



Antinociceptive effect of extracts and compounds from *Hofmeisteria schaffneri*[☆]

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ABSTRACT

Ethnopharmacological relevance: *Hofmeisteria schaffneri* (Asteraceae) is a medicinal plant widely commercialized in the most important Markets of Mexico City for the treatment of gastro-intestinal complaints and skin afflictions.

Aim of the study: The main goals of this study were to establish the potential acute toxicity and the antinociceptive activity in animal models of several preparations and compounds from *Hofmeisteria schaffneri*.

Materials and methods: The aqueous and organic extracts as well as the essential oil of *Hofmeisteria schaffneri* were prepared by infusion, maceration and hydrodistillation, respectively. Investigation of the acute toxicity was accomplished by the Lorke method. The antinociceptive effect was assessed using the writhing and the hot plate tests. Natural compounds were isolated by standard phytochemical procedures. In addition, a few thymol esters were prepared by chemical synthesis. The stability of natural and synthetic esters was qualitatively analyzed by measuring their susceptibility to hydrolysis by pig liver esterase and mouse plasma at 37 °C.

Results: The LD₅₀ for each preparation tested was higher than 5000 mg/kg revealing that they were not toxic to mice after exposure for short space of time. On the other hand, the extracts showed significant antinociceptive effect when tested in the hot plate model. The most active natural product as antinociceptive agent was hofmeisterin III (**1**) which also was the most stable in the stability study. Its pharmacological effect seems to be partially mediated by an opioid mechanism since naloxone inhibits its action. Using compound **1** as a lead molecule, several synthetic thymol esters were prepared and only compounds **13**, **15** and **17** were antinociceptive at the dose of 1 mg/kg.

Conclusions: The present investigation provided evidence of the efficacy of several preparations of *Hofmeisteria schaffneri* as antinociceptive agents. The most active preparation was the essential oil which contained large amount of hofmeisterin III (**1**) and other thymol derivatives. Some novel synthetic analogs of hofmeisterin III with antinociceptive properties were discovered. The nature of the ester chain of these analogs did not have a clear impact on the antinociceptive activity. The phyto-preparations analyzed in this study were not toxic to mice according to the Lorke's test; therefore considering their long term use of the plant they might be secure for human consumption.

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1. Introduction

In Mexico an important segment of the population relies on botanical raw materials for primary health care, therefore it is very important to investigate these herbs from the pharmacological and toxicological points of view to establish their real efficacy and safety. The results of such investigations will be also useful to integrate the scientific monographs of these plants in order to

promote their rational use. Consequently, the present investigation was undertaken to initiate the preclinical pharmacological and toxicological analyses of *Hofmeisteria schaffneri* (A. Gray) R.M. King & H. Robinson (Asteraceae), a widely commercialized medicinal species in Central Mexico. The infusion prepared from the fresh or dried aerial parts of the plant is highly valued for treating gastro-intestinal complaints, including stomach aches, related or not with irritable bowel syndrome and dyspepsia, and bleeding diarrhea (King, 1967; Mendoza-Castelán et al., 1997; Pérez-Vásquez et al., 2005, 2008). In addition, the plant is highly valued as a topic anti-septic agent.

Previous chemical work of the plant allowed isolation of several thymol and northymol derivatives (Pérez-Vásquez et al., 2005,

[☆] This work was taken in part from the PhD thesis of Guadalupe Angeles-López.

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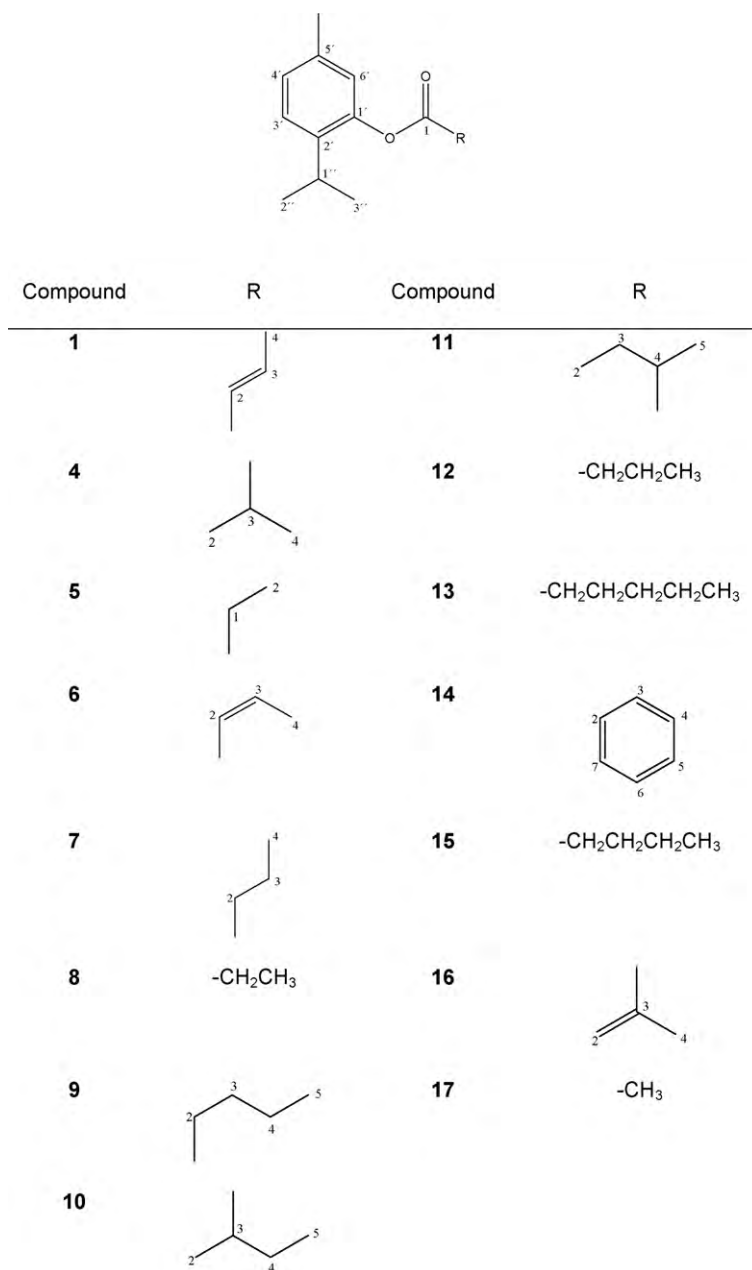


Fig. 1. Structures of thymyl esters.

2008) including hofmeisterin III (**1**), thymol itself (**2**) and 8,9-epoxy-10-acetoxythymyl angelate (**3**) (Figs. 1 and 2). Furthermore, the essential oil and infusion of the plant revealed significant antimicrobial properties against Gram+ bacteria. The antimicrobial essential oil of the plant harvested at different seasons during a year period was also chemically analyzed by GC and capillary GC–MS. Forty four compounds representing ~90% of the total constituents were identified. Compounds **1**–**3**, thymyl isovalerate (**4**), thymyl isobutyrate (**5**) were the major components of the oils but only **3** and **5** were active against *Staphylococcus aureus* and *Bacillus subtilis* (Pérez-Vásquez et al., submitted for publication).

2. Materials and methods

2.1. Plant material

The aerial parts of *Hofmeisteria schaffneri* (4 kg) were collected in San Luis Potosi, Mexico on November 2002. An authenticated

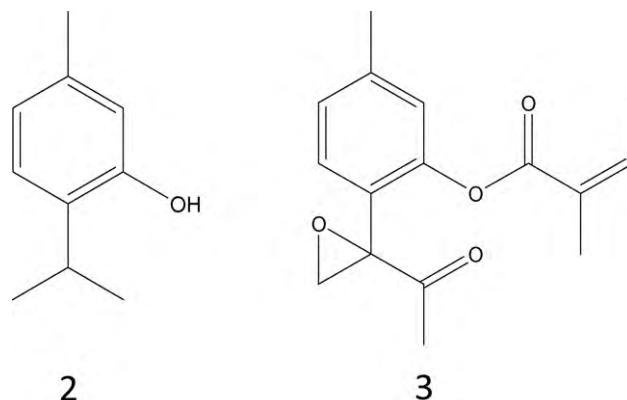


Fig. 2. Structures of thymol (**2**) and 8,9-epoxy-10-acetoxythymyl angelate (**3**).

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