Tumor Inhibitory Agent from *Magnolia grandiflora* (Magnoliaceae) I: Parthenolide

Keyphrases ☐ *Magnolia grandiflora* L.—isolation, identification of parthenolide, antitumor activity ☐ Parthenolide—isolation, identification from *Magnolia grandiflora*, antitumor activity ☐ Antitumor activity—evaluation of parthenolide, isolated and identified from *Magnolia grandiflora*

Sir:

As a result of the continuing search for plants having tumor-inhibiting constituents, it was found that the petroleum ether extract of the leaves and stems of *Magnolia grandiflora* L.[1] showed inhibitory activity toward the human epidermoid carcinoma of the nasopharynx test system (9KB cell culture)[2].

A preliminary examination of the petroleum ether extract revealed one major component. This component was isolated and shown to be the active constituent. The isolation was effected by solvent extraction followed by silica gel G, dry column chromatography. The compound was identified as parthenolide by means of its melting point; mixed melting point; IR, mass spectrometry, NMR, and elemental analyses; and comparison with an authentic sample[3]. The compound demonstrated activity at a dilution level of 2.3×10^1 mcg./ml. Activity in the 9KB cell culture is defined as ED_{50} less than or equal to a dilution of 20 mcg./ml. for plant extracts. The results are expressed as a dose that inhibits growth to 50% of the control growth 3 days after drug addition (1).

The dried leaves and stems (7 kg.) were ground, placed in a Lloyd-type extractor, and exhaustively extracted with petroleum ether (b.p. 40–60°). After removal of the solvent, the residue (160 g.) was treated several times with petroleum ether (b.p. 40–60°). The material obtained from the solution was inactive and, therefore, was discarded. The crystalline insoluble portion (30 g.) was further purified by use of silica gel G, dry column chromatography. Seven grams of the crystalline petroleum ether-insoluble material was placed on a silica gel G column and eluted with dichloromethane–benzene–ethyl acetate (12:24:3). Forty 10-ml. fractions were collected. On the basis of TLC (silica gel G, dichloromethane–benzene–ethyl acetate, 12:24:3), fractions 20–39, which showed a single spot, were combined. The solvent was removed, the residue was dissolved in chloroform and treated with activated charcoal[4], and excess ether was added after evaporation of most of the solvent. A crystalline precipitate (2.9 g.) occurred which was identified as parthenolide (2).

[1] The plant was collected on the campus of the University of Arizona, Tucson, Ariz., in January 1969. Identification was confirmed by Robert J. Barr, College of Pharmacy, and Dr. Charles Mason, Botany Department, University of Arizona. A reference specimen was also deposited in the University of Arizona Herbarium.

[2] Drug Evaluation Branch, Drug Research and Development, Chemotherapy, National Cancer Institute.

[3] The authors are indebted to Dr. B. S. Joshi, Ciba of India Ltd., Goregaon Bombay, India, for providing the authentic sample of parthenolide.

[4] Norite.

(1) *Cancer Chemother. Rep. No. 25*, Dec. 1962.

(2) T. R. Govindachar, B. S. Joshi, and V. N. Kamat, *Tetrahedron*, **21**, 1509(1965).

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Simple Method for Portal Vein Infusion in the Rat

Keyphrases ☐ Portal vein infusion method—used to study first-pass effect in rats ☐ First-pass effect—studied using simple method for portal vein infusion, rats ☐ Absorption, first-pass effect—studied using simple method for portal vein infusion, rats

Sir:

The rate and extent of drug absorption into the systemic circulation have been estimated by pharmacokinetic analysis of plasma concentration–time data or urinary excretion data (1, 2). The percent of absorption can be assessed by comparison of the relative areas under the plasma concentration–time curves after oral and intravenous administration. This method is based on the presumptions that the distribution and elimination of a drug may be expressed in terms of first-order kinetics within the dose range studied and that the parameters of the distribution and elimination remain constant after administering the same quantity of drug by different routes. Thus, the resultant areas are independent of the route of administration and proportional to the dose even when given by different routes. However, it was recently shown that the areas under the blood level–time curves for aspirin (3) and lidocaine (4) after infusion into a peripheral vein were considerably greater as compared with results observed after infusion of an equal dose into the portal vein in dogs. The reduction in area under the blood level–time curves after portal vein infusion has been attributed to a significant degree of metabolism of the drugs during the first passage through the liver.

In this communication, we report a simple method for portal vein infusion in the rat to study the first-pass