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Hypoglycaemic Effect of γ-Irradiated Clove Extract on Alloxan-Induced Diabetic Rats

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DIABETES is characterized by hyperglycaemia and elevated production of reactive oxygen species (ROS). Clove is full of natural antioxidants such as polyphenols and essential oils. The aim of the study was to investigate the hypoglycaemic effect of clove extract in diabetic rats.

The results with test rats indicated that alloxan administration induced the elevation of glucose level, activity of some liver enzymes, malondialdehyde (MDA), urea and creatinine concentrations as well as the level of some lipid contents.

While the level of insulin, total thyroid hormones triiodothyronin (T_3) and thyroxine (T_4), glutathione content (GSH) in addition to the concentration of high density lipoprotein (HDL-C) were decreased under the effect of alloxan.

As a result of treatment of diabetic rats with raw or irradiated clove extract, hyperglycaemia, hepatic, renal and endocrine abnormalities induced by alloxan were improved.

Conclusion: clove extract exerts a dietary antidiabetic benefit and affect a partial normalization of the biochemical changes associated with alloxan-induced diabetes mellitus in rats. Furthermore, the study indicated that treatment of cloves with 10 kGy of gamma irradiation had no significant effect on the antidiabetic properties of the extract made from such cloves. This confirms the suitability of irradiation for the improvement of the hygienic quality of cloves.

Key words: Diabetes mellitus, clove, Aalloxan, gamma-irradiation, rats.

Hyperglycaemia, a characteristic of diabetes mellitus tends to cause degenerative chronic complications affecting the eyes, heart, liver, blood vessels, nerves and kidneys (Yan *et al.*, 2009). Both genetic and environmental factors contribute to the pathogenesis of diabetes, which in turn negatively affects the life expectancy and quality of life of diabetic people worldwide (Tuomilehto *et al.,* 2001). Also, nutritional parameters, together with obesity, as well as lifestyle, for example physical inactivity and smoking, have been found to promote diabetes epidemics and contribute to diabetes health consequences (Koh-Banerjee *et al.,* 2004 and Trichopoulou *et al.,* 2006). According to estimates approximately 215 million people all over the world suffer from diabetes mellitus and 80-90% of them are from type II diabetes. A sustained reduction in hyperglycaemia will decrease the risk of developing microvascular diseases and reduce their complications (Kim *et al.,* 2006). The conventional therapies for diabetes have many shortcomings like side effects and high rate of secondary failure. There are many minor components of foods such as secondary plant metabolites have been shown to alter biological processes which may reduce the risk of chronic diseases in diabetic humans. On the other hand, spices extracts are expected to have similar efficacy without side effects as that of conventional drugs (Gupta *et al.,* 2008). Cloves are the dried flower buds of *Syzygium aromaticum* (L.), family *Myrtaceae* and successfully used for the management of asthma and various allergic disorders in addition to anti carcinogenic properties. Also, clove reportedly modulated physiological responses in streptozotocin-induced diabetic rats (Nangle *et al.,* 2006 and Zari and Al-Attar, 2007). Eugenol (4-allyl-2-methoxyphenol) is a naturally occurring phenol essential oil and makes up to 90% of the clove oil. It is known to be an antioxidant (Jirovetz *et al.,* 2006), a monoamine oxidase inhibitor and known to have neuroprotective effects (Kabuto *et al.,* 2007). Spice irradiation is performed to increase the hygienic quality of spices by reducing the number of pathogenicity and spoilage by microorganisms and extend the shelf life (Al-Kaisey *et al.,* 2002). Previous studies of Hamza and Mahmoud (2009) on the effect of γ-irradiation on black cumin revealed that γ-irradiation at dose 10 kGy had no real effect on the chemical contents of this spice. The aim of this study was to clarify the effect of γ-irradiated clove, as a medicinal spice, in the treatment of diabetes.

Material and Methods

Material

Dried flower bud of clove and standard commercial rodent diet were purchased from local herbal market (Cairo, Egypt). The clove was crushed to coarse powder and sieved through No. 20 mesh size. Also, alloxan monohydrate was purchased from Sigma Chemical Co., USA.

Irradiation process

Powder of clove was transferred into polyethylene bags and treated with 10 kGy of gamma rays, using a ^{60}Co source at a dose rate of 4.70 kGy/ h belonging to the NCRRT, Egypt.

Plant extracts

100 ml water was added to 10 g powdered clove and incubated at 60 ^{o}C for 2 h. Then the extract was filtered with whatman No. 1 and preserved in a refrigerator (Kreydiyyeh *et al.*, 2000). The extract of cloves was orally given to the animals at a dose of 0.2 ml/ day/ rat (Younies, 2008).

Extraction of essential oil

The essential oils of clove were obtained by water distillation in a glass apparatus for 3 h. The separated volatile oils were dried over anhydrous sodium sulphate before hold glass bottles at -20 ºC according to Guenther (1961).

Separation and identification of chemical components of the essential oil

Separation and identification of essential oil components were performed by using Gas chromatography instrument, Model Hewlett-Packard-MS (5970) series II at the Agriculture Research Centre, Giza, Egypt. Condition analysis as follow: column: 30m hp methyl silicon 0.1mm; temperature: initial 60 ºC; rate: 3 ºC/ min up to 240 ºC; carrier gas: helium 1.0 ml/min; injection port; temperature: 250 ºC; detector temperature: 270ºC; integration: by using HP software Data; injection volume: 0.3ml. The isolated peaks were identified by matching with data from the library of mass spectra and compared to those of authentic compounds and published data (Adams, 1995). Quantitative determination was carried out based on peak area integration.

Study design

Male albino rats weighing approximately 200 g were used in this study. Hyperglycaemia was induced by intraperitoneal administration of alloxan monohydrate dissolved in saline at a dose of 150 mg/ kg body wt (Noaman *et al.*, 2007). Alloxan can be induced fatal hypoglycaemia as a result of massive pancreatic insulin release; therefore, rats were treated with 30% glucose solution orally at different time intervals after 6 h of alloxan induction, and 5% glucose solution was kept in bottles in their cages for the next 24 h. After one week, blood was extracted from the tail vein for glucose analysis by the method of Trinder (1969). Experimental animals exhibited fasting blood glucose levels in the range of 200 to 250 mg/ dl.

The animal were randomly divided into 4 groups, each consisted of 7 rats. Group I: rats fed on balanced diet and served as control, group II: diabetic group and group III- IIII: received oral extract of raw or γ-irradiated clove (0.2 ml/ day/ rat) for 8 weeks and administrated with alloxan (150 mg/ kg Body wt) after the 2^{nd} week of the experimental period.

At the end of the experimental period, the rats in each group were fasted overnight, anaesthetized with diethyl ether and sacrificed. Blood samples were collected through heart puncture, allowed to coagulate and centrifuged to obtain serum for biochemical analysis. Also, liver was removed and prepared for biochemical investigation

Biochemical analysis

Serum samples were analysed for glucose (Trinder, 1969) and insulin hormone was determined by radioimmunoassay kit supplied by Diasari, Italy. The activity of serum aspartate transaminase (AST) and alanine transaminase (ALT) were assayed by the method of Reitman and Frankel (1957), as well as serum alkaline phosphatase activity (ALP) was assessed according to Kind and King (1954). The lipid peroxide content was determined calorimetrically as MDA, Yoshioka *et al.* (1979). Hepatic GSH was measured by the method of Gross *et al.* (1967). Serum creatinine and urea were measured according to Faulkner and King (1976) and Tabacco (1979). Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-C) were determined according to procedure described by Allain *et al.* (1974), Fossati and Prencipe, (1982) and Demacker *et al.* (1980), respectively. Low-density (LDL-C) and very Low-density lipoprotein (vLDL)- cholesterol was evaluated by Friedwald *et al.* (1972) and Norbert (1995) according to the equations: LDL-C= TC- (TG/ 5+ HDL-C) and vLDL= TG/ 5, respectively. Serum T_3 and T_4 levels were measured by *in-vitro* nuclear diagnostic radioimmunoassay technique as described by Burtis *et al.* (1994).

Statistical analysis

Statistical analyses were performed using computer program Statistical Packages for Social Science (SPSS, 1998) and values compared with each other using suitable tests.

Results

Essential oil contents found in clove were reported in Table 1. Eugenol (62.63%) was the main essential oil of clove and its value was elevated under the effect of γ-irradiation to 64.15%.

TABLE 1. Effect of γ-irradiation on clove essential oil.

Components	Constituents % of clove essential oil	
	Raw	10 kGy
4-(2-propenyl)-phenol	0.37	0.15
α-Cubebene	0.55	0.09
Eugenol	62.63	64.15
α-Copaene	0.93	0.56
Caryophyllene	11.74	10.85
α-Humulene	1.15	1.09
Isoledene	0.06	0.05
Muurolene	0.23	0.21
α-Farnsene	5.21	6.19
Eugenol acetate	12.17	12.31
Diethyl phthalat	0.12	0.08
Total unknown	4.84	4.27

The data in Table 2. revealed a significant elevation in glucose and remarkable decline in insulin, T_3 and T_4 levels in diabetic rats compared to normal rats. In contrast, administration of raw and γ-irradiated clove extract to diabetic rats significantly decreased the level of blood glucose and significantly increased the level of insulin, T_3 and T_4 compared to diabetic group.

TABLE 2. Effect of raw and irradiated clove on the level of glucose, insulin, T_3 and T_4 of diabetic rats.

Rat groups	I	II	III	IIII
Glucose (mg/ dl)	102.11 ± 6.3^{a}	257.50 ± 7.1^{c}	129.60 ± 5.3^{b}	127.80 ± 6.2^{b}
Insulin (µU/ ml)	33.69 ± 4.12^{a}	18.24 ± 4.56^{c}	26.63 ± 3.75^{b}	26.80 ± 4.34^{b}
T_3 (ng/ dl)	91.61 ± 1.83^{a}	53.39 ± 1.53^{c}	70.96 ± 1.75^{b}	71.44 ± 1.61^{b}
T_4 (µg/ dl)	7.35 ± 0.36^{a}	5.17 ± 0.42^{c}	6.46 ± 0.26^{b}	6.49 ± 0.33^{b}

Values are expressed as means± S.E. (n= 7).

Values in the same raw with different superscripts are differing significantly at $P< 0.05$.

Alloxan administration significantly produced adverse effects on the liver function of the rats and increased the activity of ALT, AST and ALP enzymes as compared with normal (Table 3). Treatment of diabetic rats with either raw or irradiated clove extract exhibited improvement in liver function compared to diabetic rats.

TABLE 3. Effect of raw and irradiated clove on the level of AST, ALT and ALP of diabetic rats.

Rat groups	I	II	III	IIII
AST (U/ ml)	21.76± 1.02[a]	47.93± 2.21[c]	31.97± 1.56[b]	32.06± 0.72[b]
ALT (U/ ml)	18.60± 1.13[a]	41.33± 2.62[c]	23.57± 2.03[b]	23.38± 2.24[b]
ALP (U/ 100ml)	8.76± 0.73[a]	14.25± 0.94[c]	9.62± 0.66[b]	9.68± 0.71[b]

Legends as in Table 2.

Table 4. show a significant increase in the level of MDA, urea and creatinine associated with remarkable decrease in hepatic GSH content of diabetic rats when compared with the normal group. While diabetic rats received oral extract of raw and γ-irradiated clove had a lower concentration of MDA, urea and creatinine as well as the level of GSH was significantly increased near to the normal value.

TABLE 4. Effect of raw and irradiated clove on the level of MDA, GSH, urea and creatinine of diabetic rats.

Rat groups	I	II	III	IIII
MDA (n mol/ ml)	182.36± 6.3[a]	385.15± 12.7[c]	237.0± 14.6[b]	242.0± 15.1[b]
GSH (mg/g tissue)	25.72± 2.83[a]	15.66± 1.87[c]	22.35± 2.16[b]	22.61± 2.32[b]
Urea (mg/ dl)	22.81± 0.95[a]	40.07± 1.14[c]	26.55± 0.87[b]	25.78± 1.06[b]
Creatinine (mg /dl)	0.76± 0.04[a]	1.32± 0.08[c]	0.83± 0.07[b]	0.81± 0.06[b]

Legends as in Table 2.

TABLE 5. Effect of raw and irradiated clove on lipid profile of diabetic rats.

Rat groups	I	II	III	IIII
TC (mg/dl)	161.57± 5.6[a]	231.18± 6.1[c]	185.50± 4.9[b]	183.72± 5.6[b]
TG (mg/dl)	103.84± 3.7[a]	180.67± 3.8[c]	118.78± 4.2[b]	120.11± 2.9[b]
HDL-C (mg/dl)	50.16± 2.12[a]	31.93± 1.76[c]	44.56± 1.83[b]	44.71± 1.79[b]
LDL-C (mg/dl)	90.64± 3.71[a]	163.12± 4.86[c]	117.18± 4.14[b]	114.99± 3.92[b]
vLDL-C (mg/dl)	20.77± 1.27[a]	36.13± 2.11[c]	23.76± 1.62[b]	24.02± 1.68[b]

Legends as in Table 2.

It could be noticed that alloxan induced significant elevations in the serum level of TC, TG, LDL-C and vLDL-C associated with a significant decrease in the serum HDL-C concentration in comparison with those of the non-diabetic rats. However, raw and irradiated clove extract reduced the hyperlipidaemia effect induced by alloxan (Table 5).

Discussion

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by limited insulin secretion or lower tissue sensitivity to insulin (Abel-Salam, 2011). Clove is one of spices that reportedly modulated physiological responses in streptozotocin-induced diabetic rats and reduced glucose level (Nangle *et al.,* 2006 and Zari and Al-Attar, 2007). Results in this study obtained a significant low level of insulin and high glucose level due to alloxan administration. Alloxan-induced diabetes is a well-documented model of experimental diabetes. This compound causes severe necrosis of pancreatic beta cell (Dunn *et al.,* 1943). This effect was previously explained on the basis of alloxan's ability to produce hydrogen peroxide and other free radicals, including $O_2^{\bullet}$ and $^{\bullet}OH$ that damage β-cells hence leading to their death (Lenzen and Munday, 1991). The sensitivity of β-cells to oxidative stress has been attributed to their low levels of antioxidants compared with other tissues (Lenzen *et al.*, 1996). Beta cell dysfunction eventually culminates in reduction in insulin release leading to hyperglycaemia. The alloxan induced sustained hyperglycaemia aggravates the oxidative stress status by auto-oxidation of glucose and its primary and secondary adducts (Sakurai and Tsuchiya, 1988).

Diabetic rats treated with raw or γ-irradiated clove extract have a remarkable high level of insulin accompanied by decreasing the concentration of glucose. The antidiabetic action of clove seems to be mediated through stimulation of the pancreas to produce and recreate insulin. Also, the antioxidant and hypoglycaemic effects may be related to its essential oil contents such as eugenol and eugenyl acetate (Lee and Shibamoto, 2001). In addition, it is noted that some essential oil extract of clove decreased blood glucose levels by facilitating glucose usage via extrapancreatic ways (Hassanen, 2010).

Occasionally, other endocrine disorders such as abnormal thyroid hormone levels are found in diabetes (Perros *et al.,* 1995 and Pasupathi *et al.,* 2008). The results obtained revealed that alloxan induced the reduction in the level of T_3 and T_4 hormones and that due to the effect of diabetes, which can enhance the reduction of thyroid stimulating hormone (TSH) leading to alterations in thyroid hormone system. Therefore, T_3 and T_4 production and iodide uptake by the thyroid are diminished as well as T_4 deiodination to T_3 in peripheral tissues is decreased (Calvo *et al.,* 1997 and Udiong *et al.,* 2007).

Liver cell destruction shows its effects mostly as impairment in the liver cell membrane permeability, which results in the leaking out of tissue contents into the blood stream. In diabetic rats, the activity of serum ALP, ALT and AST were significantly increased. Supporting these findings, it has been found that the liver was necrotized in diabetic rats. Therefore, the increase of the activity of liver enzymes in serum is mainly due to the leakage of these enzymes from the liver into the blood stream (Mansour *et al.*, 2002), which gives an indication on the hepatotoxic effect of alloxan. On the other hand, the administration of clove to diabetic rats reduced ALP, ALT and AST activity towards their normal values. The decrease in these enzymes activity in diabetic rats given clove shows that this spice presented liver damage (Hassanen, 2010). In addition, Ramesh and Pugalendi (2006) reported that treatment of diabetic rats with spices or their essential oils recovered the membrane damage by decreasing lipid peroxidation and improving anti-oxidants' status .

The cytotoxic action of alloxan is associated with the generation of reactive oxygen species causing oxidative damage and lipid peroxidation (Szkudelski, 2001). The most commonly used indicator of lipid peroxidation is MDA which was observed in this study by high level in the serum of diabetic rats while its level was highly reduced by administration of clove to diabetic rats. As well as, the level of GSH was significantly declined by alloxan and its level returned nearly too normal under the effect of clove extract. The increase in MDA and decrease in GSH levels due to alloxan induced production of free radicals leading to oxidative stress (Venkateswaran and Pari, 2003). Essential oils of clove such as eugenol and eugenyl can directly scavenge the free radicals in diabetic rats, may reduce the utilization of GSH and thereby exhibiting an increase in the GSH content in treated diabetic rats (Sacan *et al*., 2006). The GSH content increment in the serum of rats treated with clove may be a responsible factor for inhibition of lipid peroxidation. The elevated level of GSH protects cellular proteins against oxidation through glutathione redox cycle and also directly detoxifies reactive oxygen species generated from exposure to alloxan (Latha and Pari, 2003).

Kidney function tests help to determine if the kidney is performing their task adequately. In the present study, the diabetic rats had increased levels of creatinine and urea which are considered as significant markers of renal function and this is in agreement with the results of Sacan *et al.* (2006). The kidneys of rats with streptozotocin-induced diabetes become enlarged and may be associated with membrane damage caused by hyperglycaemia mediated oxidative stress (Ramesh *et al.*, 2007). However, diabetic rats treated with clove reversed these changes to near normal and enhanced the kidney function. The renal protective role of clove was related to its essential oil contents and that could be associated with decreased membrane damage as evidenced by improved antioxidants status, reversed fatty acid changes as evidenced by improved insulin level**,** and also supported by regulated glycoprotein components (Hassanen, 2010).

The present study showed that there were higher levels of cholesterol, triglycerides, LDL-C and vLDL-C accompanied by low level of HDL-C in alloxan induced-diabetic rats. The level of lipids is usually raised in diabetes and such an elevation represents a risk factor for coronary heart disease (Pacheco *et al.,* 2001). The abnormal high concentration of lipids in diabetes was mainly due to an increase in adipose tissue lipolysis in absence of insulin and mobilization of free fatty acids from the peripheral depots, since insulin inhibits the hormone sensitive lipase (Hassanen, 2010). The continuous administration of clove to diabetic rats reduced the elevation of serum lipids and enhanced the level of HDL-C; these results are in consequence with those found by Badee *et al.* (2005). The hypolipidaemic effect and lowering of cholesterol and triglycerides could be probably attributed to decreasing 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase activity), a key enzyme of cholesterol biosynthesis and/or by reducing the NADPH required for fatty acids and cholesterol biosynthesis (Sharma *et al.,* 2003 and Vessal *et al.,* 2003). Also, the clove might stimulate the production of insulin which in turn inhibits lipoprotein lipase activity (Ravi *et al.,* 2005). In general, the present study concluded that administration of clove extract significantly reduced blood sugar and lipid peroxide content in diabetic rats and restored the GSH content and insulin level, which indicate the antioxidant activity and the hypoglycaemic effect of clove and its essential oil.

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التأثير الخافض للسكر لمستخلص القرنفل المعامل بأشعة جاما فى الجرذان المحدث بها مرض السكر بمادة الألوكسان

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قسم بحوث تشعيع الأغذية ، المركز القومي لبحوث وتكنولوجيا الإشعاع ، ص . ب ٢٩ مدينة نصر ، القاهرة ، مصر.

يعتبر مرض السكر من أهم الأمراض المزمنة وهو يؤدي إلى تغيرات غير طبيعية في الدهون و البروتينات بالإضافة إلى انبعاث شقوق اللأكسجين الحرة. القرنفل من التوابل الشعبية التي تستخدم بكثرة لنشاطه المضاد للأكسدة وذلك لإحتوائه على المركبات الفينولية والزيوت العطرية الأساسية وأهمها الأوجينول. تهدف هذه الدراسة إلى معرفة تأثير مستخلص القرنفل في خفض نسبة السكر في الجرذان المصابة بمرض السكر. اظهرت النتائج أن حقن الجرذان بمادة الألوكسان أدى إلى ارتفاع في مستوى السكر ، نشاط بعض إنزيمات الكبد ، المالونالدهيد، تركيز اليوريا والكرياتينين بالإضافة إلى الزيادة في مستوى الدهون. بينما حدث إنخفاض في مستوى هرمون الإنسولين وهرمونات الغدة الدرقية ، محتوى الجلوتاثيون بالإضافة إلى نقص في تركيز الليبوبروتين عالي الكثافة. ونتيجة لإستخدام مستخلص القرنفل الخام أو المعامل إشعاعيا فى معالجة الجرذان المصابة بمرض السكر حدث تحسن في مستوى السكر في الدم ، و تحسن فى التغيرات المحدثة في إنزيمات الكبد ووظائف الكلى ومستوى بعض الهرمونات نتيجة الحقن بمادة الألوكسان. لذلك يمكن الإستنتاج أن القرنفل له تأثير خافض لإرتفاع مستوى السكر وتحسين الأضرار و التغيرات المحدثة في بعض القياسات البيوكيميائية المصاحبة لمرض السكر. وأيضا أشارة الدراسة أن معاملة القرنفل بإشعة جاما لم يكن لها تأثير سلبى على كفاءة مستخلص القرنفل فى علاج مرض السكر. وهذا يؤكد مدى ملاءمة المعاملة الأشعاعية فى تحسين الجودة الصحية للقرنفل.