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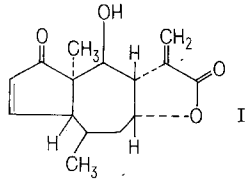
Antineoplastic Agents 32. The Pseudoguaianolide Helenalin[1, 2]

In the Pacific Northwest region of the United States, sneezeweed species (*Helenium* genus, Compositae family) are well-known poisonous plants[3]. For example, in Southern Oregon ingestion of *Helenium autumnale* by livestock leads to serious and frequently fatal consequences. As part of our broad survey of arthropod[4], marine animal[5] and plant[1] species for antineoplastic components we collected *Helenium autumnale* in Oregon in 1967. Subsequently, an ethyl alcohol extract of *H. autumnale* reached confirmed active status in the National Cancer Institute's KB (cells derived from human carcinoma of the nasopharynx) and PS (murine lymphocytic leukemia) screening systems.

Fractionation (greatly assisted by Sephadex LH-20 chromatography) of the *H. autumnale* extract guided by bioassay using the PS system led to isolation of Helenalin[6] (I) as the major cytotoxic and antileukemic component.



I

Various (anthelmintic, irritant to nose, eye and stomach, insecticidal and toxic to fish) physiological activities have been attributed to Helenalin over a 60 year period[7], including recent observations of in vitro cytotoxicity[8]. Now we are pleased to report that this substance markedly increases (T/C 220 at 3 mg/kg) the survival time of mice bearing the P388 lymphocytic leukemia (PS system). In addition, Helenalin led to 47–58% (at 1.5 to 3 mg/kg) inhibition of tumor growth in random-bred albino rats bearing the Walker 256 carcinoma (subcutaneous). Evidence of in vivo antineoplastic activity is only rarely encountered among the sesquiterpenes[9] and Helenalin represents the first pseudoguaianolide to display in vivo antileukemic activity.

Current biological results pertaining to Helenalin clearly indicated that related sesquiterpene lactones should be carefully evaluated for in vivo antineoplastic activity. Furthermore, Helenalin represents an excellent starting point for design of even more effective antineoplastic agents based, for example, on varying the lipophilicity[9] of 6-hydroxy ester derivatives. Efforts directed at these objectives are currently in progress.

Zusammenfassung. Aus der Pflanze *Helenium autumnale* (Familie compositae) wurde ein alkolischer Extrakt gewonnen, der cytotoxische und antileukämische Aktivität zeigte und die Helenalin (I) als wirksame Komponente enthielt. Die Behandlung von Mäusen, die Träger von P388 lymphocytischer Leukämie waren, ergab eine beachtliche (T/C 220) Verlängerung ihrer Lebenserwartung. Die Substanz zeigte ausserdem einen wachstumshemmenden Einfluss auf das Walker 256 Karzinom. Helenalin ist das erste Sesquiterpen vom Pseudoguaianolid Typ, welches in vivo eine solche antineoplastische Aktivität zeigt.

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[1] For part 31, refer to G. R. PETTIT, P. TRAXLER and C. P. PASE, Lloydia *36*, in press (1973).

[2] This investigation was supported by Public Health Service Research Grants No. CA-10612-01 to No. CA-10612-04 from the National Cancer Institute and was performed pursuant to contract No. NCI-C-71-2308 with the Division of Cancer Treatment, National Cancer Institute, Department of Health, Education and Welfare. A grant from the C.S.I.R. (South Africa) to G.M.C. is also gratefully acknowledged. In addition, we are indebted to Dr. L. JOHNSTON for identifying the *Helenium autumnale*, to BETTY J. ABBOTT and her colleagues at the National Cancer Institute, for the biological studies, and to J. F. DAY for assisting with both the laboratory scale and preparative scale plant extraction procedures.

[3] See, for example, USDA Information Bulletin No. 327: U.S. Govt. Printing Office, Washington, D.C.

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[8] J. L. HARTWELL and B. J. ABBOTT, Adv. Pharmac. Chemother. *7*, 117 (1969). – K-H. LEE, E-S. HUANG, C. PIANTADOSI, J. S. PAGANO and T. A. GEISSMAN, Cancer Res. *31*, 1649 (1971). – K-H. LEE, H. FURUKAWA and E-S. HUANG, J. med. Chem. *15*, 609 (1972).

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