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ScienceDirect
Phytomedicine 13 (2006) 668–676
Phytomedicine
www.elsevier.de/phymed

Evaluation of anxiolytic properties of Gotukola – (*Centella asiatica*) extracts and asiaticoside in rat behavioral models

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Abstract

The ayurvedic medicinal plant Gotukola (*Centella asiatica*) was evaluated for its anxiolytic properties. Specifically, this study assessed the effects of: Gotukola plant materials of different genotypic origin; hexane, ethyl acetate and methanol extracts of Gotukola; and asiaticoside, a triterpenic compound isolated from Gotukola. Various paradigms were used to assess the anxiolytic activity, including the elevated plus maze (EPM), open field, social interaction, locomotor activity, punished drinking (Vogel) and novel cage tests. The EPM test revealed that Gotukola, its methanol and ethyl acetate extracts as well as the pure asiaticoside, imparted anxiolytic activity. Furthermore, the asiaticoside did not affect locomotor activity, suggesting these compounds do not have sedative effects in rodents.
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Keywords: Gotukola (*Centella asiatica*); Natural health product; Asiaticoside; Anxiety; Rat trial; Elevated plus maze; Open field; Social interaction; Locomotor activity; Vogel; Novel cage

Introduction

Gotukola (*Centella asiatica* L. Apiaceae) is a psychoactive medicinal plant that has been used for centuries in Ayurvedic medicine to alleviate symptoms of anxiety and to promote a deep state of relaxation and mental calmness during meditation practices. Recent investigations using human and animal models of anxiety have confirmed that Gotukola does indeed possess anxiolytic activity. Bradwejn et al. (2000) reported that a single 12 g dose of Gotukola administered orally was more effective than placebo in decreasing acoustic startle response in healthy humans. This effect was most pronounced 60 min after treatment. In animals, Gotukola increases pentobarbitone-induced sleeping time and decreases immobility in the forced swim test (Sakina and Dandiya, 1990). Gotukola also elicits anti-anxiety effects in the elevated plus maze (Lucia et al., 1997) and an aqueous extract of Gotukola was reported to have cognitive-enhancing as well as antioxidant effects in rats (Kumar and Gupta, 2002).

The most prominent group of biologically active compounds isolated from Gotukola is the terpenes (Shukla et al., 1999a). Asiaticoside is the most abundant triterpene glycoside, which is effective in wound healing and apparently acts by enhancing the induction of antioxidant levels at an early stage of wound healing (Shukla et al., 1999b). Asiaticoside is transformed into its aglycone asiatic acid in vivo by hydrolysis. Several derivatives of asiaticoside (Inhee et al., 1999) and asiatic

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0944-7113/$ - see front matter © 2006 Elsevier GmbH. All rights reserved.
doi:10.1016/j.phymed.2006.01.011

acid (Sang-sup et al., 2000) were found to show protective effect against beta amyloid-induced neurotoxicity associated with the dementia of Alzheimer's disease.

In the Bradwejn et al. (2000) study, the effective anxiolytic dose of Gotukola in humans was estimated at 12 g of crude leaf material per subject. Administration of such large amounts of plant material is awkward and impractical. The first objective of the present study was to identify more active plant genotypes as well as the active fraction(s) and compounds from the plant. The second was to identify the efficacy of these compounds across a variety of paradigms capable of detecting anxiolytic activity, including the elevated plus maze, open field test, social interaction test, locomotor activity, Vogel test and novel environment test.

Materials and methods

Test animals

Test protocols were reviewed and approved by the University of Ottawa Animal Care Committee, according to guidelines of the Canadian Council on Animal Care. Male Sprague–Dawley (SD) rats (300–325 g body wt., each) raised in a pathogen-free colony, were obtained from Charles River Canada Inc. (St-Constant, QC) a week before the tests. Upon arrival rats were housed individually in standard rat cages measuring $45 \times 24 \times 20$ cm (Lab Products, Pennsylvania, USA) and had ad libitum access to standard Purina Rat Chow (Purina; code 5012) and tap water. The subjects were maintained in a tightly controlled environment (ventilation (100% fresh-air 20 exchanges/hour), lighting (12 h light-dark cycle; 7.00 a.m.–7.00 p.m.) and room temperature (21 °C). Bedding (Prochips; maple or birch hardwood chips) was changed once a week. During the habituation period of at least 5 days after arrival, rats were familiarized with the researcher(s).

Drug administration and testing of rats were conducted in a sound attenuated room. A mild detergent, (Quatsyl; 8 ml/l water, Pharmacia & Upjohn Animal Health, Orangeville, Ontario) was used to clean the cages between tests.

Apparatus and test procedures

Elevated plus maze (EPM)

The EPM evokes conflict between the need to explore the novel area and the need to avoid more vulnerable (or aversive) areas of the EPM (heights and open spaces). This maze comprises two open arms (or planks) transected by two perpendicularly opposing closed arms (or alleys with 40 cm high walls). The arms measure 50 cm in length and are 10 cm wide; the whole apparatus is elevated 50 cm off the floor with a stand. The floor of the EPM is made of a black rubberized runway and all interior walls are made of black Plexiglas. The apparatus was surrounded by a black curtain to minimize distractions. Light levels at the center, open- and closed arms of the EPM apparatus were 35, 40 and 4 lux, respectively. A closed circuit camera positioned above the maze permitted remote observation and scoring of animal behavior.

Following drug administration, rats were returned to their home cages for designated periods, and were tested in the open field arena for 5 min, just before placement onto the EPM. They were placed in the central, open square facing the closed arm and monitored for 5 min. The behaviors scored included: number of entries and time spent on the open arms (all four paws in open arm); time spent in the closed arms; number of occurrences and time spent in protected head dips (the animal dipping its head over the sides of open arm while part of the body is within the closed arm); and number of unprotected head dips (made from the open arm without contact with walls of closed arms). After 5 min of testing, rats were returned to their home cages.

Open field test

In this test, the aversion to the central zone (or vulnerable area) of an arena is used as an index of anxiety levels. The open-field apparatus constituted of a rectangular plexiglas arena measuring 60×60 cm with 35 cm high walls. The floor was marked with lines that divided it into 36 squares (10×10 cm). The squares immediately adjacent to the walls of the test arena constitute the 'safer' peripheral zone, whereas the inner or more centrally positioned squares were identified as the central (or vulnerable) zone. The behavior was monitored via a closed-circuit video camera mounted on the ceiling. The test apparatus was surrounded by black curtains to minimize undue distraction. Light levels at the center and perimeter of the open field test arena were 22 and 12 lux, respectively. The test was initiated by placing the rat into the center of the arena. Over a period of 5 min, the number of squares crossed and time spent in the center and the perimeter was determined.

Social interaction test

In this test, the amount of time a pair of rats spend socially interacting with one another is thought to reflect the level of anxiety in these subjects. The duration of social interaction decreases with increased anxiety. Rats were placed individually in the test arena for 7-min familiarization session on two consecutive days. During the test day, two randomly selected rats were administered the drug and placed in adjacent cages in the waiting area of the test room. One hour later, they were introduced together into the center of the test arena.

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