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Synergistic Effect of Cichorium and Chromium Supplementation on Diabetic Rats

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Abstract: Thirty five Sprague Dawley adult male rats were classified into control negative group (7 rats) and the rest were injected with a single intraperitoneal dose of streptozotocin to induce diabetes then classified into control positive group and three treated groups which were cichorium, chromium and cichorium with chromium groups. In comparing to control negative group, the mean values of nutritional results, serum insulin, total protein and globulin and also glycogen, triglyceride, antioxidant enzymes in liver were lower in control positive rat group. However, the values of glucose, glucosalated heamoglobin (HbAc), alanine and aspartate aminotransferase enzymes (ALT and AST), creatinine, uric acid, A/G, total lipids, cholesterol and malondialdehyde (MDA) were higher in control positive rat group. Synergistic effect of cichorium and chromium was proved in cichorium with chromium group which showed significant increase in nutritional performance, insulin, total protein, globulin and liver glycogen and antioxidant enzymes. However, it showed significant decrease in serum glucose, HbAc, AST, ALT, creatinine and also liver total lipids, cholesteroland MDA compared to control positive rats. The obtained results revealed that cichorium and chromium were of value for amelioration of diabetes mellitus and its side effects.

Key words: Cichorium · Chromium · Diabetes · Rats

INTRODUCTION

Diabetes is a disorder resulting from body's inability to produce enough insulin or to use the insulin properly. Insulin is an essential hormone for conversion of glucose into energy. The use of herbal medicine has become increasingly popular worldwide and efforts are on going to evaluate botanical drugs for the management of diabetes mellitus [1]. Nutritional supplementation with over the counter agents, are extensively practiced by a large number of patients and are frequently undertaken without first informing the medical provider. One supplement that has attracted considerable clinical interest is chromium [2]. Chromium is an essential mineral that humans require in trace amounts. The body needs chromium for normal health and growth. It is often sold as a nutritional supplement to prevent or treat chromium deficiency and helps enhance the action of insulin. Insulin is a critical hormone that metabolizes and stores carbohydrates, proteins and fats [3]. Cichorium (*Cichorium intybus* L.) belongs to the Asteraceae family and is a biennial plant with many applications in the food industry. Cichorium root is an herb that has been known for its curative benefits since the first century A.D and continues to be a popular herbal remedy due to its healing effects on several ailments including liver diseases, loss of appetite, jaundice, gallstones, gout and rheumatism [4]. Cichorium has a long history of herbal use and is especially of great value for its tonic affect upon the liver and digestive tract. Cichorium is an ideal food for diabetics because of its inulin content with a low glycemic index and has substances that regulate insulin production and lowers blood sugar [5].

The present study aims to investigate the synergistic effect of cichorium and chromium supplementation on diabetic rats.

MATERIALS AND METHODS

Materials

Chemicals: Streptozotocin and chromium were procured from Sigma, St. Louis, MO, USA. Casein, cellulose, starch, vitamins and biochemical kits were obtained from Alkan Co. for Chemicals and Biodignostics, in Riyadh.

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Experimental Animals: Thirty five male albino rats (Sprague Dawley strain), weighing 120±8g were provided from experimental animals center in Medicine collage of King Saud University in Riyadh.

Plant Materials: Cichorium fresh leaves (*Cichorium intybus*, Family Asteraceae) were obtained from the grocers and scientifically identified at Horticultural Research Institute, Agriculture Research Center, Egypt.

Methods

Preparation of Plant Materials: Cichorium leaves were washed with tap water, chopped into small pieces and then separately dried in an air-circulated oven at 40°C to complete dryness. The dried materials were separately reduced into powder form as far as possible and stored kept in the refrigerator at 4°C until use [6].

Animals' Adaptation: Male rats were placed for an adaptation period of one week and were fed on basal diet to allow them to adjust to the new environment. Rats were individually housed in stainless steel wire-bottom cages at room temperature of about 25±2°C with water bottles under hygienic condition and fed on basal diet *ad libitum*.

Preparation of the Experimental Diets: The basal diet consisted of 140 g casein (83 % protein), 100 g sucrose, 50 g corn oil, 50 g cellulose, 35 g mineral mixture, 10 g vitamin mixture, 1.8 g L-cystine, 2.5 g choline bitartrate and the remainder (610.6 g) corn starch. Diets were formulated according to Reeves *et al.* [7].

Experimental Design and Diet Protocols: Rats fed on basal diet and water *ad libitium* for one week for adaptation. After the adaptation period, seven rats were kept as control negative group and the rest of rats were injected with a single intraperitoneal dose of streptozotocin (55 mg/kg body weight) in 0.1M citrate buffer of pH 4.5 then supplied with 5% glucose solution for 48h after injection in order to prevent hypoglycemia [8]. After four days, blood samples were taken from orbital plexus for estimation of glucose. The rats having persistent hyperglycemia were considered as diabetic rats and used for the experiment. The diabetic rats were classified into the following groups:

- Control positive group: that provided basal diet without treatment.
- Cichorium group: that provided basal diet with 15% of cichorium powder in diet.
- Chromium group: that provided basal diet with 80 microgram chromium per kilogram body weight per day that dissolved in distilled water and given to rats by oral intubations.
- Cichorium with chromium group: that provided basal diet with 15% of cichorium powder in diet and 80 microgram chromium per kilogram body weight per day that dissolved in distilled water and given to rats by oral.

Daily food intake and weekly body weight gain were recorded. Feed efficiency ratio (FER) was determined by Chapman *et al.* [9]. At the end of experimental period (60 days), rats were fasted over night before sacrificing and blood was collected. Part of blood was centrifuged to obtain serum. The liver of sacrificing rats was collected separately and perfuse with 50 to 100 of ice cold 0.9% NaCl solution for chemical analysis.

Chemical Analysis: For each group, blood glucose was collected in tubes containing potassium oxalate and sodium fluoride for the estimation of glucose by O-toluidine method [10]. Serum insulin and glucosalated heamoglobin (Hb Ac %) were estimated according to Wilson and Miles [11] and Abraham *et al.* [12], respectively. Serum alanine and aspartate aminotransferase (ALT and AST) activity enzymes, creatinine and urea were estimated according to Reitman and Frankel [13], Bonsens and Taussky [14] and Patton and Crouch [15], respectively. Serum total protein, albumin and globulin were determined as described by the method of Weichselbaum [16], Bartholomev and Delany [17] and Coles [18], respectively. In addition, liver glycogen, triglyceride (TG), total lipids and cholesterol were determined according to Rerup and Lundquist [19], Scheletter and Nussel [20], Folch *et al.* [21] and Richmond [22], respectively. Liver superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione S-transferase (GST), catalase and malondialdehyde (MDA) were estimated according to Beuchamp and Fridovich [23], Beutler *et al.* [24], Ellman [25], Cohen *et al.* [26] and Uchiyama and Mihara [27], respectively.

Statistical Analysis: The obtained data were statistically analyzed according to the SPSS-PC (statistical package software, version, 11.0). One way analysis of variance (ANOVA) was used to test the differences between groups [28].

RESULTS

The results presented in Table 1 showed that the effect of cichorium and chromium supplementation on final weight, body weight gain, food intake and FER in diabetic rats. As shown the mean value of final weight, body weight gain and FER were lower ($p<0.001$) in control positive than control negative group. Final weight was lower in cichorium and chromium groups ($p<0.05$ and 0.01) while body weight gain and FER were significantly lower ($p<0.05$) in chromium group when compared to control negative. Food intake and growth performance of rat group administered cichorium and chromium were in non significant difference compared to control negative group. Values of treated groups were higher in final weight, body weight gain and FER compared to control positive.

Data in Table 2 illustrated the effect of cichorium and chromium supplementation on serum insulin, glucose and HbAc on diabetic rat groups. As shown in this table, the mean value of serum insulin was lower ($P<0.001$) but the values of glucose and HbAc of were higher ($P<0.001$) in control positive compared to control negative. The value of serum insulin was lower ($P<0.05$) in chromium group but the value of glucose was higher ($P<0.05$) in cichorium and chromium groups compared to control negative. All treatments increased insulin and decreased glucose and HbAc compared to control positive rats. Supplementation of cichorium with chromium gave best results indicating a synergistic effect.

The results presented in Table 3 illustrated the effect of cichorium and chromium supplementation in diets on serum AST, ALT, creatinine and uric acid on diabetic rat groups. As shown the mean value of these parameters of control positive were significantly higher ($p<0.001$) when compared to control negative. The value of serum ALT, AST were significantly higher ($p<0.01$) in chromium group while the value of creatinine was significantly higher ($p<0.05$and 0.01) in cichorium and chromium groups but the value of uric acid was significantly higher ($p<0.01$) in cichorium group when compared to control negative. At the same time, AST, ALT and creatinine of cichorium and cichorium with chromium groups were significantly lower but the value of uric acid was significantly lower in chromium and cichorium with chromium groups as compared to control positive rats. Best values of these parameters were appeared in cichorium with chromium group.

Data in Table 4 illustrated the effect of cichorium and chromium supplementation on serum total protein, albumin, globulin and A/G ratio in experimental rat groups. The mean value of total protein and globulin of control positive were significantly lower at $p<0.05$ and 0.01, respectively but A/G ratio was significantly higher at $p<0.001$ than control negative group. However, values of treated rat groups were in non significant difference compared to control negative group but were significantly higher when compared to control positive.

Table 1: Mean values ± SD of body weight gain, food intake and FER of the experimental rat groups

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
Final weight (g)	224.91 ± 17.25^{a}	$177.61\pm9.71^{d***}$	$210.41\pm11.31^{bc*}$	$202.31\pm9.11^{c**}$	221.61 ± 6.14^{ab}
Body weight gain(g)	99.81 ± 6.81^{a}	$57.31\pm5.21^{c***}$	88.11 ± 9.61^{ab}	$79.21\pm7.21^{b*}$	97.31 ± 97.31^{a}
Food intake (g/w)	16.81 ± 1.45^{a}	15.71 ± 1.21^{a}	15.91 ± 2.99^{a}	15.81 ± 1.71^{a}	16.71 ± 1.50^{a}
FER	0.098 ± 0.003^{a}	$0.060\pm0.001^{d***}$	0.092 ± 0.004^{ab}	$0.083\pm0.001^{bc*}$	0.097 ± 0.002^{a}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001
Mean values in each raw having different superscript (a, b, c, d) are significant

Table 2: Mean values ± SD of serum insulin, glucose and HbAc of the experimental rat groups

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
Insulin (µ/l)	13.96 ± 1.19^{a}	$6.71\pm0.69^{c***}$	12.78 ± 1.17^{ab}	$11.21\pm1.01^{b*}$	14.31 ± 1.29^{a}
Glucose(mg/dl)	140.96 ± 11.16^{c}	$310.31\pm22.14^{a***}$	$170.31\pm10.18^{b*}$	$175.21\pm12.16^{b*}$	155.81 ± 12.12^{c}
HbAc%	4.38 ± 0.73^{b}	$7.31\pm1.14^{a***}$	4.23 ± 0.69^{b}	5.01 ± 0.55^{b}	4.71 ± 0.64^{b}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001
Mean values in each raw having different superscript (a, b, c, d) are significant

Table 3: Serum AST, ALT, creatinine and uric acid of the experimental rat groups

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
AST(µ /ml)	45.31 ± 5.18^{cd}	$65.71\pm5.16^{a***}$	52.31 ± 6.11^{c}	$60.31\pm6.21^{ab**}$	50.31 ± 4.99^{c}
ALT(µ /ml)	39.6 ± 3.62^{c}	$51.31\pm4.96^{a***}$	37.21 ± 3.25^{cd}	$48.31\pm5.10^{ab**}$	42.71 ± 4.21^{c}
Creatinine(mg/dl)	0.69 ± 0.01^{c}	$1.59\pm0.41^{a***}$	$0.89\pm0.13^{b*}$	$1.31\pm0.56^{a**}$	0.75 ± 0.03^{bc}
Uric acid (mg/dl)	2.71 ± 0.11^{bc}	$4.96\pm0.55^{a***}$	$4.11\pm0.66^{a*}$	3.71 ± 0.25^{b}	3.61 ± 0.14^{b}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001
Mean values in each raw having different superscript (a, b, c, d) are significant

Table 4: Mean values ± SD of serum total protein, albumin, globulin and A/G of the experimental rat groups

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
Total protein (g/dl)	7.81 ± 1.11^{a}	$6.11\pm0.51^{b*}$	7.31 ± 1.31^{a}	7.31 ± 1.21^{a}	7.21 ± 1.14^{a}
Albumin (g/dl)	3.71 ± 0.16^{a}	3.71 ± 0.20^{a}	3.51 ± 0.33^{a}	3.61 ± 0.13^{a}	3.61 ± 0.17^{a}
globulin(g/dl)	4.13 ± 0.62^{a}	$2.44\pm0.47^{c**}$	3.80 ± 0.33^{a}	3.71 ± 0.33^{a}	3.62 ± 0.11^{ab}
A/G	0.90 ± 0.01^{b}	$1.52\pm0.46^{a***}$	0.92 ± 0.1^{b}	0.97 ± 0.13^{b}	0.99 ± 0.66^{b}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001

Mean values in each raw having different superscript (a, b, c, d) are significant

Table 5: The Mean values ± SD of some liver glycogen, triglyceride, total lipids and cholesterol of the experimental rat groups

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
Glycogen (mg/100g)	4.98 ± 0.33^{a}	$2.88\pm0.21^{c***}$	4.32 ± 0.43^{a}	3.76 ± 0.29^{ab}	4.51 ± 0.44^{a}
T.G(mg/dl)	2.91 ± 0.19^{a}	$2.11\pm0.14^{b*}$	2.41 ± 0.20^{ab}	1.96 ± 0.21^{bc}	2.34 ± 0.10^{ab}
Total lipids (mg/dl)	38.77 ± 3.16^{cd}	$51.31\pm5.17^{a***}$	43.91 ± 3.16^{bc}	39.11 ± 3.21^{c}	40.31 ± 3.60^{c}
Cholesterol (mg/dl)	4.20 ± 0.95^{c}	$7.20\pm1.11^{a**}$	5.17 ± 1.21^{bc}	$6.01\pm0.99^{ab*}$	5.03 ± 0.96^{bc}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001

Mean values in each raw having different superscript (a, b, c, d) are significant

Table 6: Mean values ± SD of liver SOD, GPX, GST, catalase and MDA of the experimental rat groups.

Groups variables	Control negative	Control positive	Cichorium	Chromium	Cichorium+ Chromium
SOD(µ/mg)	45.98 ± 6.03^{a}	$29.31\pm4.16^{c***}$	38.81 ± 5.14^{ab}	39.81 ± 3.12^{ab}	41.31 ± 3.71^{a}
GPX (µ/mg)	29.11 ± 2.15^{a}	$19.31\pm1.27^{d***}$	$23.91\pm2.22^{bc**}$	$20.71\pm1.14^{bc**}$	26.31 ± 2.17^{ab}
GST(µ/mg)	3.99 ± 0.22^{a}	$1.71\pm0.16^{c***}$	2.91 ± 0.54^{ab}	2.96 ± 0.27^{ab}	3.51 ± 0.43^{ab}
Catalase(µ/l)	37.2 ± 3.66^{a}	$15.41\pm1.16^{d***}$	$28.71\pm2.19^{c**}$	$25.78\pm2.80^{c**}$	32.71 ± 3.76^{ab}
MDA(nmol/g)	8.71 ± 1.36^{c}	$15.87\pm1.16^{a***}$	$10.38\pm1.13^{b**}$	$11.21\pm1.21^{bc**}$	9.31 ± 1.41^{c}

Significant with control group * P<0.05 ** P<0.01 *** P<0.001

Mean values in each raw having different superscript (a, b, c, d) are significant

Data presented in Table 5 illustrated the effect of cichorium and chromium supplementation on liver glycogen, triglyceride, total lipids and cholesterol in diabetic rat groups. The values of glycogen, triglyceride were significantly lower at p<0.001 and 0.05 while total lipids and cholesterol were significantly higher at p<0.001 and 0.01, respectively in control positive than control negative. All treated rats groups showed a significant increase in glycogen and significant decrease in total lipids when compared to control positive. The value of cholesterol was significantly higher at p< 0.05 in chromium group in comparing with control negative group but was significantly lower in all treated groups when compared to control positive.

Data in Table 6 illustrated the effect of cichorium and chromium supplementation on liver antioxidant enzymes (SOD, GPX, GSTand catalase) and MDA of the diabetic rat groups. The values of liver antioxidant enzymes were significantly lower at p< 0.001 while MDA was significantly higher at p< 0.001 in control positive compared to control negative. Liver GPX and catalase were significantly lower at p< 0.01in cichorium and chromium while MDA was significantly higher at p< 0.01 in cichorium and chromium groups compared to control negative. All treated rats groups showed a significant increase in liver antioxidant enzymes and significant decrease in MDA when compared to control positive. From these results, it could be observed that synergistic effect of cichorium and chromium was proved by non significant difference of the liver antioxidant parameters compared to control negative group.

DISCUSSION

The food intake and growth performance results were explained by Kaats *et al.*[29] and Purnell and Weyer [30] who reported that chromium supplementation may favorably modulate factors promoting weight gain commonly observed with improvement in glycemic control and also has variable effects on body weight and composition in patients with diabetes. Chromium supplementation showed decrease in weight and fat in individuals without diabetes. Sahin *et al.* [31] reported that chromium with sulfonylurea in subjects with type 2 diabetes improved glycemic control, increased insulin sensitivity and significantly attenuated body weight gain. It is known that cichorium contains inulin, which may help humans with weight loss, constipation, improving bowel function and general health. It may increase calcium absorption and bone mineral density [32]. The results of

antidiabetic study clearly showed that chromium is one of the key minerals involved in controlling both blood sugar levels and fat levels with improvements in insulin sensitivity. Chromium assists insulin in reducing blood glucose, by stimulating glucose uptake by the muscles and other tissues. Chromium is important in the burning of carbohydrates and fats in the body and in the proper functioning of insulin. That is, it helps insulin to do its work of making blood sugar available to the cells [33]. The effect of cichorium in the obtained results revealed to its an appetite stimulant. Cichorium can be used to treat digestive problems like nausea, bloating/gas and to relieve the symptoms of gallbladder disease. It also improves liver function and therefore helps clearing the blood and even lower bad cholesterol. The raised activities of the amino transfrases (AST and ALT) indicate hepatocellular damage. Cichorium contains esculetin a phenolic compound which was investigated for its anti oxidative and anti-hepatotoxic activity that may be due to presence of cichotyboside, a sesquiterpene glycoside [34, 35]. As for A/G, the mean value of control positive was higher than control negative group while the value of treated rat groups was significantly lower when compared to control positive. The alteration in A/G ratio may occur due to the reduction in albumin and or elevation of globulin. However the ratio may be increased in some cases of biliary cirrhosis [36].

It is known that the addition of chromium lowered glucose, total cholesterol and triglycerides compared in diabetic rats. Also, chromium lowered free fatty acid levels, blood urea and creatinine level [37]. The benefits of chromium also include controlling fat and cholesterol levels in the blood and if adequate amounts are provided to the body, it can help to prevent hypertension or high blood pressure [38]. Most antioxidants isolated from higher plants are polyphenols, which show biological activity. The antioxidant activity of phenolics is mainly due to their redox properties, which allow them to act as reducing agents, hydrogen donors and singlet oxygen quenchers. In addition, they have a metal chelation potential. The antioxidant effect of plant phenolics has been studied in relation to the prevention of coronary diseases and cancer, as well as age-related degenerative brain disorders [39, 40].

In the present study, supplementation of the herbal medicine as cichorium with chromium as trace element is indicating the synergism action in treatment of diabetes in experimental rats.

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