The effect of *Elettaria cardamomum* extract on anxiety-like behavior in a rat model of post-traumatic stress disorder

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**A B S T R A C T**

Post-traumatic stress disorder (PTSD) is a debilitating psychiatric condition which develops in 6–8% of the general population. Current standard pharmacological treatments for PTSD cannot be widely used due to having various side effects. Nowadays, various pharmacological properties have been related to *Elettaria cardamomum* L. (family of Zingiberaceae). The present study aims to evaluate the efficacy of *E. cardamomum* methanolic extract on anxiety-like behavior in a rat model of PTSD. Adult male Wistar rats (200–250 g) were used in this study. The rats underwent single prolonged stress (SPS) or control and intraperitoneally received either saline or different dosages (200, 400, and 800 mg/kg) of *E. cardamomum* methanolic extract before and after stress sessions. Moreover, open field, elevated plus-maze, and rotarod tests were used to evaluate locomotion and anxiety-like behavior in the rats. Findings demonstrated that *E. Cardamomum* methanolic extract, particularly at the dose of 400 mg/kg, significantly (P < 0.05) improved anxiety-like behavior in a rat model of PTSD, as examined by the open field, elevated plus-maze, and rotarod tests. Administration of *E. cardamomum* methanolic extract after stress might help to prevent the formation of anxiety-like behavior in the animals. However, further studies are required to clarify the exact mechanisms involved.

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**1. Introduction**

Post-traumatic stress disorder (PTSD) is a psychiatric illness with a life-time prevalence of 5–8% in the general population [1]. It is one of the most debilitating conditions which significantly reduces the quality of life in the patients [2]. The disease is characterized by three main symptoms, including recurring flashbacks and nightmares, hyperarousal, and numbing [3]. PTSD is an anxiety-disorder which could be classified as acute (acute stress disorder) or chronic (PTSD) [3]. Several treatment modalities have been proposed to prevent and treat PTSD in patients. Selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) agents such as fluoxetine and paroxetine have been approved for the treatment of PTSD symptoms [4]. Despite their effectiveness against the PTSD symptoms, their use is limited because of various side effects, which highlights the need for further research on therapeutic modalities [5].

During recent decades plant-derived extracts and compounds were considered as a valuable source in order to cure a wide variety of diseases such as psychiatric disorders. This rich source has some advantages including few side effects, low cost and high availability.

The cardamom (*Elettaria cardamomum* L. (Maton) from Zingiberaceae family) is one of the most important spice crops cultivated widely in India and other tropical regions worldwide. *E. cardamomum* is called “Queen of Spices” in India and “Heli” in Iran that used as a flavor agent (spice) in a variety of foodstuffs [6]. In the
folk medicine, different parts of *E. cardamomum* have been used in the treatment of gastrointestinal disorders and also used as stomachic, resolvent, retentive, digestive, astringent, carminative and anti-putrefactive during embalming [7,8]. In recent years and in modern medicine various pharmacological properties such as antimicrobial, anti-inflammatory, analgesic, anti-depression, anticonvulsant and antispasmodic activities have been attributed to this plant [9–11].

There are much evidence about *E. cardamomum* beneficial effects against many complications and diseases as mentioned above but there is no study about *E. cardamomum* effect on PTSD. Considering *E. cardamomum* constituents such as quercetin, kaempferol and rutin of which quercetin has effects on CNS function we decide to evaluate *E. cardamomum* methanolic extract effects on anxiety-like behavior in rat model of PTSD [12–14].

2. Materials and methods

2.1. Plant materials

Dry *E. cardamomum* seeds were purchased from the market. The plant seeds were identified by a botanist at the Botany Department of Shahid Bahonar University, Kerman, Iran. A voucher specimen of the plant materials was deposited at the Herbarium of Department of Pharmacognosy of School of Pharmacy, Kerman University of Medical Sciences, Iran (KF1375).

2.2. Preparing methanolic extract

The dried seeds of the plant (100 g) were grinded and extracted by percolation method and through using methanol (80%) for 72 h at room temperature. The solvents were removed in a rotary evaporator, and after filtering, the extracts were concentrated to dryness and stored at −20 °C until testing begins [15].

2.3. Phytochemical analysis of *E. cardamomum*

The *E. cardamomum* seed methanolic extract was screened for saponins, alkaloids, flavonoids, and tannins [16]. A TLC method (mobile phase composition with 46.15% chloroform, 30.77% ethyl acetate, 15.38% methanol, and 7.69% formic acid:) was used for separation and detection of different compounds in the extract. Quercetin concentration in the extract was determined by HPLC/UV detector through using different concentrations of standard quercetin [11].

2.4. Animals

Healthy adult rats of Wistar strain weighing around 200–250 g were used in the present study. The animals were housed in clean polypropylene cages and maintained in a well-ventilated temperature controlled animal house with constant 12 h light/dark schedule. The animals were fed with standard rat pellet diet and clean drinking water was made available *ad libitum*. All the procedures were performed from 12:00 to 16:00. Maximum effort was made to minimize pain for the animals.

2.5. Ethical statement

This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (Publication No. 85–23, revised 1985). The protocol was approved by the Committee on the Ethics of Animal Experiments at Kerman University of Medical Sciences (Permit Number: KNRC/92–7). Moreover, all efforts were made to minimize suffering of the rats.

2.6. Experimental design

The rats were divided into two main groups. The first main group was single prolonged stress (SPS) group I containing 96 rats, which was subdivided into four subgroups; subgroup Ia (24 PTSD rats treated with saline as vehicle), subgroup Ib (24 PTSD rats treated with 200 mg/kg of the extract), subgroup Ic (24 PTSD rats treated with 400 mg/kg of the extract), and subgroup Id (24 PTSD rats treated with 800 mg/kg of the extract). Each subgroup was also subdivided into three further subgroups (n = 8 rats): (i) pre-stress (received saline or extract 30 min before establishment of PTSD), (ii) post-stress (received saline or extract 30 min after establishment of PTSD), and (iii) pre-test (received saline or extract 30 min before behavioral test). The second main group was control group II containing 96 rats, which was subdivided into four subgroups; subgroup IIa (24 non-PTSD treated with saline as vehicle), subgroup IIb (24 non-PTSD rats treated with 200 mg/kg of the extract), subgroup IIc (24 non-PTSD rats treated with 400 mg/kg of the extract) and subgroup IId (24 non-PTSD rats treated with 800 mg/kg of the extract).

2.6.1. Stress procedure

The rats were brought to the laboratory 24 h before commencement of stress procedure to get habituated to the environment. They were individually caged one day prior to the stress session. On the stress day, the rats were brought to the laboratory. The SPS procedure was performed on them as previously described elsewhere [17]. Three consecutive stressors, including restraint stress (2 h), swimming stress (20 min) in a cylindrical tank (with 40 cm diameter, 50 cm height, 35 cm water height, and 26 °C water temperature), and loss of consciousness with Diethyl Ether were administered to the rats after a 15 min rest [18]. Seven days post PTSD, the rats were again brought to the laboratory and undergone behavioral tests after one hour habituation.

2.6.2. Open field test

The rats were brought to the testing environment after 1 h acclimation period. The rats were then put in the middle of an open field. The open field apparatus was a square arena [90 × 90 × 30 (H) cm] which was made of Plexiglas, and its floor was divided into 16 squares so the field was divided into central and peripheral squares. The vertical and horizontal activities of the rats were recorded during a five min period and then analyzed using an EthoVision software [version 7.1], a video tracking software for automation of the behavioral paradigms [Noldus Information Technology, the Netherlands]. Parameters including total distance moved in cm (TDM), number of grooming and rearing (as a measure of vertical activity), and the time spent in periphery and center were recorded for each rat. At the end of each test, the rats were removed from the chamber and the field was cleaned with a damp cloth [19].

2.6.3. Elevated plus-maze

The elevated plus-maze comprised a black wooden apparatus with arms having equal dimensions. Two of its arms were enclosed by walls (30 × 15 × 5 cm) and arranged in line with 2 opposite open arms (30 × 5 cm). The maze was elevated 50 cm above the floor. The rats were then placed at the center of the maze, facing the open arms. Two 100 W lamps brightly illuminated the arena. The rats were allowed to explore the maze, and their behavior was monitored for 10 min using the EthoVision software [version 7.1] [Noldus Information Technology, the Netherlands]. After each test, the apparatus was cleaned with 70% ethanol to eliminate the
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