white rice and fibers, as well as flavones (Ishikawa *et al.,* 2002) and glucosides (Kitajima *et al.,* 2003). Cumin is used in diabetes treatment, recent research shows cumin extraction activity to lower glucose levels in normal and streptozotocin-induced diabetic rats (Kitajima *et al.,* 2003) and to lower lipid profile (Dhandapani *et al.,* 2002) (Aruna *et al.,* 2005). Besides lower uric acid rates and average protein levels (Nabiela *et al.,* 2010) and lower levels of creatinine (Jagtap & Patil, 2010). The Reg3 was therefore measured to significantly boost the growth of island cells in the pancreas. This finding was later verified by a real-time sequential reaction to polymerase, which reported 2-4-fold rises in these RNAs rates. Interestingly, (Zhang *et al.,* 2003) the Reg family genes were also triggered after B-cell damage induced by streptozotocin and diabetes while island cells underwent regeneration. In addition, the improvement of diabetic rats was improved by calculating the reaction of the polymerase chain with the real time of the Ins1 gene and by examining the improvement to 3 times the rise in the rates of these RNAs and we find that Cumin extract has strong potency owing to its free radical effects, because of its potential to boost the diabetic rat. Production and chronic oxidative stress is implicated in diabetes mellitus pathology and complications (Jagtap & Patil, 2010). A variety of free radical species, one of which is cumin, have demonstrated survey behavior in laboratory animals. Cumin is abundant in a broad variety of antioxidant compounds including derivatives of phenolic acid, proanthocyanidins, quinones and flavonoids (Berhow & Vaughn, 1999). As with many other food products, cumin is widely used (Thippeswamy & Naidu, 2005). In this research, we examined the activity of cumin N-butanol extract in the pancreas of diabetic rats as a blood sugar driver and B-cells for regeneration.

Materials and Methods

Experimental Animals

Ninety male Sprague rat – Dawley, weighing (150-200 g) were used in this analysis. They were held in the animal room, taking into account temperature at (22 ±2) and light (14 hours light and 10 hours dark) so before beginning the experiment I have a week to get acclimatized. They were housed under the conditions of the laboratory, they maintained the standard pellet diet and were given tap water.

Drugs and chemicals

Streptozotocin was derived from natural substances Sigma (USA). Glucose kit was procured from Diagnosis Randox, USA. All the remaining chemicals used were analytical standard.

Prepare of n-butanol extract

Cumin (*Cuminum cyminum* Linn.) Bought from the local market and classified by the Ministry of Agriculture of Iraq (SBSTC), State Seed Inspection and Classification Committee. According to (Harborne, 1984)the Soxhlet was used to prepare the N-butanol extract of cumin seeds from methanol extract. The extract of methanol was processed, vaporized (40°C and 50 to 60 rpm) using around 1 kg of cumin seeds and frozen using a dry congeler. The dried extract was frozen and kept deep freezing. Depends on polarity, medium and low to achieve high polar fractures, three forms of solvents were used to isolate various sections of the crude extract, ethyl acetate, n-butanol and purified water, utilizing an isolate funnel extract. The cumin seed portion of N-butanol has been vaporized, frozen and stored at -4°C until to (Tsi & Tan, 2000).

Experimental design

Rats were subdivided into five groups. The following were eighteen animals in each division; Division I: normal control rats were fed into typical laboratory feed and water was a negative control group. Community II: Treatment for diabetes which has acted as a supportive support network. Group III: typical rats obtained 50 mg/kg b.w of cumin n-butanol extract and 0.1 ml of daily injection saline; administered insulin for four weeks. Community IV: regular rats received 100 mg/kg b.w of cumin n-butanol extract and 0.1 ml of standard injected saline; insulin therapy lasted four weeks. Community V: average rats of n-butanol cumin extract obtained 200 mg/kg b.w;And 0.1 ml of daily injection saline; four weeks of controlled insulin. Intraperitoneal (IP) STZ was given at a single dose of 60 mg/kg in the citrate solution groups II, III, IV and V (pH 4.5). Progression in diabetes is

verified three days after the STZ treatment, before blood glucose monitoring. Blood glucose rats For Diabetics, the minimum is 250 mg/dL or greater. Five days after treatment with STZ, cumin n-butanol extract was received in groups III, IV and V, until completion of the study (28 days). Between two and four weeks of handling n-butanol, blood tests from both classes were taken. Biochemical results were obtained on the last day of the trial. Later the animals were sacrificed; the pancreas was removed, cleaned and washed for gene expression analysis in ice-cold normal saline.

Determination of blood glucose

The blood glucose level was measured using the test of glucose oxidase (Braham & Trinder, 1972) using a Randox portable industrial testing package, USA.

Realtime-polymerase chain reaction

Absolute cellular RNA was removed from the pancreas using the manufacturer's RNeasy Nano, RNA insulation kit (Qiagen, Courtaboeuf, France) as per the protocol. Max RNA was solubilized with RNasc-free vapor 35 psi from matrix. Residual genomic DNA was extracted by incubating RNA solution at 2 mM MgCE at 37X for 10 min with 15 units of RNase-free DNase I, accompanied by 5 min at 90 * ^C to inactivate the DNase. Twenty-five microliters of the DNase-treated RNA solution are used for a 50 mM Tris-HCl (pH 8.3) reaction; 10 mM of dithiothreitol, 100 ng of spontaneous hexamers, 3.5 pg of bovine serum albumin,3mM MgCb, 0.5 mM deoxynucicotide triphosphate, 30 RNAguard RNase inhibitor units (Promega, Madison, WI), 200 Moloney murine leukemia virus reverse transcriptase bases (M-MLV RT) and 50 pi RNase-free water. For the output of equivalent quantities of total RNA, the reverse transcription reactions were not standardised. The reactions were incubated for 10 minutes at 26 ® C and then 45 minutes at 42°C, followed by an incubation of 3 minutes at 90°C to denature secondary RNA. Another 300 reverse transcriptase units were applied, incubating the reactions for 45 minutes at 42°C. 10 Minutes back with Transcriptase. Checks unfavorable for the RT protocol and DNA contamination regulation were performed by omitting the reverse transcriptase in parallel samples. The cDNA samples were aliquoted, deposited at -80°C. Related cDNA samples were used during the study used. Insulin-1 rat primers were forward (fw), 5'-TCAGCAGCAGCAGTTGTTCC-3 and reverse (rv), 5'-GGTGCAGCCTGATCACATG-3'. PCR conditions were 35 cycles of initial denaturation y'"C for 5 storms, 95°C for 45 s, 60°C for 30 s, 72°C for 1 min and finally 72°C for 5 minutes; RT viability; >rr > duci was regulated by a separate PCR. With housekeeping basic mRNA (GAPDH) primers (fw: 5'-TGAACGGATTGCCGTATTGGCGC3'; rv:5'-TCTTCTGGTGGCAGTGCATGCAT-3'). Rat Reg3a primers were as follows: fw: 5*-TTGTCCTGACGAACATCCAT-3'; rv: 5'-AACGATAGCTGAGCCC-3'. PCR conditions were identical to those for 35 cycles above. Electrophoresis tested the PCR items on an agarose gel of 1.5 percent. Realtime PCR was achieved using the QuantiTect SYBR Green PCR (Qiagen) package,Opticon-2 PCR (MJ Research) unit, white 965 < PCR tiles and simple PCR (MJ Research) caps. Gradient PCRs verified the correct temperature for all primers.

Statistical analysis

Both values are stated as actually imply ± SD. Test aims are assessed to use a one-way variance analysis (ANOVA I), use an F-test(Northup *et al.,* 1980). The least substantial difference (LSD) besides estimating the value of the disparity here between two groups was rendered. The P value was deemed small, with less than 0.05.

Results

Body weight was measured on day 0 and then gradually by measuring body weight every two days of the experiment to see the effect of cumin extract, blood sugar concentration was measured on day 2 after streptozotocin injection and then measured on day 0, 6, 12, 18, 28 gradually to see the effect of the extract To reduce blood sugar, the important part is reg3a gene which is responsible for beta cell regeneration and knowledge of the effect of the extract and three concentrations were measured.

Body weight

Effects of the explained regular body weight in Fig. 1 showed major discrepancies (P<0.05) amongst diabetic

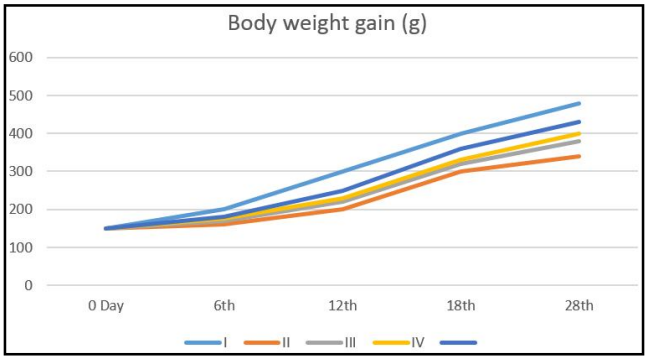

Fig. 1: Effect of N-butanol cumin extract treatment on body weight gain (g) in STZ - induced mature male rats with diabetics . The mean values are ±S.D. (p < 0.05).

classes, usual control community and cumin community only starting category on the third day and continue throughout the following days of the experiment. On the other hand, the statistical comparison between the three diabetic groups showed that the overall body weight recorded insignificant changes (P>0.05) throughout the experimental period.

Blood glucose

On the fifth day, blood glucose was measured for selection. Diabetic rats whose levels exceed 200 mg/dL. The results showed that male rats treated 200 mg/kg B.W of n-butanol extract of cumin .The N-butanol cumin treatment recorded the best. Effects of hypoglycemia compared to controlling diabetes rats. However, their blood glucose concentration .Still higher than normal control rats. On the other hand. Blood glucose showed by 100mg/kg b.w of n-butanol extract of cumin. The test rats were regular. A substantial low concentration ($p<0.05$) was achieved. Compared also with category III. On day 28 of injection of 200 mg/kg b.w of cumin n-butanol extract (group V), we found a substantial low concentration of blood glucose level, a important contrast ($p < 0.05$) with community (III, IV) as seen in Fig. 2.

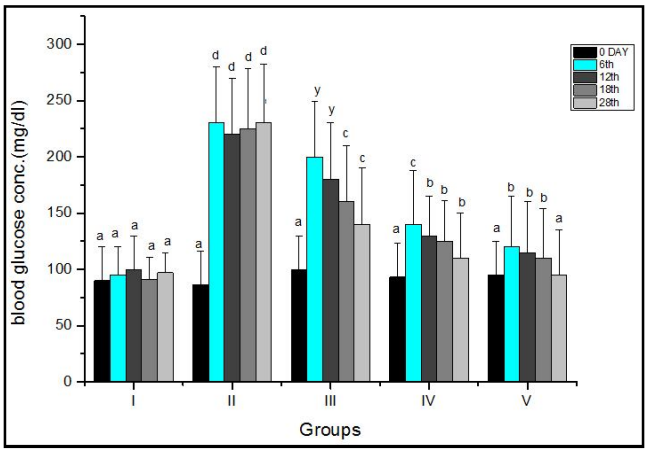

Fig. 2: Effect of N-butanol cumin extract treatment on blood glucose conc.in STZ - induced mature male rats with diabetics. The mean values are ±S.D. ($p < 0.05$).

Gene expression analysis

Results for determining InsI gene expression levels table 1 explained the gene expression. Levels have been significantly increased in the tissues of the pancreas. Obtained from rats and cumin only normal control group. The treated group compared to other groups of this. Experiment. On the other hand, in the latency group (V) treated. Diabetic rats, InsI gene expression levels increased Significantly compared to ratsthat control diabetic patients, While it decreased significantly by comparison With regular control rats. However, in the tissues of the pancreas Obtained from male diabetic rats, InsI gene Expression levels were slightly reduced Compared to male diabetic rats. Also, the (V) group renewal of B cells and the level of Reg3a gene were significantly increased with the diabetes control group, but they did not reach the level of the normal control group as well compared to the group (III, IV), but there was a significant change in Reg3a gene.

Groups	*InsI* gene	*Reg3a* gene
I	1.01±0.103	0.9±0.33
II	0.029±0.018	0.34±0.26
III	0.102±0.043	1.23±0.58
IV	0.154±0.054	1.46±0.42
V	0.162±0.064	1.63±0.61

Discussion

The findings of the current research revealed that streptozotosine injection contributes to a substantial rise in glucose rates and this findings in rats according to (Galletto *et al.,* 2004) (de Sousa Lino *et al.,* 2004) (H Aziz, 2009). This may be attributed to the degradation by treptozotosin of p-pancreas cells, which contributes to a discontinuation of insulin output (Carvalho *et al.,* 2003). This therefore allows the influx of glucose into the cells to decline, which contributes to an rise in their blood pressure (Carvalho *et al.,* 2003). Streptozotosin associates on the sugar-related side of glucokinase with two groups of SH- and leads to the production of disulfide bonding and enzyme inactivation (LENZEN & MIRZAIE-PETRI, 1991). The volume of glucose in the blood is decreased by 50, 100, 200 g/kg of feed relative to the diabetic control group consistent with the result (Roman-Ramos *et al.,* 1995) in rabbits with diabetes rats (Talpur *et al.,* 2005) (Dhandapani *et al.,* 2002) (Jagtap & Patil, 2010). Cumin ‘s presence will impair its capacity to inhibit ± -glucosiadse (Lee, 2005) and this enzyme is responsible for sugar degradation such as sucrose and sugars such as starch in monosaccharides (Lee, 2005) suggest multiphenol treatment compound derived from black cumin in rats It reduces blood glucose due to the influence of glucose. The hypoglycemic impact of cumin may be caused by the involvement of flavone (Kitajima *et al.,* 2003), Which has demonstrated that flavone has an effect on the activation of ± -glucosiadse and Aldose reductase (Mayes & Botham, 2003) and that flavone also causes a decrease in the absorption of glucose from the intestine by raising the Calcium-dependent glucose transfer (Vedavanam *et al.,* 1999). And Aldose reductase and both enzymes, inhibit high body insulin rates (Prince *et al.,* 2004). Cumin therapy reduced blood sugar and the results were compatible with (Dhandapani *et al.,*

2002) (Aruna *et al.,* 2005) (Prince *et al.,* 2004) in regular rats and streptozotosin-caused diabetics and were inconsistent with (Sambaiah & Srinivasan, 1991) findings in rats. The influence of B cell regeneration of latency may be attributed to its function as an antioxidant, which indicated that t is an antioxidant.Volume 12, No. 2, 2013 75. The influence of N-butanol extract on the regeneration of the Reg3a gene was notably observed in Cumin at a dosage of 50, 100, 200 g/kg. This result may be attributed to the fact that latency has similar properties to insulin (Prince *et al.,* 2004), since it plays a prominent function in protein synthesis by enhancing the translation of mRNA (Mayes & Botham, 2003). Our analysis indicates latency has a function to play in slowing diabetes by reducing such biochemical parameters.

In the present study, we first examined the efficacy of the primer The results showed that the initial efficiencies of Reg3a, InsI and GapdH were prefixes 1.86, 2.08 and 1.9, respectively. So the difference between Reg3a or InsI and GapdH (Internal Control) Initial efficiency was less than 5%. This is Quality control is essential when we need a real copy number, But here we need to know the folded change in expression Genes targeted for treatment samples compared to those genes Control samples. So, we used InsI primer in this The study while its efficacy was 2.08 (Livak & Schmittgen, 2001). Decreased insulin production or affecting abnormalities Insulin secretion is the key to developing almost everyone Forms of diabetes, including common type 1 (insulin-Type 2 diabetes (not insulin dependent) and The rarest forms of diabetes in adolescence in young adults (MODY). Because insulin has a central role in Causing Diabetic Forms, Insulin Gene (/ns) Jin has long been considered susceptible to disease. The current study determined the start time pattern It expresses the insulin gene and the regenerative geneiReg3a), a central issue in island development biology. Our study gives important knowledge about the role of N-butanol cumin by showing InsI gene expression Male mature rats were organized about 5.6 times (0.162 ± 0.064) in diabetic rats(V) compared to rats With male rats (0.029 ± 0.018). Whereas, Reg3a was highly organized 4.3 times (1.63 ± 0.61) inches Diabetic rats (V) compared to diabetics Male (II) control in rats (0.34 ± 0.26) but in group (III, IV) in InsI gene expression. (0.102±0.043, 0.154±0.054) Our quantitative data, respectively, did not show a desired result compared to the group (V). Likewise, (1.23±0.58, 1.46±0.42) with the gene expression of Reg3a in group (III, IV) respectively, no required duplication of good level compared to group (V) appeared. InsI and Reg3a genes are also partially supported by Increased insulin level and low blood glucose level Serum. These results confirm that the N-butanol cumin treatment leads to an increase in the level of regeneration Pancreatic tissue, especially that beta cells are on an island of Langerhans who may be attributed to the possible role It is a full ingredient of cumin. The Reg family of proteins received its name due to cDNA. The coding of the first member of this family was isolated from A. Library derived from the rat model for pancreatic regeneration (Terazono *et al.,* 1988). Reg proteins are made up of carbohydrates The identification domain was found in Type C and N-short lectures The terminal's tail (Terazono *et al.,* 1988). They have studied Mostly in the context of survival and regenerative growth, no Only in the endocrine and endocrine systems (Choi *et al.,* 2007), but also in a number of other organs and tissues (Cavard *et al.,* 2006). As mentioned before There is an important role for Reg3a in regenerating beta cells, They are the results related to diffusion and inflation Of these are cell types (Cavard *et al.,* 2006). In parallel with Increased gene expression, Reg3a and InsI, serum Insulin concentration came in a coordinated way. The literature has shown that InsI is the main responsible gene For the biological synthesis of insulin from P cells from reflux Langerhans within the tissues of the pancreas (Wang *et al.,* 2014). Thus, current results clearly confirmed that cumin extract had a potential indirect role in reduction Blood glucose levels by spreading p cellsAnd its implications for the level of expression InsI mRNA. The current results were consistent with those of (Koyama *et al.,* 2017), who found that cumin extract improves glucose Control and increase muscle acylcamitines in Zucker's diabetes rats. Moreover, the current results are consistent with thatof (Koyama *et al.,* 2017) who found that a diet with a potential content of 200 mg/kg significantly reduced blood sugar and In suiinaemic response to food but do not drink treatments when Compared to the controls.

Conclusion

It can be inferred that cumin plant extract performs well it has a positive impact in hyperglycemic diabetics male rats and their important role in the production of elevating of expression of essential genes Reg3a and InsI (responsible for Hormone-insulin biosynthesis) in pancreatic B-cell, while using across 28 days. We need further tests performed to prescribe a cumin for the entire gram multiple cracks in the clinical features of another illness, or conditions are powerful.

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