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# Analgesic and sedative activities of lactucin and some lactucin-like guaianolides in mice

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**Abstract**

Lactucin (**1**) and its derivatives lactucopicrin (**2**) and 11β,13-dihydrolactucin (**3**), which are characteristic bitter sesquiterpene lactones of *Lactuca virosa* and *Cichorium intybus*, were evaluated for analgesic and sedative properties in mice. The compounds showed analgesic effects at doses of 15 and 30 mg/kg in the hot plate test similar to that of ibuprofen, used as a standard drug, at a dose of 30 mg/kg. The analgesic activities of the compounds at a dose of 30 mg/kg in the tail-flick test were comparable to that of ibuprofen given at a dose of 60 mg/kg. Lactucopicrin appeared to be the most potent analgetic of the three tested compounds. Lactucin and lactucopicrin, but not 11β,13-dihydrolactucin, also showed sedative properties in the spontaneous locomotor activity test.
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*Keywords:* *Lactuca virosa*; *Cichorium intybus*; Asteraceae; Guaianolides; Analgesic activity; Sedative activity

## 1. Introduction

The guaiane-type sesquiterpene lactone lactucin (**1**) and its derivatives are characteristic bitter constituents of *Lactuca* and *Cichorium* species, and some other members of the tribe Lactuceae of the family Asteraceae. Lactucin was first discovered in latex of wild lettuce (*Lactuca virosa* L.) in the middle of the 19th century. The latex released from damaged lactifers of leaves or stems of the flowering plants, when left in the open, dries into a brown gummy product, known as *lactucarium* or lettuce opium. Analgesic, antitussive and sedative properties of the lettuce opium, used throughout Europe for centuries, had been attributed to the presence of lactucin (**1**) and its ester lactucopicrin (**2**) (Fig. 1.) long before their structures were known (Schenck, 1939; Schenck et al., 1939). Subsequently, compounds (**1**) and (**2**) were isolated from root latex of chicory (*Cichorium intybus* L.) (Holzer and Zinke, 1953). In herbal medicine, the plant has been used to improve digestive and metabolic functions. It is also an important remedy in Ayurveda and Unani systems of medicine, especially used for the treatment of inflammations (Gupta and Ansari, 2005).

In our earlier study (Gromek et al., 1992) crude preparations from *Lactuca virosa* 1- and 2-year-old plants showed analgesic and sedative properties in mice. In addition, our preliminary results pointed to lactucin as one of the active plant constituents. Compounds (**1**) and (**2**) were found in flowering plants in the second year of growth but not in vegetative, 1-year plants. The 1-year plants were reported to contain 11β,13-dihydrolactucin (**3**) and 8-deoxylactucin, among other sesquiterpene lactones (Gromek, 1989; Kisiel and Barszcz, 1997). We have also isolated a wide range of sesquiterpene lactones, including the above-mentioned guaianolides, from *Cichorium intybus* 1-year plants (Kisiel and Zielinska, 2001).

Based on these results, we attempted to carry out a pharmacological evaluation of lactucin (**1**), lactucopicrin (**2**) and 11β,13-dihydrolactucin (**3**) for analgesic and sedative activities in mice.

## 2. Materials and methods

### 2.1. Plant materials and isolation of compounds (1), (2) and (3)

Leaves and roots of *Cichorium intybus* L. and *Cichorium pumilum* L. were collected in July from 1-year plants growing

*Abbreviations:* COX-2, cyclooxygenase-2; NF-κB, nuclear factor-κB; $PGE_2$, prostaglandin $E_2$; RP-HPLC, reverse phase high performance liquid chromatography

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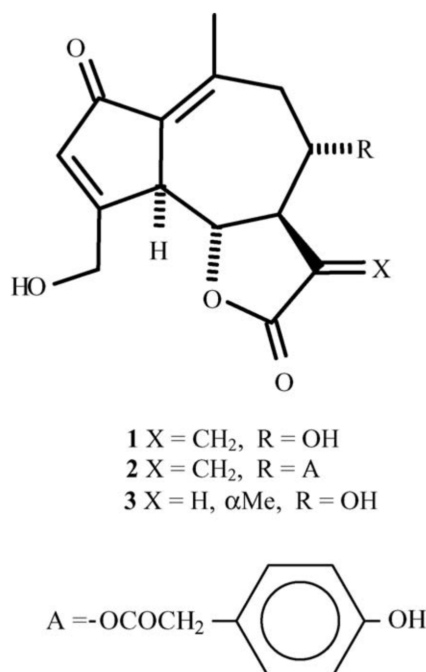


Fig. 1. Chemical structures of lactucin (**1**), lactucopicrin (**2**) and 11β,13 dihydrolactucin (**3**).

in the Garden of Medicinal Plants of the Institute of Pharmacology, Polish Academy of Sciences, Krakow, where voucher specimens were deposited under the reference numbers 97/85 and 01/195, respectively, as described previously (Kisiel and Zielinska, 2001; Kisiel and Michalska, 2003).

Compounds (**1**), (**2**) and (**3**) were isolated from ethanolic extracts of *Cichorium intybus* leaves and roots and *Cichorium pumilum* roots by a combination of column and preparative thin layer chromatographies on silica gel and semipreparative RP-HPLC, as described previously (Kisiel and Zielinska, 2001; Kisiel and Michalska, 2003). Samples of the respective compounds were analysed by analytical RP-HPLC and then combined and crystallized from methanol. The analytical RP-HPLC was carried out on a Lichrocart RP-18e column (particle size 5 μm, 3 mm × 125 mm) coupled to a dual wavelength UV–vis detector operating at 210 and 260 nm, using a $H_2O$–MeOH (6:4) mixture as a mobile phase at a flow rate of 0.5 ml/min. The $R_t$ values of (**1**), (**2**) and (**3**) were 2.8, 25.2 and 2.3 min, respectively.

### 2.2. Agents

Lactucin (**1**), lactucopicrin (**2**), 11β,13-dihydrolactucin (**3**) and ibuprofen (Polfa-Pabianice, Poland) were suspended in a 1% aqueous solution of Tween 80 immediately before their administration. All the compounds were injected intraperitoneally (i.p.) at a volume of 10 ml/kg.

### 2.3. Animals

The experiments were carried out on male Albino Swiss mice weighing 24–28 g. The animals were kept in groups of 10 to a cage (60 cm × 38 cm × 20 cm) at a temperature of 20 ± 1 °C, and had free access to food (standard laboratory pellets) and water. All the investigations were conducted in the light phase, on a natural light cycle (from August to October), between 9 a.m. and 2 p.m. Each experimental group consisted of 10 animals/dose, and the animals were used only once in each test. All the experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.

### 2.4. Hot plate test

For conventional hot plate testing, the method of Woolfe and Mc Donald (1944) was used. An HP-41 Analgesia Meter (COMT Białystok, Poland) was set to a temperature of 56 °C. The time interval from placing animals on the surface of the hot plate to a licking of the hind paws or jumping was defined as a hot plate latency. Mice were preselected 1 h before the test. Those showing a reaction time below 15 s were placed again on the hot plate and the latency was recorded 30, 60, 90 and 120 min after administration of the tested compounds. The test was terminated at 30 s in the absence of a response.

### 2.5. Tail-flick test

The tail-flick latencies were determined using an Analgesia Meter, type 812 (Hugo Sachs Electronik, Germany), according to the method described by D'Amour and Smith (1941). During the test period, the animals were restrained in a plastic tube. The tail-flick latency was recorded as the time from the onset of stimulation to the withdrawal of the tail from a light beam. The beam of light was focussed on the same spot, at about 3.5 cm from the tip of the tail of each animal. The intensity of the radiant heat was identical in all the experiments. A cut-off latency of 7 s was used to avoid a tissue damage to the tail. The tail-flick latency was recorded 30 and 90 min after administration of the investigated compounds. Time schedule of compounds administration was based on their maximal activity in hot plate test.

### 2.6. Locomotor activity test

The spontaneous locomotor activity of mice was measured in photoresistor actometers (24 cm in diameters) illuminated by two light beams, which were connected to a counter for the recording of light-beam interruptions. The mice were placed individually in the actometers and the number of crossings of the light beams was counted during 30-min experimental session. The investigated compounds were administered 60 min before the test.

### 2.7. Statistical analysis

The statistical significance was assessed by a one-way ANOVA, followed by the Dunnett's multiple comparisons test.

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