

PROTECTIVE EFFECT OF ETHANOLIC GINGER EXTRACT AGAINST CADMIUM TOXICITY IN MALE RABBITS

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ABSTRACT

This study was done to evaluate the hypoglycemic potentials of ginger (*zingiber officinale*) in controlling hyperglycemia ,hypoinsulinemia and their effect on total cholesterol in cadmium-induced pancreotoxicity in male rabbits

Twenty four of adult male rabbits were divided randomly into four equal groups. Group 1 was given distilled water orally and considered as control group, group 2 received 10mg/kg B.w of cadmium chloride, group 3 received 100mg/ kg B.w of ginger extract plus 10mg/kg B.w of cadmium chloride and group 4 received 200mg/ kg B.w of ginger extract plus 10mg/kg B.w of cadmium chloride. All treatments were given a daily dose for 35 days.

The blood sample was taken from these animal groups after 35 days of treatment for biochemical analysis to estimate : insulin hormone, blood glucose ,total cholesterol, Aspartate amino transferase (AST) , Alanine aminotranferase(ALT) and Alkaline phosphatase (ALP).

The results showed that cadmium chloride administration resulted in a decrease in the level of insulin concentration associated with an increase in glucose and total cholesterol concentration in rabbits .The enzyme activities of serum ALT, AST and ALP were also significantly increased . While , the groups of animal that received ginger showed significant decrease in serum glucose , cholesterol , AST, ALT and ALP. The level of insulin was also increased in these groups of animal.

INTRODUCTION

Some studies have shown that several hundred plants were used as an anti-diabetic therapy or prevent and reduce the diabetic complication (1). Infact , many medicinal plants such as *oleo europea* , *Nigella sativa* and *Trigonella foenum graceum* , have anti- diabetic effects (2). Ginger was found to have hypocholesterolemia and caused a decrease in blood glucose ,body weight and alkaline phosphatase in adult male rat(3). Several studies showed that ginger extract possesses hypoglycemic and hypolipidemic potential in the diabetic rats(4). Thus , ginger may be of great value in managing the effect of diabetic complication in human(5). .

MATERIAL AND METHODS

The preparation of plant material.

The fresh rhizomes of Chinese ginger (*zingiberofficinale*) were bought from the local market of Basra city /Iraq, the plant material was identified and authenticated at College of Science / University of Basra .

The fresh rhizomes were washed with distilled water and then dried at room temperature for two days under the shade , the dried rhizome was cut into small pieces and ground into powder by using electric mill for 3 minutes. 50g of powder were put in the round bottle flask, 200ml of ethanol (70%) were added to the flask and extracted for 12 hours at 70c°. the extract was filtered by using Whatman No.31 filter paper , then the extract were put in the Petri dish and left at room temperature under the shade . the resultant was viscous substance with brown color. The collection extracts were kept in tight closed container and stored at 4c° until using.

Experimental Animal Twenty four mature domestic male rabbits (*Lepuscuniculus*) , weight between (1-1.5 kg) and aged six months were used in this study. The animals were bought from the local market in Basra city they were housed in the animal house of the College of Veterinary Medicine / University of Basra. They were housed in well ventilated standard environment condition at temperature 25± C° and photoperiod 12 hrs light /dark cycle. They were supplied with standard pellet and water *add libitum* , they were allowed for two weeks for

adapting to the new environment before experimentation . The animals were given anticoccidiosis (Amprolium) through the drinking water daily for two weeks (1g / L). Finally the rabbits were randomly and equally divided into four groups (n=6/ group). The ginger extract and Cadmium chloride dissolved in distilled water and administrated as single daily orally (drenching). The treatment expended for 35days.

The Biochemical Measurements after collecting of blood samples from the heart and serum separation , some biochemical measurements were done by using special enzymatic kits which were performed as follows:

1. Estimation of Total Insulin Hormone. The serum concentration of insulin was determined by Elisa kit , according to (6). The amount of insulin in the sample was calculated by comparing the optical density of the sample to the standard curve .By using at 450nm wave length.

2. The serum blood glucose levels: serum blood glucose was determined by enzymatic method depending on the enzymatic method (7).

3. The total cholesterol determination (TC) : total serum cholesterol was done by enzymatic method depending on enzymatic method of .(8).

4.Estimation of Aspartate Aminotransferase (AST).And Alanine Aminotransferase (ALT) activities :for the estimation of ALT and AST activities in serum samples, commercially enzymatic kits, based on the reaction of 2,4 dinitrophenyl hydrazine with pyruvate and / or oxaloacetate to yield a brown colored complex in alkaline medium were used (9) . The absorbency was determined at 505nm wavelength

5. Estimation of Alkaline Phosphatase activity (ALP) Serum ALP activity was assayed by using commercial kits. The read absorbance at 510 nm wavelength against reagent blank (1°).

The Statistical analysis:

The results of the present study were analyzed by using variance (ANOVA) test. The statistical analysis was performed by using the program. The data were expressed as a means \pm SD. *P* values less than 0.05 ($P<0.05$) were considered to

be significant for all data of this study .

RESULTS

Insulin Hormone level Table (1): show the average of serum insulin level in groups treated with Cadmium chloride (10mg/kg), ethanolic ginger extract (100 and 200 mg /kg) and control group . The result shows a significant decrease ($p < 0.05$) in serum level of insulin in Cadmium chloride group as compared with the control group . However , animals received an ethanolic ginger extract showed a significant increase ($p < 0.05$) in average insulin level compared with cadmium treated group. But still significantly than that of control.

Table (1) : Serum insulin level in the control group and groups treated with cadmium chloride and ethanolic ginger extract.

Parameter	Control D.W	Cd Cl ₂ 10mg /kg B.W	G.Ex 100 mg/ kg plus CdCl ₂ 10mg/kg B.W	G. Ex 200 mg/ kg plus CdCl ₂ 10mg/kg B.W
Insulin μ Iu/ml	22.06 \pm 1.60 A	11.5 \pm 1.19 D	16.69 \pm 0.16 C	20.06 \pm 1.45 B

The difference in the latter means statistical difference ($P < 0.05$) level as compared with the control group .

Table (2) showed that serum levels of fasting blood glucose and total cholesterol in the group treated with Cadmium chloride were significantly increased ($p < 0.05$) as compared with the control group .However , the groups which treated with ethanolic ginger extract showed that significant reduction ($p < 0.05$) in serum blood glucose and total cholesterol concentrations as compared with Cadmium chloride group.

Table (2): Serum blood glucose and total cholesterol levels in the control group and groups treated with cadmium chloride and ethanolic ginger extract.

Parameters	Control D.W	Cd Cl ₂ 10mg/ kg B.W	G.Ex 100 mg /kg plus CdCl ₂ 10mg/kg B.W	G. Ex 200 mg/kg plus CdCl ₂ 10mg /kg B.W
Glucose mg/Dl	75.82 ± 2.42 D	224.31 ±30.27 A	129.91 ±1.49 B	92.31 ±10.61 C
Total cholesterol mg/dL	136.75 ±3.60 C	230.57 ±3.18 A	168.57 ±4.68 B	138.68 ±2.50 C

The difference in the latter means statistical difference (P<0.05) level as compared with control group .

Table (3) The average serum AST, ALT and ALP levels of animals which treated by Cadmium chloride (10mg/kg), ethanolic ginger extract (100 and 200mg/kg) and control group indicated that there is a significant increase (p<0.05) in serum AST, ALT and ALP levels in animals treated with Cadmium chloride compared with the control group. From the results also there is a significant decrease (p<0.05) in serumAST, ALT and ALP levels in animals treated with ethanolic ginger extract as compared with Cadmium chloride group.

Table (3): Serum AST, ALT and ALP levels in the serum control group and groups treated with cadmium chloride and ethanolic ginger extract.

Parameters	Control	Cd Cl ₂ 10mg/kg B.W	G.Ex 100 mg/kg plus CdCl ₂ 10mg/kg B.W	G. Ex 200 mg/kg plus CdCl ₂ 10mg/kg B.W
AST (IU)	7.71 ±0.83 D	37.81 ± 3.27 A	15.38 ±1.19 B	10.95 ±0.83 C
ALT(IU/L)	9.11 ±0.83 C	32.35 ±2.31 A	13.98 ±0.63 B	9.68 ±0.58 C
ALP (IU/L)	5.77 ±0.44 D	26.25 ±3.34 A	13.69 ±0.49 B	8.88 ±0.50 C

The difference in the latter means statistical difference (P<0.05) level as compared with control group .

DISCUSSION

The present results showed a significant decrease in insulin level of the rabbits treated with cadmium alone as compared with normal control. This results consistent with other (12,13) whom all found that cadmium studies concerned with cadmium exposure (1) reduce insulin levels and has a direct cytotoxic effect on the pancreas , proving that pancreatic tissue has an extremely high affinity for cadmium indicating that cadmium may be inflicting damage directly at the level of pancreatic insulin secretary mechanism .

14) reported that cadmium administration resulted in destruction of beta cells , such a decrease in the number of functional beta cell. This supports the earlier reports that cadmium induced atrophy of islets and decrease in insulin secretary activity (15).

On the other hand, some studies have shown that cadmium has a potent diabetogenic agent and its a potent SH inhibitor by which the interaction with pancreatic SH group result in pancreatic damage (16,17)

While (18) showed that insulin gene is mainly expressed in islet B-cell in pancreas. The expression of insulin synthesis mRNA was inhibited after administration of cadmium is one reason of why the change of insulin level occurs.

(19) found that cadmium reduces insulin secretion may attributed to the block of the calcium channel. The major route of cadmium influx is voltage gated $[Ca^{+2}]$ channel, cadmium combined with $-SH$ of membrane protein inhibits the $[Ca^{+2}]$ influx, decreasing free $[Ca^{+2}]$ in cell, this results in changes of calcium dependent functions are supported by earlier reports that cadmium induces inhibition of insulin secretion through an inhibition of calcium uptake by beta cells and its interfering with translocation of intracellular calcium (20). However, Co-administration of ginger extract with cadmium caused a significant increase in the level of insulin level as compared to cadmium intoxicated rabbits. This indicates that ginger extract has antidiabetic properties. These results are consistent with (21) who found that administration of ginger extract to diabetic rat alleviated the hypoinsulinemia.

(22) demonstrated that a beneficial effect of ginger extract on serotonin induce hyperglycemia and hypoinsulinemia in normoglycemic rats and reported that ginger extract inhibited this inductive effect. In support of this hypothesis the an aqueous extract of raw ginger has potential hypoglycemic properties. This hypoglycemic action of ginger may be due to effects involving serotonin receptors, an increase in pancreatic secretion of insulin from B-cell or release of bound insulin (23).

On the other hand, the antidiabetic and antioxidant properties of ginger extract can decrease the destructive effect of cadmium on the pancreas. The presence over 20 phenolic compounds, these compound displays diverse biological activities such as antioxidant, antidiabetic, hypoglycemic and aldose reductase inhibitory properties. (24, 25).

(26) concluded that ginger extract may prevent the cadmium induced oxidative damage in pancreas due to the presence of selenium which might afford protection to the pancreas by preventing the Ca- SH interaction and consequently sparing cadmium – induce Zn loss.

The present results in table (2) revealed a significant increase in the level of glucose concentration in rabbits treated with cadmium compared with normal control. this results concordance with (27) who found that the cadmium had decreased expression of the glucose transporter (GLUT4) and reduce glucose transport activity when cultured a dipoccytes that were isolated from rats previously exposure to cadmium.

Previous studies have shown that cadmium can affect glucose metabolism by acting on a variety of different organs may be due to elevation activities all four of the enzymes responsible for gluconeogenesis , enhance the release catclolamines and decreased both glucose uptake and a Na+- dependent glucose symporter (28, 29,30). Whereas , Co- administration of ginger extract with cadmium caused a significant reduction in the average glucose concentration as compared to rabbit treated with cadmium. This indicates that ginger extract has potential hypoglycemic activity similarly (31). Showed that ginger juice exhibits hypoglycemic activity in both normal and streptozotocin induced diabetic rat.

(32,33) we found that the aqueous extract of ginger has both antiglycating activity and aldose reductase 2 inhibition, ginger seems to modulate both glycation and polyolpathwas, the antiglycationg natural of ginger could be the major mechanism in ameliorating STZ- induced diabetic (34).

(35) reported that treatment with a methanolic extract of dried rhizome of ginger produced a significant reduction in fructose induced hyperglycemia and hyperlipidemia, the same authors (36) showed that administration of the methanolic ginger extract for 8 weeks to the mice , reduced goldthiogluucose – induced obesity and glucose also improved insulin sensitivity.

Recently (5) studied the hypoglycemic potential of ginger in streptozotocine- induce diabetic rats when given an aqueous extract of raw ginger daily 500mg/ kg IP for a period of 7 weeks . The raw ginger was significantly effective in lowering

serum glucose , cholesterol and Tri acylglycerol levels in the ginger treated diabetic rat.

Other studies have shown that feeding rats with ginger reduced the formation advance glycation end product in both soluble and insoluble protein fractions , normalization of aldose reductase 2 and reduction carbonyl mediated stress by ginger might be responsible for restoring ALDose reductase 2 after feeding ginger, also reducing the activity of polyol pathway , prevent sorbitol and galactiol accumulation and prevention of oxidative stress (37,38,39).

The results presented in the table (2) show a significant increase total cholesterol in rabbits treated with cadmium compared with normal control. These results in concordance with other studies (40,41,42,43). These authors have shown that cadmium damages the liver, the esterification occurs mainly in the liver , therefore , the proportion of esterified cholesterol decrease that lead to hyper cholesterolemia may be due to impairment of the liver and inhibition of enzymes which converts cholesterol into bile acid .

(44) concluded that cadmium causes hyper cholesterolemia due to reduced lipoprotein lipase activity which plays a role in the increment of plasma lipid. However , in Co- treatment of ginger extract with cadmium there was a significant decrease total cholesterol, these results are concordant with (45,46) whom reported that the total cholesterol level were significantly decreased by dietary supplementation of 1% ginger extract meal in rats . They stated that ginger treatment can reduce total serum cholesterol by enhancing the activity of liver cholesterol -7-a- hydrolase or inhibition of hydroxy- methyl- glutaryl- Co- enzyme – A (HMG- CoA) reductase , either by bile – acid conversion or fecal excretion of cholesterol (47).

The adding ginger rhizome powder to the food could be useful in the management of cardiovascular disease in which atherosclerosis is the most important factor may be due to the presence poly- phenolic and flavonoids may prevent coronary artery disease by reducing plasma cholesterol level or by inhibiting LDL oxidation , a process which is through to play a key role in the pathogenesis of atherosclerosis. (48,49,50).

On the other hand, (51, 52) stated ginger significantly lowered serum total cholesterol, LDL, VLDL and triglycerides and raised HDL. These authors attributed their results to the reducing effect of ginger acted on cholesterol biosynthesis in the liver and may stimulate cholesterol's conversion to bile acid and increase its fecal excretion, while (53) demonstrated that ginger enhanced the activity of pancreatic lipase and amylase when they were directly in contact with the enzyme.

The results are presented in the table (4,5 and 6) there was a significant increase in the levels of AST, ALT and ALP levels in the rabbits treated with cadmium. This indicates the damaging effect of cadmium in the liver is manifested by an increase of AST, ALT and ALP, which specific marker of the liver cell damage. Similar finding was reported by (54) who found that transaminases are the most sensitive biomarkers directly implicated in the extent of cellular damage and toxicity because they are cytoplasmic in location and are released into the circulation after cellular damage, however, an elevation of the serum levels of the hepatic enzymes and alkaline phosphatase are the indicators for impaired liver function (55,56,57) Showed that induction of cadmium liver cell damage releases these enzymes into the extracellular fluid and results in increased plasma levels of enzymes (AST, ALT and ALP). These characteristic features of cadmium induced liver toxicity.

(58) found that oxidative stress intensification after cadmium administration in the liver are responsible for the increase of AST, ALT and ALP activity. (59) stated that cadmium hepatotoxicity is probably affected in two ways on the one hand by the occurrence of inflammatory state, on the other hand direct toxic action of cadmium on liver cell.

The Co-administration of ginger extract with cadmium restored the levels of the enzymes in the serum of the rabbits as an indication of the protective effect of ginger extract against liver damage induced by cadmium, which consistent with the (60) stated that ginger has a protective effect on the hepatotoxicity.

(61) who found that ginger is useful and lowers the serum AST, ALT and ALP enzymes this reduction could be attributed to the fact that ginger contains high content of antioxidant that makes it a free radical scavenger. In support of this

hypothesis the antioxidant activity of ginger might be due to radical scavenging activity and their affinity to the substrates (62). While , (63) concluded that efficacy of different doses of ginger (ZingiberOfficinales Rose) extract in alleviating hepatotoxicity in male rats when administration of bromobenzene – induced hepatotoxicity . Other authors have shown that ginger extract attenuates the elevated level of AST, ALT and ALP after intoxication by cisplatin , this may be attributed to that ginger component stabilize hepatocytes plasma membrane and prevent delivery of AST, ALT and ALP to the extracellular fluid . (64,65)

(66) reported that treated with anethanolic extract of ginger in isoproterenol treated rats increased the level of endogenous myocardial antioxidants (SOD, CAT and glutathione content) and decrease the level of serum marker enzymes AST, ALT and ALP .

It may conclude that antidiabetic , hypoglycemic and hypolipidemic properties of the ginger extract . in addition a protective effect against cadmium-hypatotoxicity .

التأثير الوقائي للخلاصة الكحولية للزنجبيل ضد التسمم بالكادميوم في ذكور الأرانب

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الخلاصة

اجريت هذه الدراسة لتقييم التأثير الوقائي للخلاصة الكحولية للزنجبيل ضد التسمم بالكادميوم في السيطرة على نقص الانسولين وفرط السكر وتأثيره على الدهون ووظائف الكبد في ذكور الارانب البالغة.

تم تقسم الارانب التي استخدمت في البحث عشوائيا الى اربعة مجاميع (كل مجموعه تحوي ست حيوانات) . المجموعة الاولى مجموعه السيطرة والمجموعة الثانية جرعت فمويا (١٠ ملغم / كغم) من كلوريد الكادميوم والمجموعة الثالثة جرعت فمويا (١٠٠ ملغم/ كغم) من خلاصه كحوليه للزنجبيل و(١٠ ملغم / كغم) من كلوريد الكادميوم والمجموعة الرابعة جرعت فمويا (٢٠٠ ملغم / كغم) من خلاصه كحوليه للزنجبيل و(١٠ ملغم / كغم) كم كلوريد الكادميوم .

تبين من تحليل النتائج إن هناك زيادة في تركيز انزيمات الكبد وتركيز السكر والدهون وقلة في تركيز الانسولين في الحيوانات المعرضة الى الكادميوم . وقد تبين إن لمستخلص الكولي للزنجبيل تأثيرا

مهما وقائيا وخافض لسكر والكوليسترول الذي تبين من انخفاض مستوى الإنزيمات الكبد ولنسبة السكر والدهون وزيادة في تركيز هرمون الانسولين في الدم.

واظهر التحليل الإحصائي للنتائج مايلي:

- انخفاض معنوي ($P<0.05$) في تركيز انزيمات الكبد .
-ارتفاع معنوي ($p<0.05$) في تركيز الانسولين مقترن مع انخفاض معنوي ($P<0.05$) بنسبة السكر والدهون .
ومن خلال نتائج الذي تم التوصل اليها في هذه الدراسة تم استنتاج الفعل الوقائي للخلاصة الكحولية للزنجبيل ضد التسمم بالكاديوم

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