

Gastroprotective Effect and Cytotoxicity of Natural and Semisynthetic Labdane Diterpenes from *Araucaria araucana* Resin

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The resin of the tree *Araucaria araucana* (Araucariaceae) is used by the Mapuche Amerindians in southern Chile and Argentina to treat ulcers and has been shown to display a gastroprotective effect in animal models. A study was undertaken to isolate, identify and assess the gastroprotective effect of the resin constituents and its semisynthetic derivatives as well as to evaluate the cytotoxicity of the products in cell cultures. Eleven diterpenes (ten labdane and a pimarane) were isolated from a resin sample collected in Chile. The labdane derivatives 15-acetoxylabd-8(17)-en-19-ol as well as 15,19-diacetoxylabd-8(17)-en are reported for the first time as natural products. Six diterpenes previously described from other plant sources are reported for the first time for the *A. araucana* resin. The structure of all compounds was elucidated by spectroscopic means. Some 24 diterpenes isolated/prepared in amounts over 10 mg were evaluated for gastroprotective effects in the ethanol/HCl-induced ulcer model in mice at 100 mg/kg. The highest gastroprotective activities were provided by 15-hydroxyimbricatolal, 15-acetoxylimbricatolal, 15-acetoxylabd-8(17)-en-19-oic acid methyl ester and 15-acetoxy-19-labdanoic acid, all of them being as active as the reference drug lansoprazole at 20 mg/kg. The cytotoxicity of 30 diterpenes as well as lansoprazole was assessed towards human lung fibroblasts (MRC-5) and 26 compounds were evaluated on the human gastric epithelial cell line AGS by means of the neutral red uptake assay. A concentration-dependent cell viability inhibition was found with IC₅₀ values ranging from 27 up to > 1000 μ M. The relationship between the cytotoxicity data and lipophilicity of the products is also discussed.

Key words: *Araucaria araucana*, Gastroprotective Activity, Diterpenes