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PROTECTIVE EFFECTS OF MARJORAM OIL *(ORGANIUM MAJORANA L.)* ON ANTIOXIDANT ENZYMES IN EXPERIMENTAL DIABETIC RATS

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ABSTRACT

An attempt has been made to evaluate the presence of antioxidant properties in the oil of marjoram *(Organium majorana L.)* in streptozotocin-induced diabetes in rats. Oral administration of marjoram oil at a dose of 100 mg/kg body weight to diabetic rats significantly decreased levels of blood glucose and improved body weights. The increased levels of lipid peroxidation in tissues of diabetic rats were reverted near back to normal levels after the treatment with marjoram oil. The marjoram treatment also resulted in a significant increase in superoxide dismutase, catalase and glutathione peroxidase in the liver and kidney of diabetic rats. These results clearly show the antioxidant properties of marjoram oil. The herbal medicine was also more effective than glibenclamide (standard antidiabetic drug) in restoring values of these parameters.

Key words: *Marjoram oil, Streptozotocin induced diabetes, Tissue antioxidants, Glibenclamide.*

INTRODUCTION

Diabetes mellitus, a leading non-communicable disease with multiple etiologies, affects more than 100 million people world-wide and is considered as one of the five leading causes of death in the world (Zimmet, 1999). The number of diabetes mellitus patients is alarmingly increasing due to growing prevalence of obesity, genetic susceptibility, urbanization and aging (Wild *et al.,* 2004). Chronic hyperglycemia of diabetes is associated with damage, dysfunction and failure of various organs such as kidneys, retina, heart, liver, peripheral and central nervous system over the long term (Fajans *et al.,* 1997).

Oxygen free radicals are formed disproportionately in diabetes by glucose oxidation, non enzymatic glycation of proteins and the subsequent oxidative degradation of glycated proteins (Maritim *et al.,* 2003). Reports indicate that diabetes complications are associated with over production of free radicals and accumulation of lipid peroxidation by-products (Palanduz *et al.,* 2001).

Currently available synthetic antidiabetic agents produce serious side effects such as hypoglycemic coma and hepatorenal disturbances (Suba *et al.,* 2004). Hence, the search for safer agents has continued. Following the WHO recommendations for research on the beneficial uses of medicinal plants in the treatment of diabetes mellitus (WHO, 1980), investigations on hypoglycemic agents derived from medicinal plants have gained momentum.

Organium majorana, commonly known as marjoram, is spread world-wide. It is utilized as a spice and flavoring agent and in traditional medicine as well. Marjoram *(Organiummajorana L.)* is an aromatic herbal medicine known to posses various therapeutic properties. It contains phenolic terpenoids, flavenoids, tannins and phenolic glycosides (Al-Howiring *et al.,* 2009). The antiviral, bactericidal, antiseptic and antifungal effects of marjoram are attributed to ursolic acid and essential oils and in particular to thymol and carvacrol (Kelly 2004 and El-Ashmawy *et al.,* 2005). The extract of marjoram showed very high antioxidant effect (Chrpova *et al.,* 2010).

Based on the foregoing findings, we measured the activity of dietary marjoram oil on various oxygen radical-scavenging systems in liver and kidney in rats with STZ-induced diabetes.

MATERIALS and METHODS

Drugs: Marjoram: The oil used was obtained from a local market in Zagazig city, El-Sharkia Province, and it was used in a dose of 100 mg/kg body weight (Hanna and Nahas 2012). The oil was assuring its identity in Department of Forensic Medicine and Toxicology, Faculty of Vet. Med. Zagazig Univ.

Glibenclamide: it was used under trade name Daonil® each tablet contains 5 mg glibenclamide (standard antidiabetic agent). It was administered orally in a dose of 600µg/kg in an aqueous solution via stomach tube (Rajasekaran *et al.,* 2005). The drug

was obtained from Sanofi Avents Co. for pharmaceutical industries. Egypt.

Streptozotocin: Sigma, USA. It was used at a dose of 55 mg/kg body weight in 0.1 citrate buffer (Sekar *et al.,* 1990). STZ was used for induction of diabetes with single dose intraperitonially.

Animals: Twenty five adult male albino rats weighting 100-120 gm were used in this experiment, they were kept under hygienic condition and fed on barley and milk and water was provided *ad lib*. After one week of acclimatization, animals were allocated into 5 equal groups, each of 5 animals. The 1st group was kept as control (NC) and received only saline. The 2nd group was treated with marjoram (MT), it was given orally in form of oil. The 3rd group was diabetic control (DC); streptozotocin (STZ) was given intraperitonially (55 mg/kg b.wt.) for induction of diabetes. The 4th group was diabetic and treated with marjoram (D+MT) while the 5th group was diabetic and treated with glibenclamide (D+GT) which used as a standard antidiabetic drug.

Induction of diabetes: The animals were fasted over night and diabetes was induced by single intraperitonial injection of a freshly prepared solution of streptozotocin (55 mg/kg body weight). The animals were allowed to drink 10% glucose solution over night to overcome drug-induced hypoglycemia. The animals were considered as diabetic if their blood glucose values were above 250 mg/dl on the 3rd day after STZ injection. All treatments were given to the animals for 30 days.

Blood glucose values and body weights were recorded at zero day of induction of diabetes, 15th day and 30th day. Blood samples were obtained from tail vein to determine blood glucose values. Blood glucose values were determined according to the method described by Trinder (1969). After completion of 30 days of treatment, animals were sacrificed and a part of each rat liver and kidneys was removed immediately and kept in -20°C for assay of antioxidant enzymes activity; catalase (CAT) (Sinha, 1972), superoxide dismutase (SOD) (Misra and Fridovich, 1972) and glutathione peroxidase (GPx) (Pagalia and Valentine, 1967) and malondialdehyde concentrations (MDA) (Esterbauer *et al.,* 1982).

Statistical analysis: The obtained data were analyzed using the statistical package for social science (SPSS, 15.0software, 2008) for obtaining means and standard error. The total variation was analyzed by performing the statistical design T-test. Probability levels of less than 0.05 were considered significant.

RESULTS

Effect of marjoram oil on blood glucose levels:
In the present study, we observed a significant increase in blood glucose levels in diabetic rats (14.62 mmol/L), when compared with normal animals (4.73 mmol/L) just before the beginning of the treatment (table 1). Administration of marjoram oil and glibenclamide tended to bring the values to near normal. The blood glucose levels of diabetic rats treated with marjoram oil at the end of the experiment were 11.43 mmol/L while in glibenclamide treated animals were 10.13 mmol/L.

Effect of marjoram oil on body weights:
We have registered a significant decrease in body weights in STZ diabetic rats (189.76 and 175.64 gm versus 207.41 and 217.27 gm in control group at 15th and 30th days from the beginning of the treatment respectively (table 2). When marjoram oil was administered to diabetic rats, the weights seemed to be increased as was the ability to reduce hyperglycemia however; it did not normalize body weights completely. At the end of the experiment, body weights of diabetic rats, treated with marjoram oil were 209.26 gm while in glibenclamide treated group were 205.74 gm.

Table 1: Levels of blood glucose in control and experimental groups of rats. (n=5)

Parameter / Groups	Blood glucose (mmol/L)		
	zero day	15th day	30th day
Normal control (NC)	4.73±0.27 [b]	4.65±0.28 [c]	4.86±0.22 [c]
Marjoram treated (MT)	4.86±0.29 [b]	4.57±0.26 [c]	4.47±0.23 [c]
Diabetic control (DC)	14.62±0.56 [a]	14.67±0.71 [a]	15.29±0.86 [a]
Diabetic + Marjoram treated (D+MT)	14.60±0.64 [a]	13.44±0.72 [b]	11.43±0.45 [b]
Diabetic + glibenclamide treated (D+GT)	14.42±0.69 [a]	11.74±0.64 [ab]	10.13±0.68 [ab]

Means within the same column carrying different superscripts are significant at P≤0.05

Table 2: Body weights of control and experimental groups of rats. (n=5)

Parameter / Groups	Body weights (gm)		
	zero day	15th day	30th day
Normal control (NC)	185.22±10.23 [ab]	207.41±10.67 [a]	217.27±12.45 [a]
Marjoram treated (MT)	187.87±8.336 [ab]	205.45±11.38 [a]	209.25±10.39 [a]
Diabetic control (DC)	203.24±12.56 [a]	189.76±6.44 [ab]	175.64±8.89 [ab]
Diabetic + Marjoram treated (D+MT)	204.50±10.36 [a]	206.11±10.12 [a]	209.26±12.3 [a]
Diabetic + glibenclamide treated (D+GT)	199.23±11.68 [a]	201.72±12.48 [a]	205.74±13.46 [a]

Means within the same column carrying different superscripts are significant at P≤0.05

Tissue free radical-scavenging capacity:
The general pattern of changes seen in diabetic animals was a tendency of enzyme activities that were low in control tissues to be increased and that were high in control tissues to show some degree of reduction in diabetic animals. Measurements of tissue scavenging enzymes in the present study showed clearly that, antioxidant enzyme activities were significantly decreased and malondialdehyde (MDA) levels were significantly increased in diabetic rats.

The concentrations of lipid peroxides were increased in liver and kidney of diabetic rats, indicating an increase in the generation of free radicals (table 3). MDA levels in diabetic animals were 73.64 and 44.64 nmol/gm tissue in liver and kidney versus 56.7 and 24.72 nmol/gm tissue in controls. A significant decrease was recorded in marjoram oil treated group of diabetic rats in MDA levels, 61.73 and 27.46 nmol/gm tissue in both liver and kidney tissues respectively.

Levels of catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were significantly reduced in the hepatic and renal tissues of STZ-diabetic rats (table 4, 5 and 6) when compared to those of the controls. Levels of CAT in diabetic rats were (516.71 and 287.32 µmol of H_2O_2 degraded/mg tissue/min) versus (723.50 and 458.30 µmol of H_2O_2 degraded/mg tissue/min) in liver and kidney tissues of the control animals respectively, while the levels of SOD in diabetic rats were (0.41 and 0.16 µmol of superoxide anion reduced/mg tissue/min) versus (0.83 and 0.33 µmol of superoxide anion reduced/mg tissue/min) in liver and kidney tissues of the control animals respectively.

The levels of GPx in the liver and kidney tissues if diabetic animals were 5.22 and 4.64 µmol of NADPH oxidized/mg tissue/min versus 9.35 and 7.62 µmol of NADPH oxidized/mg tissue/min in liver and kidney tissues of normal animals.

Treatment of streptozotocin induced diabetes with marjoram oil (100mg/kg body weight) significantly increased values of CAT, SOD and GPx activities in liver and kidney tissues of diabetic rats.

Levels of catalase activities after treatment of diabetic rats with marjoram oil were (692.43 and 416.25 µmol of H_2O_2 degraded/mg tissue/min) versus (516.71 and 287.32 µmol of H_2O_2 degraded/mg tissue/min) in liver and kidney tissues of diabetic non treated rats respectively. Superoxide dismutase levels in marjoram oil treated rats were 0.79 and 0.32 µmol of superoxide anion reduced/mg tissue/min versus 0.41 and 0.16 µmol of superoxide anion reduced/mg tissue/min in liver and kidney tissues of diabetic non treated rats respectively.

Glutathione peroxidase levels in marjoram oil treated animals were 8.33 and 6.60 µmol of NADPH oxidized/mg tissue/min versus 5.22 and 4.64 µmol of NADPH oxidized/mg tissue/min in the hepatic and renal tissues of diabetic animals respectively.

Table 3: Levels of MDA activities (nmol of malondialdehyde/gm tissue) in liver and kidney of control and experimental groups of rats. (n=5)

Organs / Groups	Liver	Kidney
Normal control (NC)	56.7±4.82 [c]	24.72±1.88 [c]
Marjoram treated (MT)	52.31±5.76 [c]	21.65±2.1 [c]
Diabetic control (DC)	73.64±4.88 [a]	44.64±2.88 [a]
Diabetic + Marjoram treated (D+MT)	61.73±5.62 [b]	27.46±1.89 [ab]
Diabetic + glibenclamide treated (D+GT)	67.27±4.22 [ab]	33.5±2.1 [b]

Means within the same column carrying different superscripts are significant at P≤0.05

Table 4: Levels of CAT activities (µmol of H_2O_2 degraded/mg tissue/min) in liver and kidney of control and experimental groups of rats. (n=5)

Organs / Groups	Liver	Kidney
Normal control (NC)	723.50±15.62 [a]	458.30±12.98 [a]
Marjoram treated (MT)	762.67±14.36 [a]	467.81±15.47 [a]
Diabetic control (DC)	516.71±10.128 [c]	287.32±10.28 [d]
Diabetic + Marjoram treated (D+MT)	692.43±15.22 [b]	416.25±15.33 [b]
Diabetic + glibenclamide treated (D+GT)	617.38±20.21 [b]	342.88±12.336 [c]

Means within the same column carrying different superscripts are significant at P≤0.05

Table 5: Levels of SOD activities (µmol of superoxide anion reduced/mg tissue/min) in liver and kidney of control and experimental groups of rats. (n=5)

Organs / Groups	Liver	Kidney
Normal control (NC)	0.83±0.092 [a]	0.33±0.034 [a]
Marjoram treated (MT)	0.85±0.12 [a]	0.34±0.05 [a]
Diabetic control (DC)	0.41±0.05 [c]	0.16±0.011 [c]
Diabetic + Marjoram treated (D+MT)	0.79±0.085 [ab]	0.32±0.06 [a]
Diabetic + glibenclamide treated (D+GT)	0.62±0.11 [b]	0.25±0.032 [b]

Means within the same column carrying different superscripts are significant at P≤0.05

Table 6: Levels of GPx activities (µmol of NADPH oxidized/mg tissue/min) in liver and kidney of control and experimental groups of rats. (n=5)

Organs / Groups	Liver	Kidney
Normal control (NC)	9.35±0.342 [a]	7.62±0.41 [a]
Marjoram treated (MT)	9.27±0.416 [a]	7.83±0.766 [a]
Diabetic control (DC)	5.22±0.32 [c]	4.64±0.22 [d]
Diabetic + Marjoram treated (D+MT)	8.33±0.62 [b]	6.60±0.52 [b]
Diabetic + glibenclamide treated (D+GT)	7.85±0.22 [b]	5.91±0.6 [c]

Means within the same column carrying different superscripts are significant at P≤0.05

DISCUSSION

Diabetes mellitus is a life-threatening metabolic disorder and it is estimated that its annual incidence rate will continue to increase in the future world-wide. Hyperglycemia, the primary clinical manifestation of diabetes mellitus, is associated with the development of micro and macro-vascular diabetic complications. Traditional plant remedies have been used for centuries in the treatment of diabetes (Kesari *et al.,* 2005), but only a few have been scientifically evaluated. Therefore, we have investigated the dietary effect of marjoram oil on biomarkers of oxidative stress and lipid peroxidation in tissues of STZ-induced diabetic rats.

In the present study, we observed a significant increase in blood glucose levels in diabetic rats just before the beginning of the treatment (table 1). This may be due to the destruction of pancreatic beta cells by STZ, reinforcing the fact that STZ induces diabetes probably through the generation of oxygen free radical (Gupta *et al.,* 2004). The elevation of glucose in rats received STZ was due to an oxidative stress produced in the pancreas, due to a single strand break in pancreatic islets DNA (Yamamoto *et al.,* 1981). Administration of marjoram oil and glibenclamide tended to bring the values to near normal as shown in table (1).

We have registered a significant decrease in body weights in STZ diabetic rats at 15^{th} and 30^{th} days from the beginning of the treatment (table 2). This characteristic loss in body weights of diabetic animals is due to increased muscle wasting during diabetes (Ravi *et al.,* 2004).

The administration of marjoram oil to STZ diabetic rats reduced blood glucose levels however, to the best of our knowledge; no previous study had focused on establishing the relationship between marjoram and blood glucose levels. In the present study, the blood glucose data clearly showed that dietary marjoram oil restrained the level of hyperglycemia resulting from the experimental destruction of beta pancreatic cells induced by STZ. The hypoglycemic effect of marjoram increased gradually and was observed to be maximal at the end of the study period.

The hypoglycemic activity of marjoram oil was compared with glibenclamide, a standard hypoglycemic drug. Sulfonylureas such as glibenclamide have been used for many years to treat diabetes, to stimulate insulin secretion from pancreatic b-cells principally by inhibiting ATP-sensitive K^+ (K_{ATP}) channels in the plasma membrane. The inhibition of ATP sensitive channels leads to membrane depolarization, activation of voltage gated Ca^{+2} channels, increased Ca^{+2} influx, a rise in cytosolic [Ca^{+2}] and thereby insulin release (Proks *et al.,* 2002). From the results of the present study, it may be suggested that the mechanism of action of marjoram oil is similar to glibenclamide action.

Marjoram is herbal medicine used for treatment of chest infection, cough, sore throat, rheumatic pain, nervous disorders, stomach disorders, cardiovascular diseases and for skin care. There is increasing evidence that *Organium majorana* possesses extensive range of biological activity including antioxidant, antimicrobial, anti-inflammatory and hepatoprotective (Vagi *et al.,* 2005 and Al-Harbi 2011).

Streptozotocin-induced experimental diabetes is a valuable model for induction of diabetes mellitus. Further, the STZ diabetic animals may exhibit most of the diabetic complications namely, myocardial cardiovascular, gastrointestinal, nervous, kidney and urinary bladder dysfunctions through oxidative stress (Ozturk *et al.,* 1996).

In the present study, antioxidant enzyme activities were significantly decreased and MDA levels were significantly increased in diabetic rats. Reactive oxygen species- induced oxidative damage had been implicated in the pathogenesis of several disorders including diabetes mellitus (Slater, 1984).

Oxidative stress is the imbalance between production and removal of reactive oxygen species (ROS). Increased oxidative stress contributes substantially to the pathogenesis of diabetes complications and it is a consequence of either enhanced ROS production or attenuated ROS- scavenging capacity. Several studies had demonstrated both lower non-enzymatic antioxidant levels and enzymatic antioxidant activities in streptozotocin-induced diabetes in rats (Genet *et al.,* 2002; Prakasam *et al.,* 2003 and Ananthan *et al.,* 2004). They had reported an elevated lipid peroxidation and lowered antioxidants in STZ-induced diabetes mellitus.

The concentrations of lipid peroxides were increased in liver and kidney of diabetic rats, indicating an increase in the generation of free radicals. Increased lipid peroxidation in diabetes may be attributed to increased oxidative stress in the cell as a result of depletion of antioxidant scavenger systems. The present finding as shown in table (3) indicates significantly increased lipid peroxidation of rats exposed to STZ and its attenuation by marjoram oil treatment (100mg/kg body weight). This suggests protective role of this oil, which could be due to the antioxidative effect of flavenoids present in the plant which act as strong superoxide radical and singlet oxygen quenchers. The biological mechanisms of flavenoids have been attributed to their antioxidant properties through several possible mechanisms, such as their ability to scavenge free radicals, break radical chain reactions, directly reducing peroxides, and stimulating the antioxidative defense enzyme activities (Cook and Samman, 1996).

Reduced activities of SOD and CAT in liver and kidney of diabetic rats have been observed in our study. The decreased activities of SOD and CAT in both liver and kidney tissues during diabetes may be due to increased production of reactive oxygen radicals that can themselves reduce the activity of these enzymes (Wohaieb and Godin, 1987). SOD is an important defense enzyme, which converts superoxide radicals to hydrogen peroxide (McCord *et al.,* 1976). CAT is a hemeprotein, which decomposes hydrogen peroxide and protects the tissues from highly reactive hydroxyl radicals (Chance *et al.,* 1952). The reduction in the activity of these enzymes may result in a number of deleterious effects. Glutathione peroxidase (GPx), an important antioxidant enzyme, was significantly decreased in diabetic liver and kidney tissues in this study which indicate impaired scavenging of H_2O_2 and lipid hydroperoxides. This result is consistent with Friesen *et al.* (2004). The authors mentioned that there was a failure in antioxidative response including glutathione peroxidase in multiple low doses of streptozotocin-induced diabetes in mice.

Treatment with marjoram oil (100mg/kg body weight) significantly increased values of CAT, SOD and GPx activities in liver and kidney tissues of diabetic rats as shown in table (4, 5 and 6). This may be attributed to the antioxidant components of marjoram as it contains phenolic terpenoids (thymol and carvacrol), flavenoids (diosmetin, luteolin, apigenin, tannins and hydroquinone), phenolic glycosides (arbutin, methyl arbutin, vitexin, orientin and thymonin), triterpenoids (ursolic and oleanolic acids), triacontan, sitosterol and cis-sabinene El-Ashmawy *et al.* (2005).

Phenolic compounds, chain-breaking antioxidants, react with lipid radicals to form non-reactive radicals, interrupting the propagation chain. These compounds are able to donate an electron or a hydrogen atom to the lipid radical formed during the propagation phase of lipid oxidation and stabilizes the resulting phenoxyl radical (Huang *et al.,* 2005). Phenolic compounds exert their antioxidant abilities by scavenging peroxyl and alkoxyl radicals and by chelation of transition metal ions present in trace quantities (Visioli *et al.,* 1998).

The antioxidant enzymes CAT, SOD and GPx limit the effects of oxidant molecules on tissues and are active in defense against oxidative cell injury by means of their being free radical scavengers (Kyle *et al.,* 1987). These enzymes work together to eliminate active oxygen species and small deviations in physiological activities may have a dramatic effect on the resistance of cellular lipids, protein and DNA to oxidative damage (Mates *et al.,* 1999).

In conclusion, the antioxidant potential of *Organium majorana* may be attributed mainly due to the amelioration of hyperglycemia induced oxidative stress by its normoglycemic effect. The presence of flavenoids and phenolic terpenoids further strengthens the efficacy of marjoram oil in protecting the tissue defense system against oxidative damage in streptozotocin-induced diabetes.

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التأثيرات الوقائية لزيت البردقوش على الانزيمات المضادة للاكسدة فى الجرزان المصابة معمليا بمرض السكرى

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فى هذه الدراسة ،كان هناك محاولة لتقييم مدى وجود الخصائص المضادة للأكسدة فى زيت البردقوش فى الجرزان المصابة معمليا بمرض السكرى بواسطة الستربتو زوتوسين. حيث تم أعطاء زيت البردقوش عن طريق الفم بجرعة قدرها١٠٠ ملليجرام/ كجم من وزن الحيوان فاحدثت نقصان معنوى فى نسبة جلوكوز الدم فى الجرزان المصابة معمليا بمرض السكرى كما احدث تحسنا فى وزن الجرزان المصابة. الزيادة فى مادة المالوندای ألديهيد الدالة على تأكسد الدهون فى انسجة الكبد والكلى كانت قد انخفضت انخفاضا معنويا بعد أعطاء زيت البردقوش. حدث ارتفاع معنوى فى نسبة الكاتاليز والسوبرأكسيد ديسميوتيز والجلوتاثيون بيرأوكسيديز. وخلصت هذة الدراسة ان زيت البردقوش لة تأثير وقائى لمرضى السكرى المحدث بواسطة الستربتوزوتوسين فى الجرزان وكان تأثيرة كمضاد للاكسدة افضل من عقار الجليبنكلاميد والذى يعطى فى الاصل كعلاج لمرضى السكرى.