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The Occurrence of Senecionine in *Tussilago farfara*

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Introduction

The herb *Tussilago farfara* L. (Compositae), commonly known as coltsfoot, has found widespread use in teas, cough syrups, and other preparations as an anti-tussive and expectorant (1-3). The plant has been shown to be carcinogenic in the diet of rats (4), a finding which has aroused considerable concern over the plant's medicinal use. Several authors who have extracted the pre-blooming flowers (5) and leaves (6) have isolated the pyrrolizidine alkaloid senkirkine (fig. 1), which may be the carcinogenic principle. Senkirkine has been previously shown to be hepatotoxic (7), carcinogenic (8), and mutagenic (9). *Lüthy* et al. (10) have recently reported a trace of a second alkaloid from pre-blooming flowers of *Tussilago farfara* of Chinese origin. By gas chromatography-mass spectrometry (GC-MS) they tentatively identified this component as senecionine (fig. 2), but could not distinguish between senecionine and senecivernine, an isomeric alkaloid with very similar GC-MS behavior (11).

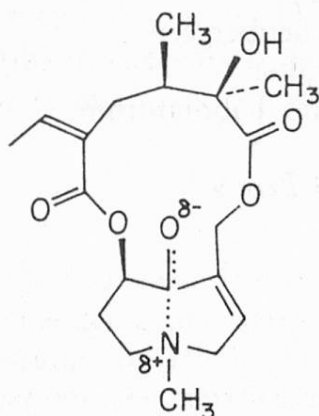


Fig. 1. Senkirkine

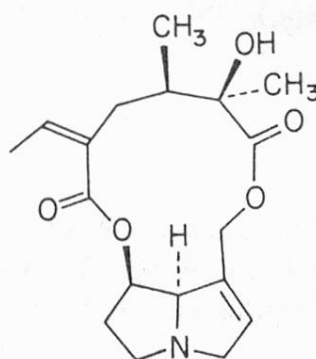


Fig. 2. Senecionine

Our work has focused upon the leaves of the plant, which are used in folk medicine in North America (3). In locally-collected plants, senkirkine is the major alkaloid present, but we also observe a second, less polar alkaloid. Isolation

of this alkaloid by preparative thin layer chromatography and characterization by standard methods (^1H NMR, IR, MS, UV, and TLC) proved it to be senecionine, identical to an authentic sample.

Experimental

Plants were collected on the Cornell University campus in Ithaca, New York, USA during September 1980 and April-May 1981. A voucher specimen is deposited in the herbarium of this university. Immediately after collection, the plants were immersed in ethanol and the alkaloids extracted as described by Bull et al. (12). Reduction of any N-oxides with zinc dust in dilute sulfuric acid did not affect the yield of alkaloids or their relative ratio. To remove neutral impurities from the crude alkaloid mixture, it was again dissolved in 0.5 N H_2SO_4 and washed repeatedly with chloroform before making basic with ammonia to pH 10 and extracting the alkaloids into several portions of chloroform. After drying (Na_2SO_4) and evaporation of solvent, analytical thin layer chromatography showed essentially only two components present. Pure alkaloids were then isolated by preparative thin layer chromatography according to Sharma et al. (13). The isolated alkaloids showed ultraviolet, infrared, proton magnetic resonance, and mass spectra in agreement with published data for senkirkine (14) and senecionine (15). Alternately, for quantification, the alkaloid mixture was taken up in ethanol and analyzed by high performance liquid chromatography on a 4.60 mm x 25 cm Whatman ODS-3 column using an isocratic methanol-0.01 M KH_2PO_4 (30 : 70) solvent system (16). The ultraviolet absorption of the eluate was monitored at 225 nm and the flow rate was 2.5 ml/min. Under these conditions, senecionine and senkirkine had retention times of 17.8 and 22.2 minutes, respectively. The peaks were integrated and compared to elution curves of the pure alkaloids for quantification. All determinations were performed in triplicate.

Results and Discussion

Our experiments show that the total alkaloid content of locally-collected *Tussilago farfara* is quite low and that the alkaloids exist entirely in the free base form rather than as amine oxides. In all parts of the plant investigated senecionine occurs as a minor component along with senkirkine, which is the major alkaloid. The identification of senecionine follows from the proton NMR of the isolated alkaloid, which conclusively rules out the isomeric senecivernine as a possibility.

To evaluate the health risk involved in ingesting preparations of *Tussilago farfara*, we have determined levels of senkirkine and senecionine in various parts of freshly-collected plants. Our results (table 1) show that the highest levels of both alkaloids occur in the pre-blooming flowers. The level of senecionine is never greater than 7 ppm on a dry weight basis, and in mature plants this alkaloid is barely detectable (1 ppm). Our findings on senkirkine content are in good agreement with previously published values (5, 6).

Table 1. Alkaloid content of *Tussilago farfara* (ppm on a dry weight basis)

Sample	Senkirkine	Senecionine	Total
Pre-blooming flowers	140	7	147
Young leaves	71	6	77
Mature whole plants	49	1	50

Senkirkine and senecionine are both easily extracted into hot water, and so are presumably ingested in teas prepared from the fresh plant. Based on our data, a cup of tea prepared from the maximum recommended dose of 10 g of pre-blooming flowers (2) may contain at most 0.07 mg senecionine and 1.4 mg senkirkine; tea from young leaves or mature plants contains significantly less. Given the known hepatotoxicity of senecionine (intravenous LD₅₀ 64 mg/kg in mice) (17), it can contribute only minimally to any health hazard attributable to the senkirkine content, which is itself minor (10). Furthermore, we observe considerable loss of both alkaloids upon prolonged storage of dried plant material – a fact which will further reduce any risk incurred in preparation of medicinal teas from this plant.

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Summary

The hepatotoxic pyrrolizidine alkaloid senecionine has been identified as a minor alkaloid of the carcinogenic, medicinal herb *Tussilago farfara* L. (coltsfoot). Levels of both senkirkine, the major alkaloid, and senecionine have been determined for pre-blooming flowers, young leaves, and mature plants. The senecionine content contributes only minimally to any health hazard associated with the plant.

Zusammenfassung

Eine Nebenkomponente der krebserregenden Medizinalpflanze *Tussilago farfara* L. (Huflattich) wurde als das hepatotoxische Pyrrolizidin-Alkaloid Senecionin identifiziert. Der Gehalt an Senkirkin, Hauptalkaloid von *T. farfara*, und Senecionin wurde in Knospen, jungen Blättern und ausgewachsenen Pflanzen bestimmt. Senecionin trägt nur minimal zu den gesundheitsschädlichen Eigenschaften der Pflanze bei.

Résumé

La sénécionine, alcaloïde hépatotoxique de structure pyrrolizidinique, a été identifiée comme alcaloïde en traces dans la plante médicinale cancérigène *Tussilago farfara* L. (tussilage).

La concentration de ce composé ainsi que celle de l'alcaloïde principal, la senkirkine, ont été déterminées dans les fleurs en boutons, les jeunes feuilles et la plante adulte. La teneur en sénécionine ne contribue que de façon marginale à la toxicité de la plante.

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