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The analgesic effect of *Carum copticum* extract and morphine on phasic pain in mice

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Abstract

Pain is a universal complaint, which needs further investigations for new pain relieving agents. *Carum copticum* (L.) Sprague ex Turrill is a plant in Umbelliferae family, which is mentioned to have some therapeutic effects on headache and joint pains in Iranian traditional literature, but there are not enough scientific reports to prove its effects on pain. So, we conducted to design an experimental clinical trial study to assess and compare the analgesic effect of ethanolic extract of *Carum copticum* fruit with morphine by using a tail-flick analgesiometer device. Our results indicate that the test drug produced significant increase in tail-flick latency (TFL) during 2 h post-drug administration ($p < 0.05$). The peak of the effect was observed at 45 min after drug injection, which was comparable to that of 1 mg/kg morphine (i.p.). Positive results in this type of analgesiometric test indicate that the antinociceptive action may be of the opoid type. The present study supports the claims of Iranian traditional medicine showing that *Carum copticum* extract possesses a clear-cut analgesic effect. However, further investigations are required to evaluate the efficacy and safety of this herbal medication in man.

Keywords: Pain; *Carum copticum*; Tail-flick; Mice

1. Introduction

Carum copticum (L.) Sprague ex Turrill is a plant in the Umbelliferae family and constituents of it's seed are: an aromatic volatile essential oil, and a crystalline substance stearoptene. The stearoptene is known as ajowan-ka-phul (crude thymol) (Asghari and Lockwood, 1996; Farooq, 1953; Lockwood, 2002; Nadkarni, 1976). A phenolic glucoside has been isolated from the seeds and identified as 2-methyl-3- glucosyloxy-5-isopropylphenol (Garg, 1980). Thymol crystallizes easily from the oil extracted from seeds of *Carum copticum* and the remainder consists of p-cymene, b-pinene, dipentene β-terpinene and carvacrol (Chopra, 1982). This plant has been mentioned in Iranian traditional literature to have therapeutic effect on flatulence, indigestion, colic, dyspepsia and diarrhea (Astarabadi, 1966; Nadkarni, 1976; Avesina, 1985). It is also applied to eradicate worms and to relieve urticaria, rheumatic and neuralgic pain such as joint pains and headache (Garg, 1980). Although there are a few scientific reports about antibacterial, antihelmentic, antiflatulent and antidiarrheal effects of this plant (Ashebir and Ashenafi, 1999; Fisseha et al., 1999; Rani and Khullar, 2004; Singh et al., 2002). We did not find any scientific reports to prove its effects on pain. So, we conducted an experimental clinical trial to assess and compare the analgesic effect of ethanolic extract of *Carum copticum* fruit with different doses of morphine sulphate in a model of phasic pain in mice.

2. Materials and methods

In this study, the stimulus for pain induction was a heat stimulus produced by a light beam, applied to the tail of the animals by using an Analgesiometer, type 812 (Hugo Sachs Electronik, Germany). For behavioral testing permission of the animal ethics committee of Shahid Sadughi Medical University (Yazd, Iran), in accordance with the internationally accepted principles for laboratory animal use and care mentioned by the European Community guidelines, were obtained. The animals used in this study were Syrian mice, housed in five groups of seven in a controlled

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environment with a temperature of 20 ± 1 °C and 12-h dark:12-h light cycle. The animals had free access to food and water. Drugs were given by acute systemic intraperitoneal (i.p.) administration 15 min before the test. The drugs given were of different concentrations 0.5, 1 and 2 mg/kg morphine sulphate (Temad Co., Tehran, Iran) and ethanolic extract of *Carum copticum* fruit (10 mg/kg) in a volume of 0.5 ml for test groups and 0.5 ml normal saline as vehicle in control group. *Carum copticum* (L.) Sprague ex Turrill was identified by botanists in the herbarium of Yazd herbal drug research center. The plant extract was prepared by maceration of 50 g of the chopped, dried fruit of *Carum copticum* in a mixture of 200 ml of ethanol and 200 ml of distilled water by shaking them for 48 h and pressing the solution out of the material using a filter press. The extract's solvent was then removed under reduced pressure until the extract was completely dry as a gum. The extract dose was selected according to Dhawan (1982). Tail-flick latency (TFL) was determined according to the method described by D'Amour and Smith (1941). The TFL was recorded as the time onset of stimulation to the withdrawal of the tail from the light beam. A cut-off point of 10 s was used to avoid tissue damage. The data were considered as mean TFL in each group and assessed by Student's *t*-test and one-way ANOVA. The statistical significance was considered as $p \leq 0.5$.

3. Results

In the present study, tail-flick latency was recorded before (as base line latency) and every 15 min after drug administration (as test latency) for 2 h. Data were expressed as mean ± S.E.M. for the percentage of analgesia index (AI %) of each response, calculated with the method indicated by D'Amour and Smith (1941) [AI% = (test latency − base line latency/base line latency − cut-off) × 100]. The data obtained from all groups throughout 2 h post-drug administration are illustrated in Fig. 1. These results indicate that in the test drugs produced a significant increase in tail-flick latency during this period ($p < 0.05$). Although different doses of morphine sulphate showed a dose-dependent analgesic effect, AI% for animals receiving *Carum copticum* extract was significantly less than the group of 2 mg/kg morphine sulphate ($p = 0.04$) but it was not significantly different from that of 1 and 0.5 mg/kg morphine sulphate ($p = 0.27$ and 0.25, respectively, Fig. 1). The peak of the *Carum copticum* effect was observed at 45 min after drug injection, which was also approximately

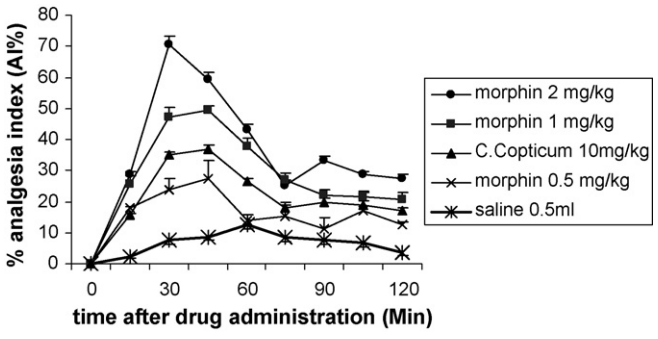

Fig. 1. The effect of *Carum copticum* and different doses of morphine on phasic pain in mice during 2 h after drug administration ($N = 7$).

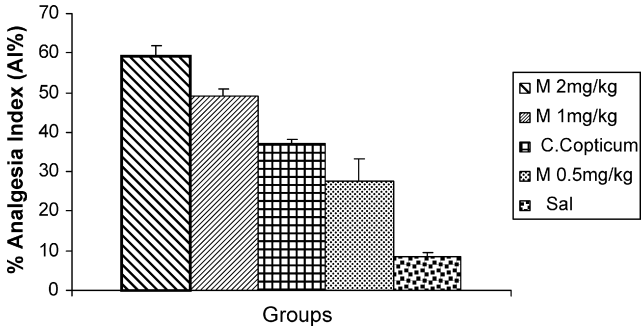

Fig. 2. Analgesic effect of *Carum copticum* and different doses of morphine on phasic pain in mice 45 min after drug administration ($N = 7$) AI% in *Carum copticum* group was significantly less than morphine 1 and 2 mg/kg ($p = 0.014$ and 0.002, respectively) but the same as 0.5 mg/kg morphine sulphate ($p = 0.28$).

the same as 0.5 mg/kg morphine sulphate ($p = 0.28$), but significantly less than 1 and 2 mg/kg morphine sulphate ($p = 0.014$ and 0.002, respectively, Fig. 2).

4. Discussion

Thymol is the major component of *Carum copticum* (Gersbach and Reddy, 2002), which is known as an antiparasitic agent (Fisseha et al., 1999; Garg, 1980). It has been mentioned that the healer of Mudpar village use special herbal combination including *Carum copticum* for treatment of patients suffering from gout (Patnaik, 1993). It is also applied to eradicate worms and to relieve urticaria, rheumatic and neuralgic pain such as joint pains and headache (Kloos et al., 1978). There is a report describing that essential oil of *Carum copticum* has parasympathomimetic activity and produces contraction of the smooth muscle, such as guinea pig's ileum and the bronchial musculature (Devasankaraiah et al., 1974). Recent reports indicate its relaxant activity on guinea pig's tracheal chain (Boskabadi et al., 2003) via inhibitory action on H_1 Histaminic receptors (Boskabadi and Shaikhi, 2000). Also the antitussive effect of *Carum copticum* is reported in guinea pigs (Boskabady et al., 2005). Ajowan oil is shown to be toxic at different dilutions to pathogenic bacteria and is shown inhibitory to various microorganisms (Ashebir and Ashenafi, 1999; Saxena and Singh, 1983; Singh et al., 2002). The antifungal activity of *Carum copticum* in combination with other essential oils is also known (Kalpana and Ramanujam, 1994). This plant is also recorded in the literature as anti-diarrheal (Fisseha et al., 1999; Kloos et al., 1978) and Hypolipidaemic activity (Khanna, 1991). In an experimental clinical trial study, the *Carum copticum* extract increased gastric acid secretion by a cholinergic mechanism (Vasudevan et al., 2000). The anti-inflammatory effect of *Carum copticum* seed extract is also reported in a double blind clinical study (Thangam and Dhananjayan, 2003). Recently, in a series of clinical trial studies the curative effect of many herbal extracts including essential oil of *Carum copticum* as eye drops, in the management of various ophthalmic disorders including the computer vision syndrome was reported (Biswas et al., 2001; Biswas et al., 2003). We could not find any scientific literature concerning the antinociceptive effect of *Carum copticum*. In the present

study, which used a model of acute (phasic) analgesiometric test, we found an analgesic action for the ethanolic extract of *Carum copticum*. This effect may be due to its parasympatomimetic action on descending pain modulating pathways. On the other hand, the correlation between the analgesic effect of the tested drug and 1 mg/kg morphine sulphate indicates that the effect may be of the opioid type. The present study, supports the claims of Iranian traditional medicine showing that *Carum copticum* extract possesses a clear-cut analgesic effect. Although there is not any scientific report in the available literature that the products of this plant are toxic to humans, further investigations are required to evaluate the efficacy and safety of this herbal medication in man as well as its mechanisms of action in animal trials.

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