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AMELIORATIVE EFFECT OF VOLATILE OIL FROM *CINNAMOMUM ZEYLANICUM* ON HYPERALGESIA IN ALLOXAN DIABETIC RATS

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ABSTRACT

Diabetic neuropathy is generally considered to be one of the most common complications of diabetes. Neuropathic pain is the most troublesome and early symptom of diabetic neuropathy, and has been recognized as one of the most difficult types of pain to treat due to its multifactorial pathogenesis. The aim of the present study was to evaluate the antinociceptive effect of volatile oil from *Cinnamomum zeylanicum* on hyperalgesia due to alloxan induced diabetes in rats. Diabetes was induced with single intra peritoneal injection of alloxan monohydrate (150mg/kg b.w.). Animals were divided into different groups. Treatment groups received cinnamon oil from 3rd day onward upto 14th day at different doses (5, 10 and 20mg/kg b.w.; i.p.). Diabetic control animals received normal saline (0.9% NaCl; 1ml/kg). After 2 weeks, rats were tested in tail immersion and hot plate assays. Diabetic control rats exhibited significant hyperalgesia along with increased plasma glucose levels as compared with normal rats. Cinnamon oil treatment significantly decreased thermal hyperalgesia and the plasma glucose levels as compared with diabetic control rats. These results indicate the protective effect of volatile oil from the bark of *Cinnamomum zeylanicum* on hyperalgesia due to alloxan induced diabetes in rats.

Keywords: *Cinnamomum zeylanicum*, diabetic neuropathy, hyperalgesia.

INTRODUCTION

Diabetic neuropathy (DN) is generally considered to be one of the most common complications of diabetes, affecting both types of diabetes equally (Vinik *et al.,* 1992). DN affects up to 50% of patients with diabetes (Dyck *et al.,* 1993). It is generally related to the duration and severity of hyperglycaemia. However, it may also occur acutely even with hypoglycaemia (Harati, 1996). Pain is the most troublesome and early symptom of diabetic neuropathy (Vinik, 2004). Neuropathic pain is mostly characterized by pain which can occur spontaneously as a result of exposure to normally mildly painful stimuli, i.e. hyperalgesia (Brown and Asbury, 1984). Although hyperglycaemia (Green *et al.,* 1992), neuronal loss (Dyck *et al*., 1985) have been reported to be responsible for the change in pain perception, the exact aetiological factors involved are still under investigation (Anjaneyulu and Chopra, 2006). Experimentally induced diabetic rats have been used as a model of chronic pain with signs of hyperalgesia and allodynia due to diabetic neuropathy that may reflect symptoms observed in humans (Anjaneyulu and Chopra, 2006). Alloxan at a dose of 150mg/kg bw i.p., has been reported to induce reproducible and persistant hyperglycaemia in rats (Ryle *et al.,* 1984; Diniz *et al.,* 2008). Alloxan-injected diabetic rats have been reported to exhibit thermal allodynia and hyperalgesia, tested on hot-plate and tail-immersion assays (Morani and Bodhanker, 2007). Both hyperalgesia and allodynia have been reported to be established after 14 days of alloxan treatment (Aubel *et al.,* 2004).

Currently, there is growing interest in herbal remedies due to a number of side effects associated with hypoglycaemic agents used in allopathic medicine (Kim *et al.,* 2006). The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. It is believed that herbal medicines have lesser side effects and also have slow onset of these side effects (Habib *et al.,* 2005).

Cinnamon is one of the most common traditional folk herbs used in Korea, China and Russia for diabetes mellitus (Bailey and Day, 1989). Cinnamon bark is widely used as a spice and flavouring agent. Common cinnamon correctly refers to "true cinnamon", or its synonym Ceylon cinnamon (*Cinnamomum verum, C. zeylanicum)* (Jellin, 2006). Common and cassia cinnamon have been shown to be generally safe when ingested and to have many pharmacological properties, such as antioxidant activity (Singh *et al.,* 2007), antimicrobial activity (Tabak *et al.,* 1999; Ooi *et al.,* 2006) anti inflammatory activity (Tung *et al.,* 2008) and antifungal activity (Cheng *et al.,* 2008). Common and Cassia cinnamon are well known for their pharmacological properties in the treatment of diabetes (Khan *et al.,* 2003;

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Verspohl *et al.,* 2005). The analgesic and anti-inflammatory effects of *Cinnamomum zeylanicum* have been described in experimental studies (Atta and Alkofahi, 1998). Moreover, the major component found in cinnamon leaf and bark volatile oil, cinnamaldehyde (Singh *et al.,* 2007) has been studied for its inhibitory effects on pro-inflammatory mechanisms (Chao *et al.,* 2008), NF-κB activation (Liao *et al.,* 2008), nitric oxide production (Lee *et al.,* 2005) and cyclooxygenase-2 inhibitory activity (Guo *et al.,* 2006). However, the role of cinnamon in diabetic neuropathy has not been investigated so far. Therefore, the present study was designed to investigate the effect of cinnamon oil on diabetic neuropathy.

MATERIALS AND METHODS

Plant Material

C. zeylanicum (Lauraceae) was purchased from National Medicos, Amritsar, India. The species was identified and authenticated by Dr. Amarjit Singh Soodan, Guru Nanak Dev University, Amritsar. [voucher specimen (SR./Bot.Sci./0345) is deposited in the herbarium of the Department of Botanical and Environmental Sciences, Guru Nanak Dev University, Amritsar, India].

Extraction of volatile oil

Volatile oil was extracted according to the method reported by Chang and Cheng (2002) with little modification. Briefly, 500g of the dried bark was taken, broken into small pieces and hydrodistilled with a *Clavenger* apparatus for 6 h. The light yellow coloured essential oil was collected and dried over anhydrous sodium sulphate and, after filtration, stored in screw tight bottle at – 10°C.

Experimental Animals

Wistar albino rats of either sex (150-200g) were housed in 3 per cage, with food and water *ad libitum* for several days before the beginning of the experiment. The animals were kept on straw bedding in cages with a natural light: dark cycle and had free access to standard rodent food pellets and water. Animals were acclimatized to the laboratory conditions (room temperature 25±5°C) for one week before the start of experiment. All the experiments were conducted between 09.00 and 17.00 hrs.

Preparation of Drugs

Preparation of Alloxan solution (15mg/ml)

150mg of alloxan was accurately weighed and then dissolved into 10 ml of distilled water. Freshly prepared solution was used in each experiment.

Preparation of Cinnamon Oil (5, 10 & 20mg/ml)

50, 100 & 200µL of Cinnamon Oil was taken out and dissolved in 10ml of dimethyl sulfoxide (DMSO; 0.05%) to produce 5, 10 & 20 mg/ml of the cinnamon oil.

Preparation of Glipizide (10mg/ml)

50mg of Glipizide was accurately weighed and dissolved in DMSO (0.05%) and volume made upto 5ml.

Preparation of Fluoxetine (2mg/ml)

20mg of fluoxetine was accurately weighed and dissolved in 10ml of distilled water.

Experimental Protocols

In the present study, total of 42 rats were used. The rats were divided into 7 groups of 6 rats each.

Group I- Non-Diabetic group (n=6). The animals were injected with normal saline (0.9%, NaCl; 1 ml/kg) instead of the corresponding treatments.

In the rest of the groups the animals were fasted overnight prior to alloxan treatment and diabetes was induced by a single intraperitoneal injection of freshly prepared alloxan (150mg/kg bw) and the treatment with the cinnamon oil and glipizide was started on day 3. The blood glucose levels were estimated on 3rd day of alloxan treatment and the animals with fasting blood glucose levels more than 150mg/dl were considered diabetic and included in the study. The treatment with different drugs was as follows:

Group II- Diabetic control group (n = 6). The animals were administered normal saline (1 ml/kg) from 3rd day onward upto 14 days.

Group III- Diabetic vehicle group (n = 6). The diabetic animals were administered a daily dose of vehicle dimethyl sulfoxide (DMSO; 0.05%; 1ml/kg) from 3rd day onward upto 14 days.

Group IV- Glipizide treated group (n = 6). The animals were treated with glipizide at a dose of 10mg/kg; ip., from 3rd day onward upto 14 days.

Group V- Fluoxetine treated group (n = 6). The animals were treated with fluoxetine at a dose of 20mg/kg; i.p. dissolved in distilled water from 3rd day onward to 14 days. Fluoxetine was used as the standard for assessment of thermal hyperalgesia.

Group VI - Cinnamon oil (5mg/kg) group (n = 6). A daily dose of 5mg/kg of cinnamon oil was administered from 3rd day onward to 14 days.

Group VII - Cinnamon oil (10mg/kg) group (n = 6). A daily dose of 10 mg/kg was administered from 3rd day onward to 14 days.

Group VIII - Cinnamon oil (20mg/ kg) group (n = 6). A daily dose of 20mg/kg was administered from 3rd day onward upto 14 days.

Estimation of Fasting Blood Glucose (FBG)
For the estimation of blood glucose, blood samples were taken from retro orbital plexus. Blood samples were kept at room temperature for 5-10 minutes and were allowed to clot. After clotting the samples were centrifuged at 2000 rpm for 10 minutes to separate plasma. Separated plasma was used for the estimation of fasting blood glucose by GOD/POD method using commercial kit (Span Diagnostics Ltd, Surat).

Assessment of thermal hyperalgesia
Thermal hyperalgesia was assessed with tail-immersion and hot plate tests. Preliminary threshold to tail-immersion and hot-plate responses, by taking the means of two consecutive stable values which did not differ by more than 10% were determind (Chopra and Anjaneyulu, 2006). Nociceptive latency was measured at 15, 30, 60, 120 and 180 min. after the administration of drug. The nociceptive latency was expressed as mean ± S.E.M.

Tail-immersion (warm water) test
The tail was immersed in a warm water bath (52.5 ± 5^0C) until tail withdrawl (flicking response) or signs of struggle were observed, the cut-off time was 12s. The hyperalgesic response in the tail withdrawl test is generally attributed to central mechanisms (Chopra and Anjaneyulu, 2006).

Hot-Plate test
The hyperalgesic response on the hot plate is considered to result from a combination of central and peripheral mechanisms (Chopra and Anjaneyulu, 2006). In this test, animals were individually placed on a hot-plate (Eddy's Hot-Plate) with the temperature adjusted to 55 ± 1^0C. The latency to the first sign of paw licking or jump response to avoid the heat was taken as on index of the pain threshold; the cut-off time was 10 s in order to avoid damage to the paw.

STATISTICAL ANALYSIS

Results were expressed as Mean±SEM. The intergroup variation was measured by one way analysis of variance (ANOVA) followed by Tukey's test. Statistical significance was considered at $p < 0.05$. The statistical analysis was done using the Sigma Stat Statistical Software version 2.3.

RESULTS

Yield of Volatile Oil from Bark of *C. zeylanicum*
6.5ml of volatile oil was obtained from hydrodistillation of 500g of cinnamon bark. The percentage yield of the cinnamon oil was 1.3%. The density of the oil was found to be 1.059g/ml. The crude volatile oil so obtained was more than 98% pure cinnamaldehyde as evidenced the ^{1}H & ^{13}C NMR and IR spectra of the oil. In the ^{1}H NMR (400 M Hz, $CDCl_3$ solvent) the aldehydic proton showed up at δ 9.67 (1 H, doublet, J = 7.22 Hz), aromatic protons along with Cβ-olefinic H formed a 6H multiplet at δ7.76 – 7.28 and the Cα-olefinic H appeared as a double doublet at δ6.89 (1H, J = 16.00 and7.72 Hz); there was no other significant resonance signal in the proton NMR of the oil. Presence of only cinnamaldehyde is also corroborated by ^{13}C NMR through resonances at δ 192.91 (CHO), δ152.23 (olefinic Cβ), 133.85 (quaternary aromatic carbon) and other resonances at δ 1309.974 (olefinic C α), 128.873 (m-C of aromatic ring), 128.395 (o-C of aromatic ring), 128.263 (p-C of aromatic ring). The aldehyde band in the IR spectrum appeared at 1681 cm^{-1}. The determined density of the oil 1.059g/ml is also close to the value reported for pure cinnamaldehyde (1.048).

Effect of alloxan injection on Fasting Blood Glucose (FBG) in rats
The levels of fasting blood glucose were found to be significantly higher in diabetic rats than those of normal (non-diabetic) rats after 1 and 2 weeks of intraperitoneal administration of alloxan (Fig.1).

Effect of various therapeutic interventions on Fasting Blood Glucose in alloxan induced diabetic rats
The fasting blood glucose levels were estimated in different groups on 7th and 14th day of the alloxan treatment. Glipizide treatment was found to produce a significant decrease in fasting blood glucose in treated rats as compared with that of untreated control rats. The treatment with the vehicle did not alter the increase in FBG of alloxan treated animals. The treatment with cinnamon oil at 5, 10 and 20mg/kg dose was found to decrease the fasting blood glucose significantly in dose dependent manner on 7th and 14th day as compared to diabetic control group. The maximum decrease in fasting blood glucose was achieved in 20mg/kg treatment group and was similar to that of glipizide treatment (Fig. 2).

Effect of alloxan injection on tail immersion nociceptive threshold in rats
The tail immersion nociceptive threshold was observed to be significantly decreased in diabetic rats as compared with that of normal rats. Hyperalgesia was evident in tail immersion test after 1 week, the maximum decrease in pain threshold was observed at 2 weeks after alloxan injection in rats (Fig. 3).

Effect of various therapeutic interventions on tail immersion nociceptive threshold in alloxan – inducted diabetic rats
A significant increase in nociceptive threshold in tail immersion test was observed in diabetic rats treated with fluoxetine (20mg/kg) i.p. as compared with that of untreated diabetic control rats. Treatment with vehicle did

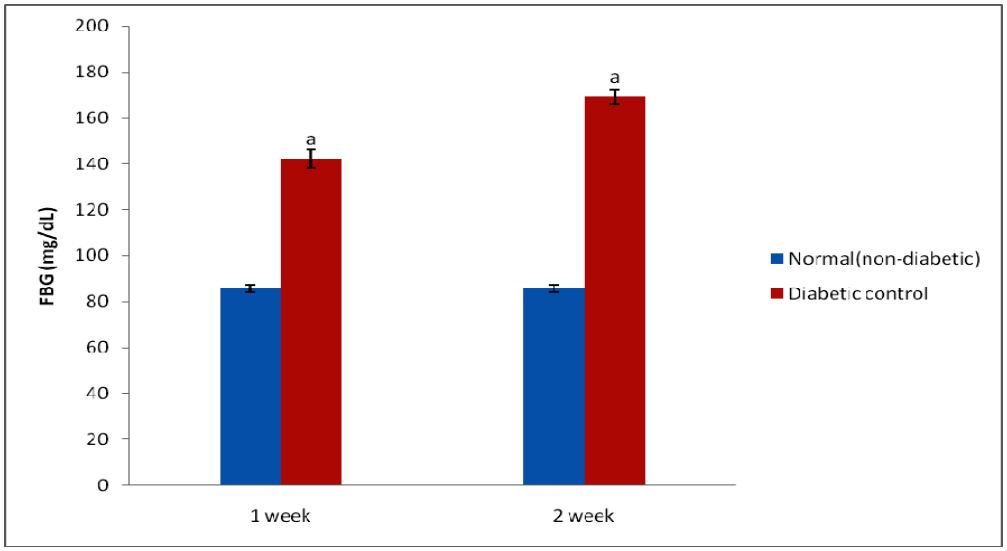

Fig. 1. Effect of alloxan-injection on Fasting Blood Glucose in Rats after 1 and 2 weeks.
$p < 0.05$; a, as compared to normal.

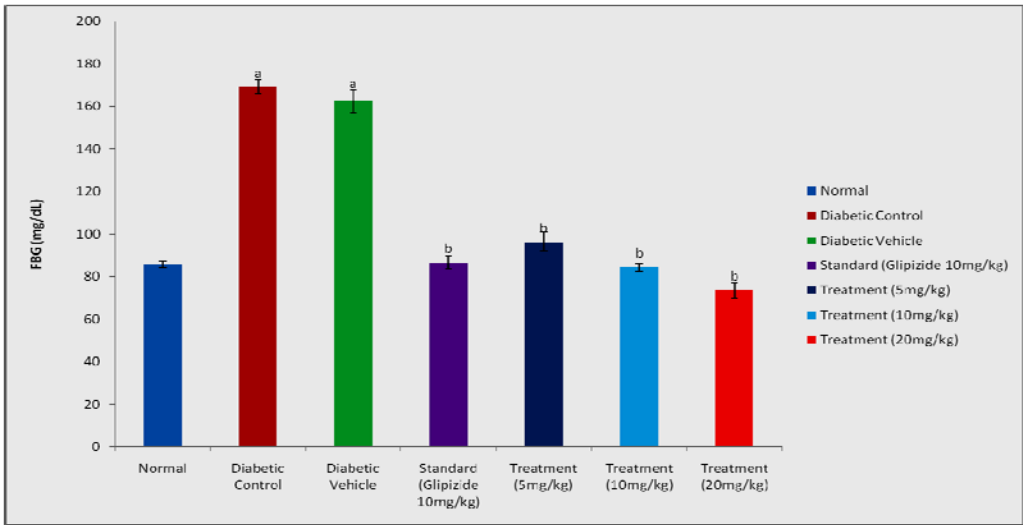

Fig. 2. Effect of various pharmacological interventions on Fasting Blood Glucose Diabetic Rats on Day 14.
$p < 0.05$; a, as compared to normal; b, as compared to Diabetic Control.

not produce any change in the nociceptive threshold in rats. Treatment with cinnamon oil at doses 5, 10 and 20 mg/kg was found to increase the nociceptive threshold in tail immersion test significantly in the treated rats as comared to that of untreated diabetic control rats. The data is expressed as mean ± S.E.M. The maximum protective effect against thermal hyperalgesia was observed at 30 min. after administration of volatile oil from *C. zeylanicum*. The protective effect produced by cinnamon oil on thermal hyperalgesia was found to be more than that of standard dug fluoxetine in tail-immersion assay. The maximum dose-dependent decrease in nociceptive threshold in tail-immersion assay was observed at the dose of 20mg/kg in alloxan-induced diabetic rats (Fig. 4).

Effect of alloxan injection on hot plate nociceptive threshold in rats

The nociceptive threshold was observed to be significantly decreased in diabetic rats as compared with that of normal rats in hot plate assay. Hyperalgesia was evident in hot plate test after 1 week, the maximum decrease in pain threshold was observed at 2 weeks after alloxan injection in rats (Fig. 5).

Effect of various therapeutic interventions on hot plate nociceptive threshold in alloxan – inducted diabetic rats

A significant increase in nociceptive threshold in hot plate test was observed in diabetic rats treated with fluoxetine (20mg/kg) i.p. as compared with that of untreated diabetic

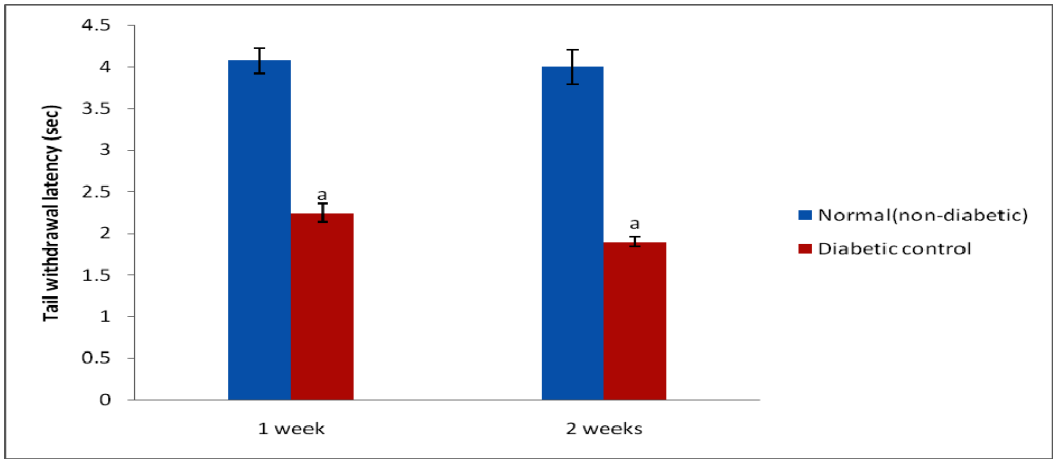

Fig. 3. Effect of alloxan-injection on tail-withdrawl latency in tail-immersion test in rats, as observed after 1 and 2 weeks.
a=p<0.05 vs normal (non-diabetic).

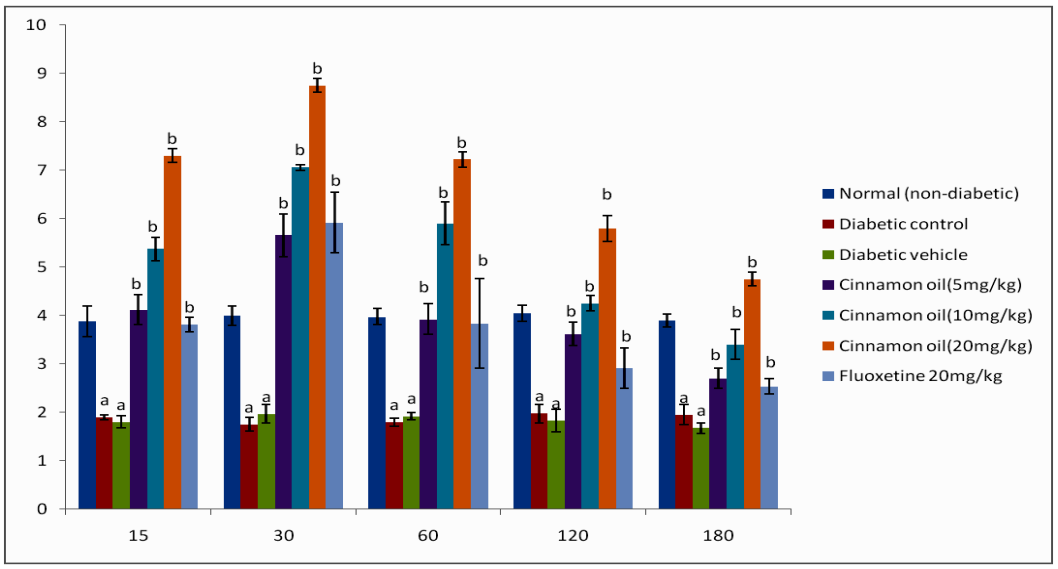

Fig. 4. Effect of various pharmacological interventions on tail-withdrawl latency (expressed as Mean ± S.E.M.) in tail-immersion test in alloxan-induced diabetic rats, as observed on day 14.
a=p<0.05 vs normal (non-diabetic); b=p<0.05 vs Diabetic control.

control rats. Treatment with vehicle did not produce any change in the nociceptive threshold in rats. Treatment with cinnamon oil at doses 5, 10 20mg/kg was found to increase the nociceptive threshold in hot plate test significantly in the treated rats as compared to that of untreated diabetic control rats. The data is expressed as mean ± S.E.M. The maximum protective effect against thermal hyperalgesia was observed at 30min. after administration of volatile oil from *C. zeylanicum*. The protective effect produced by cinnamon oil on thermal hyperalgesia was found to be more than that of standard dug fluoxetine in hot plate assay. The maximum dose-dependent decrease in nociceptive threshold in tail-immersion assay was observed at the dose of 20mg/kg in alloxan-induced diabetic rats (Fig. 6).

DISCUSSION

The aim of this study was to evaluate the protective effect of *C. zeylanicum* bark volatile oil on alloxan induced diabetic neuropathy in rats. Diabetes was induced by single intraperitoneal injection of 150mg/kg of alloxan monohydrate. Alloxan at the similar dose has been reported to induce reproducible and persistant hyperglycaemia in rats (Ryle *et al.*, 1984; Diniz *et al.*, 2008). Experimentally induced diabetic rats have been used as a model of chronic pain with signs of hyperalgesia and allodynia due to diabetic neuropathy that may reflect symptoms observed in humans (Anjaneyulu and Chopra, 2006). In the present study, the tail-immersion and hot-plate latency was observed to be significantly shorter in

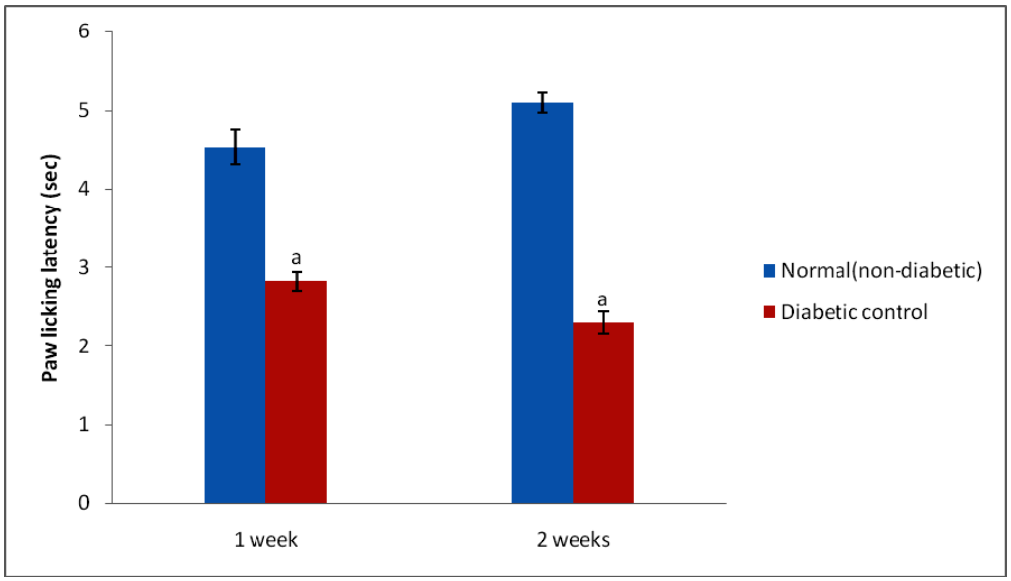

Fig. 5. Effect of alloxan-injection on paw-licking latency in hot-plate test in rats, as observed after 1 and 2 weeks.
a=p<0.05 vs normal (non-diabetic).

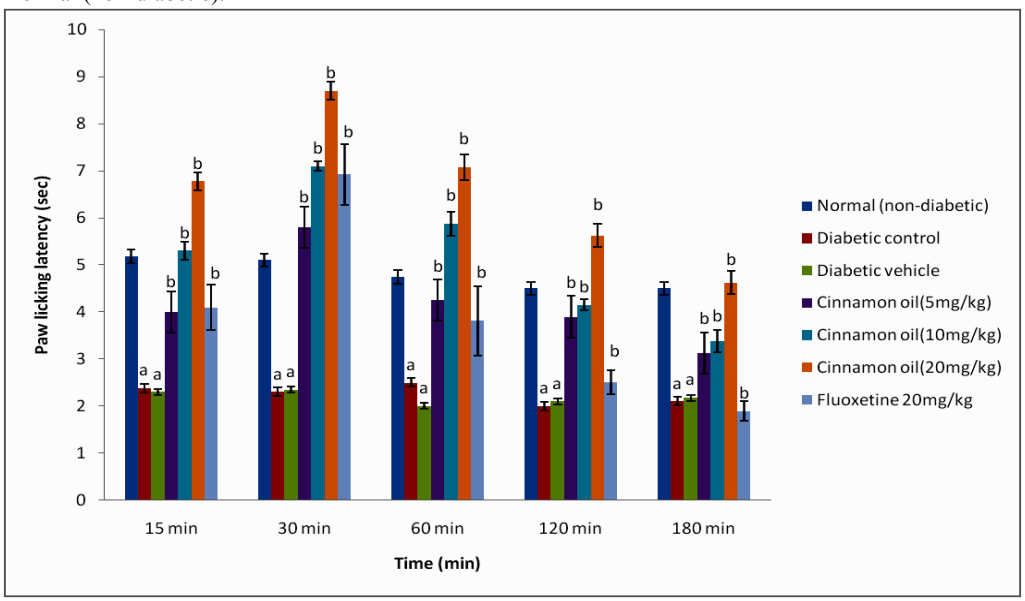

Fig. 6. Effect of various pharmacological interventions on paw licking latency (expressed as Mean ± S.E.M.) in hot plate test in alloxan-induced diabetic rats, as observed on day 14.
a=p<0.05 vs normal (non-diabetic); b=p<0.05 vs Diabetic control.

the diabetic control rats as compared to that of the normal (non-diabetic rats) indicating that alloxan-induced diabetic rats exhibit thermal hyperalgesia. It has been reported that alloxan-injected diabetic rats exhibit thermal allodynia and hyperalgesia, tested on hot-plate and tail-immersion assays (Morani and Bodhanker, 2007). Both hyperalgesia and allodynia have been reported to be established after 14 days of alloxan treatment (Aubel *et al.,* 2004), which was observed behaviorally. The hyperalgesic response in tail-withdrawal test is generally attributed to central mechanisms whereas the hyperalgesic response on hot plate is attributed to the combination of both central and peripheral mechanisms (Anjaneyulu and Chopra, 2004). The altered pattern of nociception may not be due to the inherent neurotoxicity of alloxan, but alloxan may induce various pathological alterations that can lead to altered nociceptive responses in the present study, cinnamon oil produced a marked dose-dependent antinociception in alloxan-induced diabetic rats tested in the both tail-immersion and hot-plate assays. Diabetic neuropathy develops as a result of hyperglycaemia-induced local metabolic and microvascular changes (Sharma *et al.,* 2006). Pathogenetic mechanisms underlying the progressive nerve fiber loss seem to be

multifactorial, include the polyol pathway (Finegold *et al.,* 1983), glycation (Wada and Yagihashi, 2005) and oxidative stress (Chung *et al.,* 2003; Vincent *et al.,* 2004). Oxidative stress could damage the nerves by direct toxic effects or with different biochemical changes that lead to endothelial dysfunction (Goycheva *et al.,* 2006). The volatile oil from *C. zeylanicum* has been reported to possess antioxidant activity (Shobana and Naidu, 2000; Singh *et al.,* 2007). Cinnamaldehyde which is the chief component of the cinnamon oil may be responsible for the antioxidant activity. Cinnamon has been reported to have a very high concentration of antioxidants chiefly cinnamaldehyde which make it an excellent candidate for disorders arising from oxidant stress (Su *et al.,* 2007; Jang *et al.,* 2007). Also cinnamon is documented to inhibit aldose reductase (Aida *et al.,* 1987), the latter plays a vital role in conversion of glucose to sorbitol. This sorbitol is further converted to fructose by sorbitol dehydrogenase which leads to the depletion of organic osmolites such as taurine, myoinositol etc. (Zhu *et al.,* 1999). Myoinositol depletion results in inactivation of Na^+/K^+ ATPase, Na^+ retention and cellular edema (Brownlee, 2001). Also the conversion of glucose to sorbitol depletes the cellular stores of NADPH which are required for the conversion of oxidized glutathione to reduced glutathione (Brownlee, 2001). All these factors play vital role in various complications of diabetes (Brownlee, 2001). From the above discussion it may tentatively be suggested that the protective effect of cinnamon oil may be attributed to its insulin enhancing and antioxidant effects.

Further, studies have demonstrated that even with stringent blood glucose control, the prevention of neuropathy is not successful which suggest that there may be a release of early mediators between hyperglycaemia-induced metabolic and enzymatic changes and the nerve damage (Sharma *et al.,* 2006). Once these mediators are released, it is possible that they modulate neuronal homeostasis independly of the initial metabolic stimulus (Sharma *et al.,* 2006). Previous studies have shown that chronic hyperglycaemia accelerates the production of endogenous tumor necrosis factor-α (TNF-α) in microvascular and neuronal tissues (Kuhad *et al.,* 2008).

Cinnamaldehyde has been reported to have inhibitory effects on TNF-α (Liao *et al.,* 2008). Cinnamaldehyde has been demonstrated to inhibit TNF-α-induced signaling pathways by inhibiting the expression of cell adhesion molecules in endothelial cells by suppressing nuclear factor-kappa B (NF-κB) activation (Liao *et al.,* 2008). It has been shown that clinical application of the agents that suppress the production and/or activity of TNF-α may inhibit the development and exacerbation of chronic diabetic complications (Satoh *et al.,* 2003).

Superoxide and nitric oxide have been reported as the other key mediators which combine to form peroxynitrite, which rapidly causes protein nitration or nitrosylation, lipid peroxidation, DNA damage and cell death and to have direct toxic effects on the nerve tissue leading to neuropathic pain (Kuhad *et al.,* 2008). Cinnamon has been evaluated for its NO-suppressing activity via different pathways such as the blocking of inducible nitric oxide synthase (iNOS) expression, the inactivation of iNOS catalytic function and the scavenging of NO (Tsai *et al.,* 2007).

Cinnamaldehyde has also been reported to reduce IL-1β-induced cyclooxygenase-2 (COX-2) activity in rat cerebral microvascular endothelial cells significantly (Guo *et al.,* 2006). It has been reported that COX-2 is upregulated in the peripheral nerves and dorsal root ganglia neurons in experimental diabetes and that COX-2 gene inactivation or selective COX-2 inhibition provides protection against various diabetic peripheral neuropathy defects (Kellogg *et al.,* 2008). COX-2 upregulation leads to an altered prostaglandin profile with an increased production of vasoconstricting PGH_2, thromboxane-A_2 (TXA_2) and $PGF_{2\alpha}$ and reduction of vasodilatory prostacyclin (PGI_2), thereby favouring vasoconstriction and ischemia (Kuhad *et al.,* 2008). It has also been demonstrared that COX-2 gene deficient experimental diabetic rats showed a differential protection against biochemical and functional markers of experimental neuropathy and that the extent of this protection appeared to be dependent on the degree of COX-2 gene deficiency (Kellogg and Pop-Busui, 2005).

CONCLUSION

On the basis of present results and above discussed mechanisms, the antinociceptive effect of cinnamon oil in alloxan-induced diabetic rats as observed in the present study may be attributed to its hypoglycaemic, antioxidant and pro-inflammatory inhibitory effects i.e. suppressing TNF-α signaling pathway, inhibiting NF-κB activation, suppressing NO production and activity, and reducing IL-1β-induced COX-2 activity. In conclusion, it may tentatively be stated that volatile oil from *Cinnamomum zeylanicum* could provide a novel therapeutic approach in attenuation of hyperalgesia due to diabetes.

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