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Effect of dietary antioxidant supplementation (*Cuminum cyminum*) on bacterial susceptibility of diabetes-induced rats

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Abstract

Diabetic patients are at risk of acquiring infections. Chronic low-grade inflammation is an important factor in the pathogenesis of diabetic complication. Diabetes causes generation of reactive oxygen species that increases oxidative stress, which may play a role in the development of complications as immune-deficiency and bacterial infection. The study aimed to investigate the role of a natural antioxidant, cumin, in the improvement of immune functions in diabetes. Diabetes was achieved by interperitoneal injection of streptozotocin (STZ). Bacterial infection was induced by application of Staphylococcus aureus suspension to a wound in the back of rats. The antioxidant was administered for 6 weeks. Results revealed a decrease in blood glucose levels in diabetic rats ($p < 0.001$), in addition to improving immune functions by decreasing total IgE approaching to the normal control level. Also, inflammatory cytokine (IL-6, IL-1β and TNF) levels, as well as total blood count decreased in diabetic rats as compared to the control group. Thus, cumin may serve as anti-diabetic treatment and may help in attenuating diabetic complications by improving immune functions. Therefore, a medical dietary antioxidant supplementation is important to improve the immune functions in diabetes.

Key words: *Cuminum cyminum, streptozotocin (STZ), diabetes, immunity, Staphylococcus aureus.*

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Introduction

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by hyperglycemia resulting from defective insulin secretion and resistance to insulin action or both [1]. In addition to the classical complications of the disease, DM has been associated with the immune dysfunction (e.g., damage to the neutrophil function, depression of the antioxidant system, and humeral immunity) [2]. It has been also associated with an increase in oxidative stress through the enhanced formation of superoxides as well as a decrease in anti-oxidant capacity [3]. One of the effects of hyperglycemia is that electron transport chains in mitochondria become overloaded, which leads to the release of electrons that react with oxygen producing superoxides, increasing oxidative stress inside the cell. These reactive oxygen species (ROS) can also lead to stimulation of an innate immune response through the induced production of pro-inflammatory cytokines as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and IL-1β. The functional role of diabetes, enhanced ROS in contributing to dysregulation of innate immunity and diabetic complications has been demonstrated with antioxidant therapy. Treatment of STZ induced diabetic rats with the antioxidant butylated hydroxyanisole decreased production of TNF-α and IL-1β by peritoneal macrophages [4, 5]. Likewise, treatment of diabetic rats with the antioxidant *Astragalus saponin* reduced oxidative stress [6].

Another ramification is the diabetic foot, which is particularly considered one of the main grounds of hospital admissions for a substantial percentage of patients with diabetes, and is a major reason of prolonged hospitalization among these patients [7]. Foot infections in the patients with diabetes are frequently polymicrobial. Besides, methicillin-resistant *Staphylococcus aureus* is a major pathogen in these infections [8]. The emergence of *Staphylococcus aureus* strains resistant (to multiple antibiotics) has made the treatment of infections problematic. The future management of infectious diseases had been uncertain [9]. So, screening of several medicinal plants for its potential antimicrobial activity was shown to be important. Herbal

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and aromatic plants have traditionally been used in folk medicine and they are used to extend the shelf life of food, showing inhibition against bacteria, more than yeasts [10]. In addition, the spices that are generally used as food additives to provide taste, smell, and color also exhibited antibacterial activity. Agaoglu *et al.* reported that the antibacterial activity of different spices including cumin, exhibited an antibacterial activity against gram-negative and gram-positive bacteria including *Staphylococcus aureus* [11].

Cumin is widely used as a spice in many countries. Besides its antimicrobial effect, it has an antioxidant activity [12]. Therefore, the present investigation was designed to assess the potential beneficial effect of cumin (*Cuminum cyminum*) as a natural dietary antioxidant. Furthermore, to correct the oxidative stress produced by hyperglycemia in diabetic rats, and improving their immune functions.

Material and methods

Materials

Animals: Sixty four adult albino Wistar rats, weighing 170 ±10 g, were used in this study. Rats were allowed 2 days for acclimatization at room temperature with a 12 h light/dark cycle before beginning the experimental work. Animals were fed on normal rodent chow (El-Nasr Pharmaceuticals, Chemicals Industries, Egypt), allowed free access to drinking water, and observed daily. Rats were divided into the following eight groups (each group consists of 8 rats): Group I (GI): normal control rats; Group II (GII): Control supplemented with cumin; Group III (GIII): Diabetic control rats.; Group IV (GIV): Infected control rats; Group V (GV): Infected diabetic rats; Group VI (GIII*): Diabetic rats supplemented with cumin; Group VII (GIV*): Infected rats supplemented with cumin and Group VIII (GV*): Infected diabetic rats supplemented with cumin. Animal experiments were conducted according to the guidelines of animal care and the ethics committee of the National Research Center (NRC, Egypt).

Preparation of streptozotocin for diabetic induction: Streptozotocin (STZ) was freshly prepared before induction by dissolving it in 0.1 M citrate buffer (PH 4.5, Sigma-Aldrich Co., USA).

Preparation of bacterial suspension for infection: *Staphylococcus aureus* (ATCC 29213) was used as a standard strain for inoculation. A part of the standardized suspension was diluted with Tryptic Soy Broth (TSB) to the desired concentration (10^4 colony-forming units per milliliter). The 1×10^4 colony-forming units per rat inoculum were used as in previous studies by Stratford *et al*. and Barker *et al.* on animal wound infection models [13, 14].

Preparation of *Cuminum cyminum* oil (as antioxidant): Essential oil of cumin (as an antioxidant) was prepared by the Clevenger apparatus, using the hydro-distillation method. The dried, powdered seeds of cumin were placed in a distillation apparatus with distilled water and hydro-distilled for three hours, according to the European Pharmacopoeia [15]. The oily product was stored in sterile dark glass vials at 4°C until used. Dilutions of the oils were made with dimethyl sulphoxide (DMSO) to obtain different concentrations.

Determination of minimal inhibitory concentration (MIC): The MIC was considered as the lowest sample's concentration that prevented visible bacterial growth. Bacterial strains were streaked on Mueller Hinton agar plates using sterile cotton swabs. Five microliters of DMSO, loaded on sterile blank disks, were placed on the agar plates and were incubated at 37°C for 24 h. In that spot, where there was no antibacterial activity on the plates, DMSO was selected as a safe diluting agent for the oil. The minimum inhibitory concentration (MIC) of cumin for *Staphylococcus aureus* (ATCC 29213) was determined (using different concentrations of oil) according to Mandal *et al*. [16].

Methods

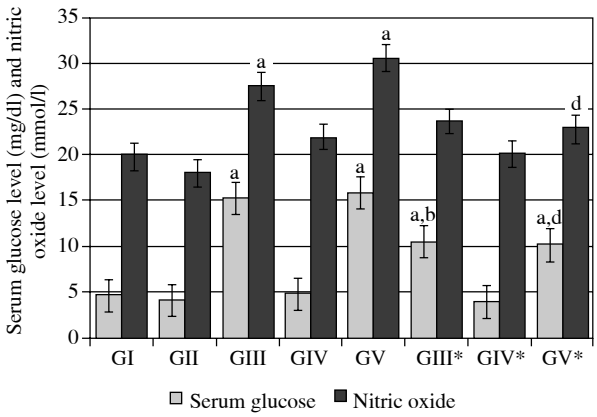
Induction of diabetes: Diabetes in groups III, V, III* and V* rats was induced with a single injection of freshly prepared streptozotocin STZ (50 mg/kg body weight) by intraperitoneal route in a manner based on previously published protocols [17, 18]. Four days after STZ administration, diabetes was confirmed by determination of fasting blood glucose concentration with the help of glucometer. The animals with blood glucose more than 200 mg/dl were selected to compose the diabetic rats, infected diabetic rats, and the diabetic supplemented groups (groups III, V, III* and V*).

Infection with bacteria: The backs of diabetic rats were shaved with a razor blade and cut wounds 1 cm in length were brought on by surgical blades. After skin wounding, rats were inoculated locally with 1×10^4 CFU of *Staphylococcus aureus* at sites of skin wounds. Infection was induced by applying bacterial suspension (ATCC strain 29213, 1×10^4 CFU/rat) through a micropipette to the wounded region. One week later, the bacterial infection was confirmed by the appearance of abscess [19].

Treatment with antioxidant supplementation: The minimum inhibitory concentration (MIC) of cumin for *Staphylococcus aureus* (ATCC 29213) was determined according to Mandal *et al.* [16]. The previously prepared cumin oil was fed orally with normal rodent chow at a dose of 50 mg/kg of body weight to rats of group II, III*, IV* and V* for 6 weeks. At the end of 6 weeks of treatment, body weight was recorded, then a blood sample was withdrawn.

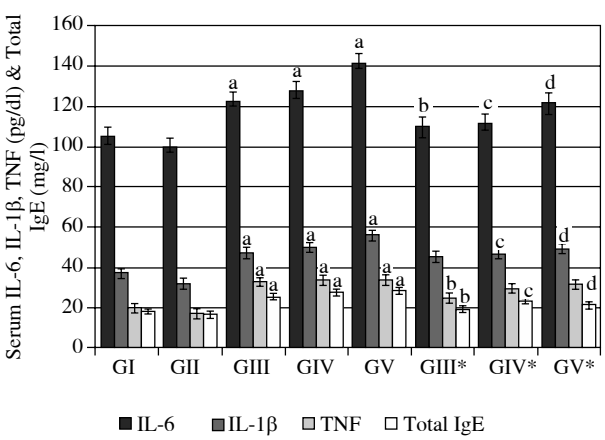
Blood collection and biochemical analysis: At the end of the experiment, rats were fasted overnight and blood was withdrawn through the retro-orbital plexus using

a glass capillary and collected into EDTA tubes and dry tubes. Blood collected underwent the following analysis: 1) An EDTA tube for determination of total and differential leukocyte counts and 2) Dry tube which was left for 15 min at room temperature, centrifuged for 10 minutes at 3000 rpm.



Data expressed as mean ± SE
GI: Normal control
GII: normal control + cumin group
GIII: Diabetic control
GIV: Infected control group
GV: Infected diabetic group
GIII: Diabetic control + cumin group*
GIV: Infected + cumin group*
GV: Infected diabetic + cumin group*
[a] p < 0.001 vs. normal control
[b] p < 0.001 vs. diabetic control
[d] p < 0.05 vs. infected diabetic group

Fig. 1. The serum level of glucose and nitric oxide in diabetic, infected groups (GIII, GIV & GV) and cumin supplemented groups (GIII*, GIV* & GV*)



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GV: Infected diabetic + cumin group*
[a] p < 0.001 vs. normal control
[b] p < 0.001 vs. diabetic control
[c] p < 0.05 vs. infected control
[d] p < 0.05 vs. infected diabetic group

Fig. 2. The serum level of cytokines and total IgE in diabetic, infected groups (GIII, GIV& GV) and cumin supplemented groups (GIII*, GIV* & GV*)

The separated serum was used for estimation of a serum glucose by glucose oxidase/peroxidase method (GOD/POD) using a standard commercial kit supplied by Biodiagnostic Co. [20], b-determination of serum nitric oxide (as nitrate) by a commercial kit supplied by Biodiagnostic Co. [21], c-determination of serum TNF-α, IL-6, and IL-1β by the sandwich ELISA method with a commercially available kit supplied by Abcam, Cambridge, USA [22-24] and d-determination of total IgE levels by the sandwich ELISA method with a commercially available kit obtained from Glory Sciences Co., Ltd, USA.

Statistical analysis

The collected data were statistically analyzed through the SPSS package version 18. Quantitative data were represented as mean ± standard error (SE). Quantitative comparisons were done through Analysis of Variance (ANOVA). The difference was considered significant at *p*-value 0.05 levels.

Results

Effect of *Cuminum cyminum* (cumin) oil on serum glucose and nitric oxide level

For both diabetic rats and infected diabetic rats (group III, V, III*, V*) there were significant increases in serum glucose ($p < 0.001$) compared to normal control rats. In addition, the level of nitric oxide revealed a significant increase in the diabetic group (GIII) and infected diabetic group (GV) ($p < 0.05$ and $p < 0.001$, respectively) in comparison to normal control one. On the other hand, treatment with cumin oil for 6 weeks demonstrated a significant reduction in blood glucose ($p < 0.05$) in the cumin supplemented diabetic group (GIII*) and cumin supplemented infected diabetic group (GV*) compared to the diabetic group and diabetic infected groups (GIII, GV) (Fig. 1).

Effect of *Cuminum cyminum* (cumin) oil on different serum cytokines and serum total IgE level

The levels of different cytokines (IL-6, IL-1β and TNF) and total IgE demonstrated significant increases in diabetic, infected and infected diabetic groups (GIII, GIV & GV) compared to the normal control one ($p < 0.001$). Figure 2 shows a slight non-significant increase in the infected diabetic group (GV) compared to the diabetic one (GIII). In addition, supplementation with cumin oil for 6 weeks (GIII*, GIV* &GV*) brought a slight significant decrease in different cytokines and total IgE levels compared to the diabetic group, infected and infected diabetic groups (GIII, GIV & GV). It should be noted that the levels tend to return to the values of normal controls after supplementation (Fig. 2).

Effect of *Cuminum cyminum* (cumin) oil in total leukocyte count (TLC)

The total leukocyte count (TLC) showed a significant increase in diabetic and infected diabetic groups (GIII, GIV & GV) as compared to the control group ($p < 0.001$). This increase in TLC was combined with a significant increase in the differential lymphocyte percentage and a non-significant decrease in segmented neutrophils in the same groups compared to the normal control group ($p < 0.001$). The total leukocyte and lymphocyte count percentages were decreased while neutrophil percentage was increased upon supplementation with cumin oil in GIII*, GIV* and GV* compared to diabetic (GIII) or infected diabetic (GV) groups (Table 1).

Table 1. Effect of cumin oil on total leukocyte count (TLC) and differential blood count

Group	TLC $\times 10^9$/l	Lymphocyte (%)	Segmented (%)
Normal control (GI)	7.97 ±1.01	58.67 ±6.1	41.33 ±5.89
Normal control + cumin (GII)	6.88 ±0.99	48.8 ±5.2	51.2 ±5.53
Diabetic control (GIII)	12.37 ±3.13[a]	78.67 ±9.5[a]	21.33 ±4.37
Infected group (GIV)	14.87 ±3.13[a]	79.93 ±5.65[a]	20.07 ±4.37
Infected diabetic group (GV)	15.65 ±6.58[a]	80.83 ±5.88[a]	19.17 ±8.89
Diabetic control + cumin (GIII*)	10.52 ±2.01[b]	67.33 ±12.6[b]	32.67 ±4.86
Infected group + cumin (GIV*)	12.57 ±2.93[c]	72.26 ±11.7	27.74 ±3.97
Infected diabetic group + cumin (GV*)	11.73 ±2.99[d]	73.17 ±6.52[d]	26.83 ±9.99

Data expressed as mean ± SE
[a] *$p < 0.001$ vs. normal control*
[b] *$p < 0.001$ vs. diabetic control*
[c] *$p < 0.05$ vs. infected control*
[d] *$p < 0.05$ vs. infected diabetic group*

Discussion

STZ-induced diabetes in rats is the most widely used animal model of human diabetes mellitus. Diabetes causes the autoxidation of glucose. These changes accelerate generation of reactive oxygen species and increase oxidative stress. Oxidative stress may play an important role in the development of complications in diabetes such as immune-deficiency and bacterial infection. In recent years, there has been a gradual revival of interest in the use of medicinal and aromatic plants in developed and developing countries, because plant-derived drugs have been reported to be safe and free of side effects [25]. Accordingly, we selected a natural antioxidant compound, cumin, to test its effects on immune functions of diabetic rats and diabetic rats infected with *Staphylococcus aureus*. Cumin contains major anti-inflammatory, antimicrobial and antioxidant compounds [12]. Diabetic rats showed symptoms of polyuria, polyphagia, polydipsia and reduced body weight, which was reversed on supplementation with cumin oils. Treatment with cumin decreased a blood glucose level. This may be through stimulation of surviving β-cells to produce insulin. In addition, it is known that the antioxidant effect of cumin suppressed apoptosis and exerted beneficial effects on pancreas β-cells [26]. Thus, the anti-hyperglycemia effect of cumin may lead to protection of pancreatic β-cells and increase in insulin secretion.

In diabetes, oxidative stress results in an increase in reactive oxygen species (e.g. NO) formation. Also, during phagocytosis, the first step in macrophage response is to invade the microorganism, nitric oxide (NO) is generated in excess as a result of host response against infections and inflammatory conditions [27]. In this study, the NO level has been increased in both diabetic and infected rats compared with diabetic groups and reduced after treatment with cumin. This result is in agreement with Jagtap and Patil who revealed that cumin decreases the nitric oxide level [26]. In the present study, the decrease in NO level after treatment with cumin suggests the role of cumin as an antioxidant in reducing oxidative stress due to diabetes and bacterial infection and in turn regulating inflammatory responses.

It is known that NO regulates inflammatory responses, including cytokine production, depending on its concentration [28]. Cytokines are a class of signaling proteins which are used extensively in immune function. Interleukin 1β, IL-6 and TNF-α are the most important immune response modifying cytokines. Diabetes is a frequent underlying medical condition among individuals with *Staphylococcus aureus* infections, and diabetic patients often suffer from chronic inflammation and prolonged infections [7]. This complication correlated to dysregulation of the immune function during diabetes in the form of an increased expression of inflammatory cytokines and enhanced generation of reactive oxygen species [29]. Our results showed increased levels of total IgE, and the most important immune response cytokines (IL-1β, IL-6 and TNF-α) in diabetic and infected diabetic rats, which was in agreement with Pannathur and Heinecke study on diabetic patients [30]. Treatment of these rats with cumin oil reduced total IgE and cytokine levels, suggesting an overall improvement of the immune function by reducing levels of pro-inflammatory cytokines in diabetic and diabetic infected groups. This is in agreement with other studies, which reported potential effects of cumin oil as an antioxidant [26, 31].

One of the key steps during inflammation is leukocyte infiltration [32]. Peripheral blood leukocytes are composed of polymorphonuclear cells, including monocytes and lymphocytes. They are activated and secrete cytokines in the diabetic state [33]. A number of studies have shown that diabetic patients have leukocytosis [34]. Our results showed a significant increase in total leukocytes count (TLC) as well as a significant increase in lymphocyte percentage in diabetic and infected rats with diabetes in comparison to the control group. Otton suggested that a high proportion of apoptotic lymphocytes in diabetic states may explain the impaired immune function in poorly controlled diabetic patients [35]. Our study showed a decrease in TLC and lymphocyte percentage after supplementation with cumin. These percentages returned to normal control levels. Thus, cumin supplementation improves the immune function in diabetic rats.

Neutrophils are short-lived but there are abundant leukocytes. They are rapidly recruited to the site of a bacterial infection and are generally considered a part of the "first line of defense" of the host innate immune system. Because of their sheer numbers as well as their toxic contents and elaboration of proinflammatory cytokines, neutrophil clearance is crucial for the resolution of the inflammatory response and hence tightly regulated [36]. Neutrophil apoptosis (either spontaneous or pathogen induced) is crucial for neutrophil uptake and subsequent elimination by macrophages at the site of infection, leading to the resolution of the inflammatory process [37]. Previous studies have reported an impaired bactericidal function and decreased phagocytic activity by neutrophils in diabetic hosts [38]. In addition, Hanses *et al.* suggested that defects in neutrophil apoptosis may contribute to the chronic inflammation and the inability to clear staphylococcal infections observed in diabetic patients [39]. Our results revealed a decrease in neutrophils percentage during infection and diabetes, indicating decreased phagocytic activity by neutrophils i.e. defect in the immune response. These abnormalities might contribute to the increased susceptibility and severity of infections in diabetic patients. The results showed that cumin oil supplementation decreases the NO level (improving oxidative stress) with increasing the neutrophils percentage which lead to improving the bactericidal process. Thus, cumin oil has anti-inflammatory activities in staphylococcal infected diabetic rats.

Conclusions

The present study concluded that *Cuminum cyminum* oil exhibits a potent anti-hypoglycemic activity in STZ induced diabetic rats. In addition, our results demonstrated that *Cuminum cyminum* oil exhibits an antioxidant role in reducing oxidative stress in STZ supplemented rats, both diabetic and diabetic infected rats. Beside it has a role in improving immune functions, decreasing inflammatory cytokines (IL-6, IL-1β and TNF) and decreasing total blood count with decreasing neutrophil percentage. Thus, *Cuminum cyminum* oil may serve as a hypoglycemic natural antioxidant compound and may help in attenuating diabetic complications by reducing oxidative stress and improving immune functions.

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