Eucalyptus globulus (Eucalyptus) Treatment of Candidiasis in Normal and Diabetic Rats

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ABSTRACT

Background: The leaves of *Eucalyptus globulus* (eucalyptus) are used for treatment of diabetes mellitus in traditional medicine. The aim of this study was to evaluate the effects of eucalyptus in treatment of established systemic infection with *Candida albicans* in normal and streptozotocin-induced diabetic rats. **Methods:** Sixty normoglycemic male Wistar rats, weighing 200-250 g, were selected and randomly divided into six groups (n= 10): normal control, control + *C. albicans*, control + eucalyptus + *C. albicans*, diabetic control, diabetic + *C. albicans*, diabetic + eucalyptus + *C. albicans*. Diabetes was induced after a single intraperitoneal injection of streptozotocin (60 mg/kg body weight) and eucalyptus was added to the diet (62.5 g/kg) and drinking water (2.5 g/L) of treated animals for 4 weeks. The concerned groups were inoculated with *C. albicans* 15 days after diabetes induction. At the end of one month experiment, fasted rats were killed by cervical decapitation. Blood was collected from neck vein for estimation of glucose. *C. albicans* concentrations were estimated in liver and kidneys using serial dilution culture of tissue homogenates. **Results:** Eucalyptus administration significantly improved the hyperglycemia, polydipsia, polyphagia, and it also compensated weight loss of diabetic rats ($P<0.05$). Moreover, eucalyptus caused a significant reduction in *C. albicans* concentration in liver and kidney homogenates ($P<0.01$). **Conclusion:** The results revealed that eucalyptus improves *Candidia* infection in normal and diabetic rats that in some ways validates the traditional use of this plant in treatment of diabetic patients. *Iran. Biomed. J. 14 (3): 121-126, 2010*

INTRODUCTION

Diabetes mellitus is a complex disease characterized by hyperglycemia and associated with insulin insufficiency or insensitivity of target organs to insulin. In diabetes, high blood glucose produces the classical symptoms of polyuria, polydipsia, polyphagia and diabetes complications [1]. Diabetes mellitus causes various dysfunctions in the body including vascular disorder, retinopathy, cardiomyopathy, alters immune functions, changes in the intestinal function, peripheral neuropathy, and dysfunction of the central nervous system [2]. Diabetic patients are also more susceptible to microbial infections including candidiasis.

In modern medicine, no satisfactory effective therapy is still available for management of diabetes mellitus [3]. Synthetic oral hypoglycemic drugs such as sulfonylurea and biguanides have undesirable side effects or contraindications [4]. Even insulin therapy has several drawbacks like insulin resistance, anorexia nervosa, brain atrophy and fatty liver after chronic treatment [5]. For the same reasons, search for safer and more effective drugs of plant origin for the treatment of diabetes has been continued [6]. Ethnobotanical information indicates that more than 800 plants are used as traditional remedies for the treatment of diabetes, but only a few have received scientific scrutiny [7].

Eucalyptus globulus (eucalyptus) is a tall, fast-growing, evergreen tree, native to Tasmania and

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south-eastern Australia. It also grows in a wide range of climatic conditions and is widely distributed throughout Sistan and Baluchestan Province (Iran). Eucalyptus has been used as a traditional medicine for management of diabetes mellitus in South America, Africa and Iran [7, 8]. Studies in streptozotocin-diabetic animal models confirmed anti-hyperglycemic [7, 8] and anti-inflammatory [9] effects of eucalyptus.

The oil and leaves of eucalyptus are used for medicinal purposes. Eucalyptus oil is used as an anti-microbial element in different kinds of cream, soap and toothpaste [10]. Laboratory studies have revealed that eucalyptus oil contains substances with strong anti-bacterial and anti-fungal properties [12, 14]. The leaves of eucalyptus also contain substances that have anti-bacterial properties [15, 16].

There is a possibility that dietary administration of eucalyptus may be associated with decrease in candidal colonization in normal and diabetic rats. To the best of our knowledge there is no data regarding the effects of eucalyptus supplemented diet and drinking water on systemic candidiasis in streptozotocin -induced diabetic rats. Therefore, this study was conducted to assess the anti-candidial effects of eucalyptus in normal and diabetic rats.

MATERIALS AND METHODS

Animals. The study was performed on sixty matured normoglycemic male Albino rats (*Rattus norvegicus*) of Wistar strain, weighing 200-250 g, separately housed in cages (one per cage), with free access to water and food. The animals were kept in a room at $22 \pm 2°C$ with a fixed 12-hour artificial light period. All animals were fed with standard rodent diet with the following composition (w/w): 20% protein, 3% fat, 2% fiber, 6% minerals and 69% starch and vitamin supplements (Pasteur Institute of Iran, Tehran). This study was approved by the Ethical Committee of Zahedan University of Medical Sciences (Zahedan, Iran).

Plant materials. Dried eucalyptus leaves were obtained from a commercial source. Leaves were homogenized to a fine powder and stored at room temperature $(20 \pm 2°C)$ until use. For animal diets, eucalyptus powder was incorporated into pulverized rat diet (62.5 g/kg), thoroughly mixed, then distilled water was added and mixed to a stiff paste [17]. The mixture was then pelleted and dried at 45°C until

dry. Control diet was prepared by the same method to ensure that our method of preparing the diet did not change vitamin and mineral contents of the diet. Aqueous extract of eucalyptus (AEE) was prepared by 15 minutes decoction of the powdered material, as described by Gray and Flatt [17]. Briefly, 2.5 g of powdered material was placed in 100 ml of distilled water, brought to the boil, then removed from the heat source and allowed to infuse for 15 min. This suspension was filtered from Whatman No.1 and the volume readjusted with distilled water to 100 ml. To be ready to use, 10 ml aliquots of AEE was diluted 10-fold with tap water (2.5 g/L).

Microorganism. C. albicans (*ATCC 10731*) was cultured at 37°C for 24 hours on Sabouraud Dextrose Agar (SDA). The morphological and biochemical characteristics of yeast cells were verified by microscopic observations, colonial morphology on SDA, formation of germ tubes in serum, formation of chlamydospores on chlamydospore agar, and sugar fermentation reactions. Fifteen days after diabetes induction, rats in groups II, III, V and VI were inoculated intraperitoneally with 0.2 ml of 10^5 CFU (colony forming unit) ml^{-1} suspension of organism in sterile saline [18]. *Candida albicans* concentration was confirmed using serial SDA pour plates of 10-fold dilutions of the original suspension.

Experimental induction of diabetes. Rats in groups IV to VI were injected with a freshly prepared streptozotocin solution (60 mg/kg body weight in 0.15 M NaCl with 100 mM sodium citrate buffer, pH 4.5) [18]. Control rats (groups I to III) were treated with the same amount of citrate buffer without streptozotocin. The injection volume was 1 ml/kg. Successful induction of diabetes was confirmed by measuring the fasting blood glucose concentration in rats 48 h after injection of streptozotocin. Rats with a fasting blood glucose levels >180 mg/dl were considered diabetic and included in the study.

Experimental design. Sixty rats were divided into six following groups (n = 10):
(I) Normal control: normal rats receiving unsupplemented diet and drinking water, (II) Control + *C. albicans*: normal rats receiving unsupplemented diet and drinking water and inoculated with *C. albicans*, (III) Control + eucalyptus + *C. albicans*: normal rats receiving eucalyptus supplemented diet and drinking water and inoculated with *C. albicans*, (IV) Diabetic control: diabetic rats   receiving

Table 1. Effects of eucalyptus administered in the diet (62.5 g/kg) and drinking water (2.5 g/L) on body weight, water intake, food intake and serum glucose concentrations of normal and diabetic rats.

	Normal control	Control + *C. albicans*	Control + eucalyptus + *C. albicans*	Diabetic control	Diabetic + *C. albicans*	Diabetic + eucalyptus + *C. albicans*	between Groups sig.
Body weight (g)							
Study Day 0	211.5 ± 4.9	206.1 ± 5.2	208.3 ± 3.8	207.4 ± 3.5	208.8 ± 3.0	210.3 ± 5.8	0.225
Study Day 15	288.7 ± 2.4	274.9 ± 5.9	278.6 ± 6.4	215.1 ± 3.8	210.1 ± 4.2	240.3 ± 6.6	0.009
Study Day 30	335.0 ± 4.1	319.0 ± 7.0	320.1±5.8	220.4±4.1 [a]	215.8±3.7	270.6 ± 6.9 [c]	0.045
Water intake (ml/day)							
Study Day 0	35.7 ± 5.1	34.0 ± 3.3	33.5 ± 3.1	34.2 ± 2.3	33.5 ± 2.5	34.0 ± 1.3	0.216
Study Day 15	45.5 ± 1.8	45.4 ± 0.9	44.7 ± 1.1	88.2 ± 7.9	91.0 ± 8.3	65.0 ± 11.2	0.048
Study Day 30	51.2 ± 2.0	47.3 ± 1.7	47.5 ± 1.9	98.5 ± 3.7 [b]	102.2 ± 4.6	70.2 ± 5.3 [d]	0.009
Food intake (g/day)							
Study Day 0	12.9 ± 1.1	12.4 ± 0.9	12.5 ± 1.0	12.4 ± 0.8	12.2 ± 0.9	12.6 ± 0.7	0.285
Study Day 15	19.2 ± 1.8	15.7 ± 0.8	18.8 ± 0.6	38.3 ± 1.9	36.9 ± 1.8	42.2 ± 2.3	0.009
Study Day 30	23.1 ± 0.7	21.8 ± 1.0	23.1 ± 0.6	44.6 ± 1.1 [b]	43.2 ± 1.0	35.5 ± 2.4 [d]	0.008
Serum glucose (mg/dl)							
Study Day 0	90.6 ± 2.3	90.3 ± 1.7	90.9 ± 1.9	90.2 ± 1.6	90.7 ± 1.1	90.5 ± 1.8	0.142
Study Day 15	90.0 ± 2.2	88.7 ± 1.1	89.9 ± 1.6	228.2 ± 3.6	224.2 ± 4.1	180.3 ± 2.8	0.032
Study Day 30	91.1 ± 2.7	87.3 ± 1.4	88.9 ± 1.7	281.4±5.5 [a]	273.2 ± 5.2	229.2 ± 4.1 [a]	0.047

The values present the mean ± SEM for ten rats in each group. Comparisons were made by one-way ANOVA test. [a]$P<0.05$ compared to normal control rats, [b]$P<0.01$ compared to normal control rats, [c]$P<0.05$ compared to diabetic control rats and [d]$P<0.01$ compared to diabetic control rats.

unsupplemented diet and drinking water, (V) Diabetic + *C. albicans*: diabetic rats receiving unsupplemented diet and drinking water and inoculated with *C. albicans*, (VI) Diabetic + eucalyptus + *C. albicans*: diabetic rats receiving eucalyptus supplemented diet and drinking water and inoculated with *C. albicans*. Food and fluid intake of all groups were measured daily whereas body weight and blood glucose were measured every week.

Glucose measurement. Blood samples were collected from the neck vein. The samples were collected in sterilized tubes and the serums were separated by centrifugation. Serum glucose levels were measured by glucose-oxidase method [19] using commercially available kit (Zistchemi Company, Iran).

Quantification of Candida in organs. Thirty days after treatment, overnight-fasted rats were killed by cervical decapitation. To quantitate *Candida* organism in organs, kidneys and liver were removed, rinsed of any adhering blood, and homogenized in 5

ml of phosphate buffer saline, pH 7.0. Serial 100-fold dilutions of the homogenates were plated (at 0.1 ml amounts) on Petri dishes containing SDA, and were incubated at 37°C for 48 h. The CFU per gram of tissue for kidneys and liver from each rat was determined and then was converted to $\log_{10}$ value [18].

Statistical analysis. All data are expressed as the mean ± SEM for ten rats in each experimental group. Statistical analysis was performed using SPSS 10.0 software. One-way analysis of variance (ANOVA) followed by the Tukey post hoc test was used to compare mean values of quantitative variables among groups. The criterion for statistical significance was $P<0.05$.

RESULTS

Bodyweight, water and food intake, and serum glucose. Table 1 shows significant differences in water and food intake, body weight and serum glucose in the different experimental groups. Daily consumptions of water and food in normal rats were

Table 2. *C. albicans* concentration in liver and kidney homogenates for rats in different experimental groups.

		Normal control	Control + C. albicans	Control + Eucalyptus + C. albicans	Diabetic control	Diabetic + C. albicans	Diabetic + eucalyptus + C. albicans	Between groups sig.
Mean log $_{10}$ CFU g^{-1} of tissue	Liver	0.00 ± 0.00	3.66 ± 0.07	2.39 ± 0.09^{b}	0.00 ± 0.00	5.35 ± 0.18^{a}	4.40 ± 0.22^{b}	0.009
	Kidney*	0.00 ± 0.00	4.91 ± 0.19	3.24 ± 0.14^{b}	0.00 ± 0.00	5.51 ± 0.16^{a}	4.71 ± 0.20^{b}	0.008

The values represent the mean ± SEM for ten rats in each group. Comparisons were made by one-way ANOVA test. * Mean for right and left kidneys. [a]$P<0.05$ compared to control rats. [b]$P<0.01$ compared to control rats.

51.2 ± 2.0 ml and 23.1 ± 0.7 g, respectively but these data in diabetic rats were 98.5 ± 3.7 ml and 44.6 ± 1.1 g, respectively. Diabetic rats showed a significant weight loss ($P=0.042$), polydipsia ($P=0.009$) and hyperphagia ($P=0.008$) by the end of the study period. Eucalyptus administration compensated the weight loss ($P=0.042$), and reduced polydipsia ($P=0.009$) and hyperphagia ($P=0.008$). The level of serum glucose in normal and diabetic rats was 91.1 ± 2.7 mg/dl and 281.4 ± 5.5 mg/dl, respectively. There was a significant elevation in serum glucose ($P=0.045$) in diabetic rats compared with control ones. Serum glucose concentrations in diabetic rats receiving eucalyptus were significantly lower ($P=0.045$) than unsupplemented diabetic rats. Eucalyptus administration did not change serum glucose levels in normal rats.

C. albicans in liver and kidney homogenates. Table 2 shows the *C. albicans* content in liver and kidney homogenates for rats in different experimental groups. There was a significant increase ($P<0.05$) in the concentration of *C. albicans* in liver and kidney homogenates in diabetic rats compared with control ones. There was a significant increase ($P<0.01$) in the concentrations of *C. albicans* in the kidney homogenates compared with the liver homogenates in both control and diabetic rats and eucalyptus administration significantly reduced *Candida* in these organs in all infected rats ($P<0.01$).

DISCUSSION

The present study showed that treatment of diabetic rats with eucalyptus for four weeks compensated the diabetic state and significantly reduced blood glucose levels. Some studies have demonstrated that oral administration of eucalyptus exhibited a significant, dose-dependent hypo-glycemic effect in streptozotocin diabetic rats [20, 21]. Some evidences indicate that free radicals,

membrane lipid peroxidation and protein oxidation significantly increase in experimental diabetic animals [22, 23]. Our previous reports indicated that the anti-hyperglycemic and improving effects of eucalyptus on loss of body weight and polydipsia may be due to its antioxidant activity [24, 25].

In normal rats, no significant changes in serum glucose were observed after administration of eucalyptus. The anti-hyperglycemic activity of eucalyptus is attributed to the high concentration of manganese chloride [26], modulating insulin secretion and/or insulin action [17]. Mahmoudzadeh-Sagheb *et al*. [25] showed that eucalyptus could compensate streptozotocin induced cell damage of pancreatic beta cells.

We used *C. albicans* for inducing systemic candidiasis in rats. The model of candidiasis used in the present experiment is a subacute systemic infection that is usually well tolerated by the animals for several weeks, is not cleared spontaneously and mimics human infection [18]. In some earlier studies, rats [7, 18, 23] and mice [27, 28] have been used for induction of experimental candidiasis. We found a significant increase in *Candida* colonization in diabetic rats compared with normal cases. In similar studies, diabetic animals were more susceptible to microbial infections [18, 27]. Diabetic patients are more susceptible to microbial infections and it seems that diabetes improvement can prevent subsequent infections.

Eucalyptus showed a considerable inhibitory effect on the growth of *C. albicans* in both normal and diabetic rats. Several *in vitro* studies confirmed anti-bacterial [15, 16, 29, 30] and anti-fungal [29, 31] effects of eucalyptus but there is no evidence about its *in vivo* anti-microbial effects. The major anti-microbial constituents of eucalyptus leaves have already been investigated. Sartorelli *et al*. [12] have analyzed eucalyptus leaves by gas chromatography and reported monoterpenes as major anti-microbial agents of the plant. In addition, Barry *et al*. [32] have reported tannins and Ahmad and Beg [33] have reported alkaloids, phenols and tannins as major

anti-candidial components present in eucalyptus. However, the anti-microbial effects of eucalyptus could be due to a synergism between the mentioned constituents.

We found a significant increase in the concentration of *C. albicans* in the kidney homogenates in both normal and diabetic rats. In agreement with our results, Baghian and Lee [28] showed that in experimentally induced systemic infections, kidneys were the organs that bore the heaviest foci of infections throughout the experiments. Although it is not very clear why kidneys are so susceptible to *Candida* infections, the physiological conditions, anatomical architecture, and the poor phagocytic system of kidneys may be contributing factors for predisposition of kidneys to the long-term systemic *Candida* infections [28].

Our study showed that liver is the second organ which is colonized with *C. albicans*. This organ is an important barrier in the control of hematogenous dissemination of *C. albicans*. Renna *et al.* [34] reported that in rats infected with *C. albicans*, liver limits the growth of the yeast and mounts an efficient inflammatory reaction. They also reported that in rats infected and exposed to oxidative stress, the hepatic inflammatory reaction is compromised and the outcoming of the fungal infection is more severe. Eucalyptus showed a considerable inhibitory effect on the growth of *C. albicans* in both liver and kidneys. The ameliorating effects of eucalyptus could be related to its antioxidant and anti-microbial constituents.

In conclusion, using eucalyptus leaves exhibits inhibitory effects against candidiasis which, in turn, validates the traditional use of the plant in fungal infections in diabetic patients. Further comprehensive chemical and pharmacological investigations with isolated active principles of the plant may shed more light on the use of eucalyptus for anti-microbial activity in diabetic animals and patients.

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