REVIEW

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Medicinal plants containing pyrrolizidine alkaloids in the *New Kreuterbuch* by Leonhart Fuchs (1543)

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In mid-16th century, three scientific books have been edited, which have been a real sensation, each one in its own scientific field. The first one, published in Nürnberg by Nikolaus Kopernikus, named: "*De Revolutionibus Orbium Celestium Libri VI*" put the sun in the center of the universe, and takes the human being out of the middle of the world. The second one, published in Basel by Andreas Vesalius: "*De Humani Corporis Fabrica*", describes the anatomy of the human body and the third one, also published in Basel by Leonhart Fuchs, was named *"New Kreuterbuch"*. It shows woodcuts of the most important medicinal plants of its time along with botanical descriptions and therapeutic uses. This book emerged as one of the most influential botanical works of the 16th century and is still interesting. Here, we used it to investigate which medicinal plants of the Early Modern times contained pyrrolizidine alkaloids. In total, 15 species were identified.

1. Introduction

Leonhart Fuchs (Fig. 1) was born in 1501 near Nördlingen in Wemding as son of the mayor. After an excellent education at the Marienschule in Erfurt he studied medicine from 1519 onwards at the University of Ingolstadt, where he received his doctorate in medicine in 1524. After a medical career at different places, he was appointed as professor of medicine University of Tübingen in 1535, where he worked until his death in 1566. During this time he reformed the whole medical teaching business and taught medicine according to the original writings of Dioscorides, Galen and Hippokrates.

Fig. 1: Leonhart Fuchs

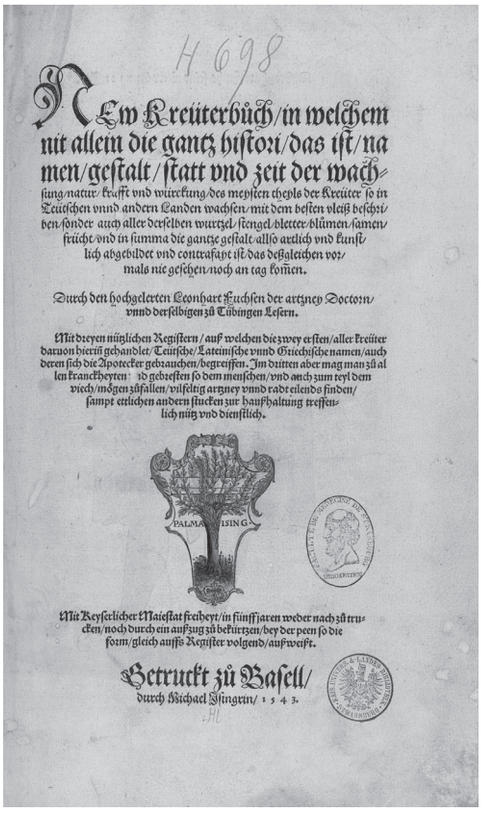


Fig. 2: New Kreuterbuch, coloured edition

Because of the exceptional importance of medicinal plants that time, he intensively studied the flora around Tübingen. He was the first teacher of an university who created a botanical garden at the university that still exists today, and he was also the first teacher of an university who regularly offered botanical field trips for students, so that they could get to know the native medicinal plants. He tried to find the medicinal plants which were mentioned by the Greeks, in the local flora. By correctly comparing plants from different locations he founded the basis of today´s botany as a science. By his knowledge of the described ancient plants he tried to find similarities to the native plants. He researched them and later on used them therapeutically.

In numerous scientific publications he described their botanical particularity, their medical effects and instructed artists to manufacture woodcuts (Heide 2001; Mayer-Nicolai and Mayer 2001).

The culmination of his activities were two books. In 1542 he published his first book of herbs in Latin language, a year later he published the second one in German language: *New Kreuterbuch* (Fig 2). This contains 509 plant monographs in total (Friedrich and Müller-Jahncke 2005). As more and more knowledge from America was transferred to Europe, also plant species from overseas were includes, e.g. corn, *Zea mais.* The plants described by him also formed the basis of his therapeutic activities. The woodcuts have a special scientific and also artistic quality (Friedrich and Müller-Jahncke 2005; Baumann 1998).

At his time, Leonhart Fuchs could not know that some of the plants he described could have highly toxic properties, as scientists of the 20th century eventually discovered. Numerous deaths in livestock and severe intoxications of the liver and lungs in humans were reason to look for the origin. It soon became apparent that alkaloids of a certain structure occurring in plants of some families were responsible for the toxic effects. According to their basic structure they were named as pyrrolizidine alkaloids.

2. Pyrrolizidine alkaloids in plants of the *Kreuterbuch*

The basic structures of these alkaloids are the 1-hydroxymethyl derivatives of bicyclic system called pyrrolizidine.

Substances containing the structure of the saturated necine belong to the non-toxic alkaloids, while those with a double bond in 1,2 position (Fig. 3) are toxic, the proposed mechanism of toxicity is shown in Fig. 4. The hydroxy groups are esterified with mono- or dicarboxylic acids. The plants are able to synthesize a large number of carboxylic acids in addition to necines, which is why such a large number of these alkaloids exists. If a necindiol is esterified with a dicarboxylic acid, 11- to 14-membered ring-shaped alkaloids can be formed. Biosynthesis takes place in the roots; meanwhile, more than 660 alkaloids are known**.**

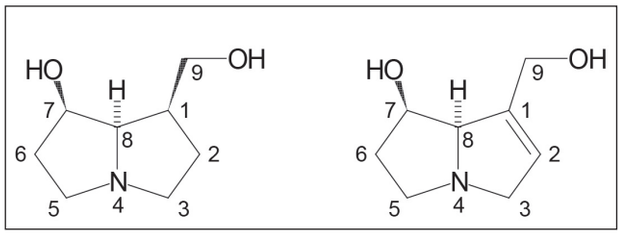


Fig. 3: Non toxic (left) and toxic pyrrolizidine alkaloids (right)

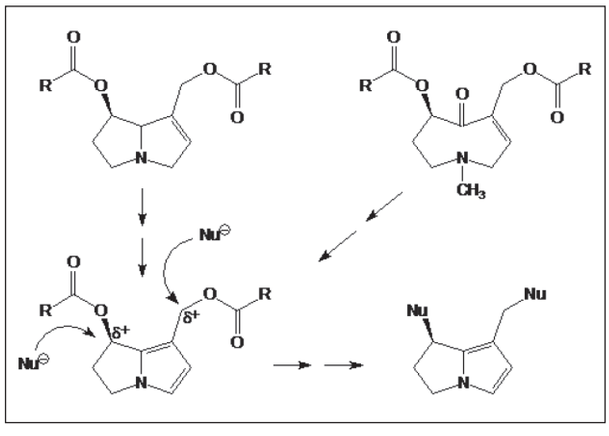


Fig. 4: Toxicity mechanism proposed for pyrrolizidine alkaloids

The following plants containing pyrrolizidine alkaloids are already described in the "*New Kreuterbuch*" by Leonhart Fuchs. Their structures are shown in Fig. 8.

Anchusa azurea Mille.H.C. syn. ***A. italica*** CXCIIII (194)*

Italienische Ochsenzunge, Große Ochsenzunge (Boraginaceae, Boraginoideae)

Occurence in Southern Europe, predominantly at the Mediterranean Sea in Southern France and Southern Switzerland. In former times used as a diuretic. Alkaloids are present, their structure is unknown (Al-Snafi 2014).

Anchusa officinalis L. CXCIII (193)*

Ochsenzunge (Boraginaceae, Boraginoideae)

Native in the Southern European area. Used against colds and skin diseases, as a vegetable, and as a colorant in cosmetics. It contains the intensively red colorant alkannine and the toxic alkaloids intermedine (**1**) and lycopsamine (**2**) (Al-Snafi 2014; Broch-Due et al. 1980).

Borago officinalis LXXVI (77, Fig. 5) *

Borretsch (Boraginaceae, Boraginoideae)

Native to the Mediterranean area, from there widespread throughout Europe. It was and also is used as a spice and as a medicinal plant. Medicinally used against heart problems, rheumatism, kidney inflammation, urinary retention, diarrhea and "blood purification". It contains the alkaloids intermedine (**1**), 7-acetylintermedine (**3**), lycopsamine (**2**), 7-acetyl-lycopsamine (**4**), supinin (**10**), amabiline (**11**) (Dodson 1986; Larson 1984; Lüthi 1983). These alkaloids are moderately toxic.

Cynoglossum officinale L. CLV (155)*

Hundszunge (Boraginaceae, Boraginoideae)

Widely used in Europe, medicinally used for wound healing. Contains the alkaloids echinatin (**11**), heliosupin (**12**) (Pedersen 1970, 1975a; Resch 1982).

Echium vulgare L**.** CCXXIX (229)*

Natternkopf (Boraginaceae, Boraginoideae)
Widespread in Europe, Caucasus, Turkey, Cyprus. In former times it has been used against snake bites, to-day it is recommended to treat urinary complaints, coughing and sweating. It contains echimidine (**5**), 3´-acetylechimidine (**6**) as main alkaloids in addition to numerous secondary alkaloids of low concentration (Boppré et al. 2005; El-Shazly et al. 1996).

Lithospermum officinale L**.** CCLXV (275)*

Echter Steinsame (Boraginaceae, Boraginoideae)
Widespread in Central Europe, West and Central Asia. The seeds were used against bile and urinary disorders, rheumatism and gout. It contains echinatine (**9**), heliosupine (**12**), 3- acetylheliosupine (**13**) (El-Shazly 1996; Krenn 1994; Resch 1982).

Lithospermum arvense L. syn. *Buglossoides arvensis* CCLXVI (276)*

Acker-Steinsame (Boraginaceae, Boraginoideae)
Widespread in the Mediterranean area, in Scandinavia and Germany. It has been used against rheumatism, gout, biliary and urinary stone diseases. It contains pyrrolizidine alkaloids of unknown structure.

Pulmonaria officinalis L. CCCLXIII (363)*

Lungenkraut (Boraginaceae, Boraginoideae)
It is very common in the deciduous forests of Europe. It has been used against cough, hoarseness and mucus. It contains the alkaloids intermedine (**1**), lycopsamine (**2**) , O7-acetyllycosamine (**4**), acetylintermedine (**3**), supinine (**8**), amabiline (**9**). These alkaloids are of medium concentration, some occur only in traces, they are relatively little toxic (Lüthy 1984).

Symphytum officinale L. CCCXCVII (397)*

Echter Beinwell (Boraginaceae, Boraginoideae)
The distribution area extends from Spain to Siberia and China. It has been naturalized in America since 1800. In former times it has been used and is still used against skin diseases and bone damage, bruises, ulcers, wounds and rheumatic symptoms. It contains the alkaloids intermedine (**1**), 7-acetylintermedine (**3**), lycopsamine (**2**), 7-acetyllycopsamine (**4**), symphytine (**7**) (Furuya et al. 1968; Brauchli et al. 1982).

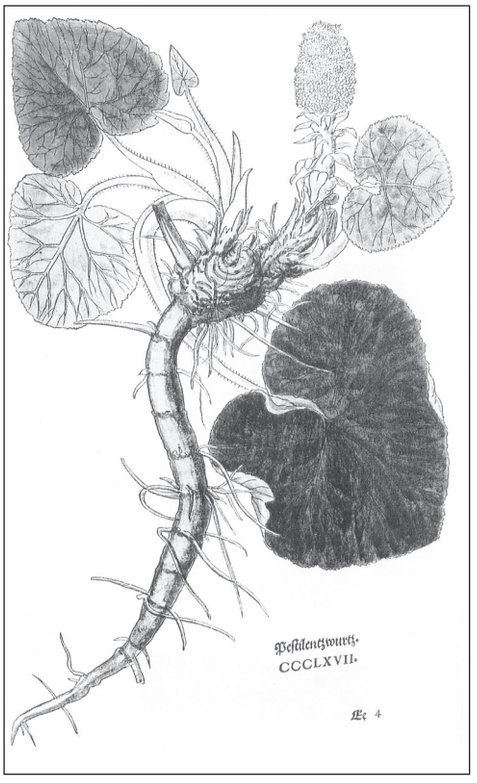
Eupatorium cannabinum L. CXLVII (147)*

Wasserdost (Asteraceae, Subtribus Eupatorieae)
Widespread in Europe, West Asia, North Africa. Effective against colds, cough, runny nose, flu, gout, rheumatism. It contains the alkaloids intermedine (**1**), lycopsamine (**2**), supinine (**8**), rinderine (**10**), echinatine (**11**) (Pedersen 1975b; Edgar et al. 1992; Hendriks et al. 1987). The alkaloids are of moderate toxicity but are contained in high concentration.

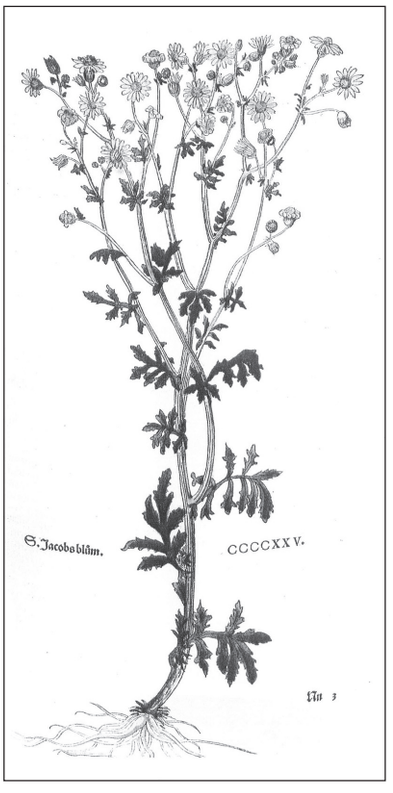
Pestwurz, Großer Huflattich (Asteraceae, Asteroideae)
Widespread over Europe. Has been used against stomach complaints, cough, bronchial catarrh, asthma. The following alkaloids have been found: integerrimine (**13**), senecionine (**14**), seneciphylline (**16**), senkirkine (**17**), and their N-oxides. These are very toxic alkaloids which are responsible for numerous intoxications of humans and animals (Lüthi et al. 1983; Sener et al. 1996; Wildi et al. 1998).

Senecio ovatus (Gärtn), syn. ***Senecio fuchsii*** C.C.Gmel. CCCCXVI (416)*

Fuchs-Greiskraut, Fuchs-Greiskraut, Heydnisch Wundtkraut (Asteraceae, Asteroideae)
Widespread over Europe. It has blood-quenching and antispasmodic effects, antidiabetic properties have been suggested. It contains the alkaloids senecionine (**14**) and the untoxic fuchsisenecionine (**22**) (Röder and Wiedenfeld 1977; Wiedenfeld and Röder 1979). Fuchsisenecionine is not toxic due to its structure, but because it is associated with the very toxic senecionine, the plant should not be used medicinally. The former name *Senecio ovatus* was changed to the botanical name *Senecio fuchsii in* honour to the author Leonhart Fuchs.



Petasites hybridus L**.** CCCXV (367, Fig. 6)*



Senecio jacobaea L. CCCCXXV (425, Fig. 7)*

Jacobs-Greiskraut (Asteraceae, Asteroideae).
It is widespread over Europe. It contains the alkaloids senecionine (**14**), seneciphylline (**16**), jacozine (**18**), jacobine (**19**), jacoline (**20**), jaconine (**21**). The plant is very toxic and many intoxications and deaths of humans and farm animals have been caused by this plant. (Bradbury et al. 1954; Lüthi et al. 1982; Resch et al. 1982; Segall et al. 1978; Macel et al. 2004).

Senecio vulgaris L. CLIX (159)*

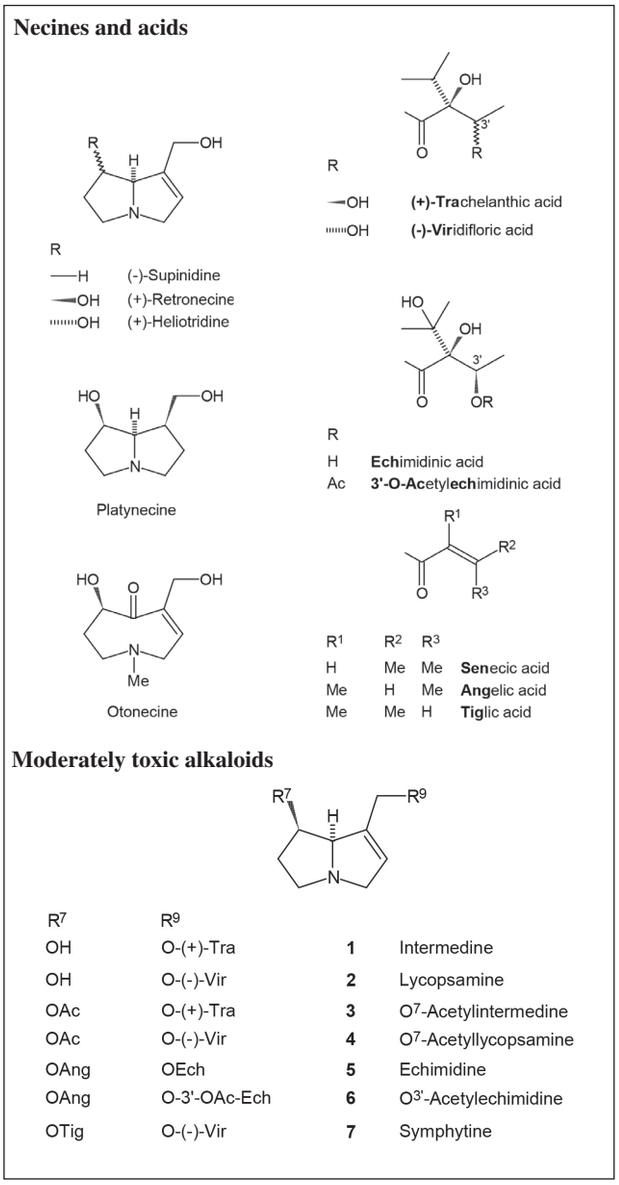
Gewöhnliches Greiskraut (Asteraceae, Asteroideae)
It is widespread in temperate climates in Europe and West Asia and also in Australia, Argentina, America and New Zealand. It contains the alkaloids senecivernine (**12**), senecionine (**14**), retrorsine (**15**), seneciphylline (**16**), and their N-oxide and senkirkine (**17**). *Senecio vulgaris* is as toxic as *S. jacobaea* (v. Borsel 1989; Flade 2019). Numerous intoxications of humans and animals are registered.

Tussilago farfara L…LXXVI (77)*

Huflattich (Asteraceae, Asteroideae)
It is widespread in Europe, Asia and Africa and has been naturalized in North America since two centuries. It contains the very toxic alkaloids senecionine (**14**) and senkirkine (**17**). (Culvenor et al. 1976; Rosberger et al. 1981; Lebada et al. 2000).

3. Discussion

At this point it should be noted that traces of lower and higher concentrations of pyrrolizidine alkaloids were found in many medicinal tea mixtures. The toxic plants are harvested as weeds together with the medicinal plants in the beds, where the latter have been cultivated (Dohrmann 2019). Although plants and plant extracts containing pyrrolizidine alkaloids may not be traded due to the Federal Office of Public Health, teas and products with those plants are still offered in the internet or in tea shops.
Even more dangerous are so-called "herbal – hikes" which are mostly guided by laypeople who encourage their clients to collect



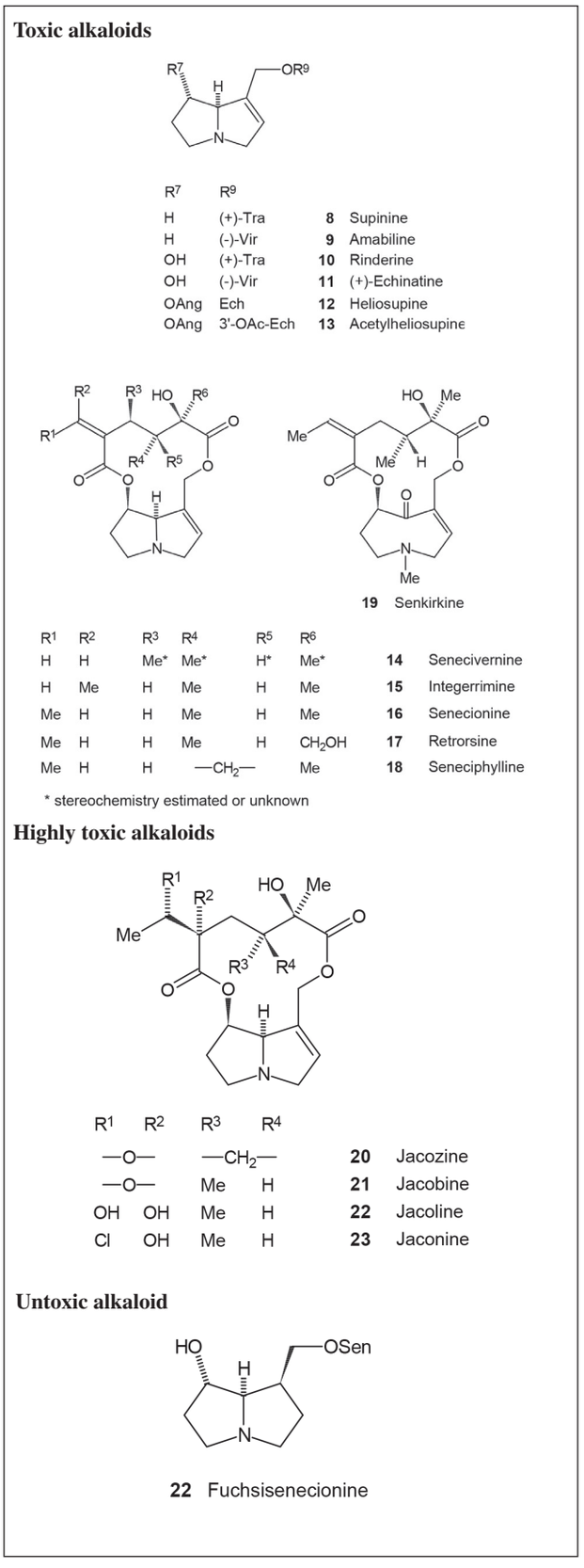


Fig. 8: Structures of PA contained in the Species described.

often unknown herbs and plants for dishes, juices or liqueurs. An urgent warning is needed here, as nowadays, we are able to prevent poisoning by PA-containing plants; Leonhart Fuchs in his time was, unfortunately, not.

*The Roman numbering from Fuchs was supplemented in parenthesis by to-days numerals.

Conflicts of interest: None declared.

References

Al-Snafi AE (2014) The pharmacology of *Anchusa italica* and *Anchusa strigosa*. A review.
Int J Pharm Pharm Sci 6: 4.

Baumann S (1998) Pflanzenabbildungen in alten Kräuterbüchern. Die Umbelliferen in der Herbarien- und Kräuterbuchliteratur der frühen Neuzeit. Heidelberger Schriften zur Pharmazie- und Naturwissenschaftsgeschichte, 15. Heidelberg 1998.

Boppré M, Colegate SM, Edgar JA (2005) Pyrrolizidine alkaloids of *Echium vulgare* honey found in pure pollen. J Agric Food Chem 53: 594–600.

v. Borstel K, Witte L, Hartmann T (1989) Pyrrolizidine alkaloid patterns in populations of *Senecio vulgaris, S. vernalis* and their hybrids. Phytochemistry 28: 1635–1638.

Brauchli J, Lüthy J, Zweifel U, Schlatter C (1982) Pyrrolizidine alkaloids from *Symphytum officinale* L. and their percutaneous absorption in rats. Experientia 38: 1085–1087.

Bradbury RB, Culvenor CCJ (1954) The alkaloids of *Senecio jacobaea* L. I. Isolation of the alkaloids and identification of jacodine as seneciphylline. Aust J Chem 7: 378–383.

Broch-Due, AJ, Aasen AA (1980) Alkaloids of *Anchusa officinalis* L. Identification of the pyrrolizidine alkaloid lycopsamine. Acta Chem Scand 34: 75–77.

Culvenor CJ, Edgar JA, Smith LW, Hirono I (1976) The occurrence of senkirkine in *Tussilago farfara* L. Aust J Chem 29: 229–230.

Dodson CD, Stermitz FR (1986) Pyrrolizidine alkaloids from *Borago officinalis* (seeds and flowers). J Natural Prod 49: 727–728.

Dohrmann A (2019) Bitterer Beigeschmack, PAs in Heilpflanzen, Öko-Test 2019 (12): 84–89.

Edgar JA, Lin HJ, Kumana CR, Ng MMT (1992) Pyrrolizidine alkaloid composition of three Chinese herbs, *Eupatorium cannabinum, E. japonicum* and *Crotalaria assamica.* Am J Chin Med 281: 281–288.

El-Shazly A, Sarg T, Ateya A, Abdel Aziz A, Witte L, Wink M (1996) Pyrrolizidine alkaloids of *Cynoglossum officinale* and *Cynoglossum amabile* (family Boraginaceae). Biochem Syst Ecol 24: 415–421.

Flade J, Beschow H, Wensch-Dorendorf M, Plescher A, Wätgen W (2019) Occurrence of nine pyrrolizidine alkaloids in *Senecio vulgaris* L. Plants 8: 54–66.

Friedrich C, Müller-Jahncke WD (2005) Schmitz – Geschichte der Pharmazie, vol. II, Eschborn, pp. 106–110.

Fu PP, Xia Q, Lin G, Chou MW (2004) Pyrrolizidine alkaloids – genotoxicity, metabolism, enzymes, metabolic activation, and mechanisms. Drug Metabol Rev 36: 1–55.

Furuya T, Araki K (1968) Studies on constituents of crude drugs. I. Alkaloids of *Symphytum officinale* Linn. Chem Pharm Bull 16: 2512–2516.

Heide L (2001) Das New Kreuterbuch als Grundlage der modernen Phytotherapie. Pharm Ztg 146: 3469–3476.

Hendriks H, Balraadjsing W, Bruins AP (1987) Investigation into the presence of pyrrolizidine alkaloids in *Eupatorium cannabinum* by means of positive and negative ion chemical ionization GC-MS. Planta Med 53: 456–461.

Krenn L, Wiedenfeld H, Röder E (1994) Pyrrolizidine alkaloids from *Lithospermum officinale*. Phytochemistry 37: 275–277.

Larson KM, Roby MR, Stermitz FR (1984) Unsaturated pyrrolizidine from Borage (*Borago officinalis*), a common garden herb. J Nat Prod 47: 747–748.

Lebada R, Schreier A, Scherz S, Resch C, Krenn L, Kopp B (2000) Quantitative analysis of the pyrrolizidine alkaloids senkirkine and senecionine in *Tussilago farfara* L. by Capillary Electrophoresis. Phytochem Anal 11: 366–369.

Lüthy J, Zweifel U, Schmid P, Schlatter C (1983) Pyrrolizidine alkaloids in Petasites *hybridus* and *P. albus*. Pharm Acta Helv 58: 98–100.

Lüthi J, Brauchli J, Zweifel U, Schmid P, Schlatter C (1984) Pyrrolizidin-alkaloide in Arzneipflanzen der Boraginaceen: *Borago officinalis* L. und *Pulmonaria officinalis* L. Pharm Acta Helv 59: 242–246.

Macel M, Vrieling K, Klinkhamer PGL (2004) Variation in pyrrolizidine alkaloid patterns of *Senecio jacobaea.* Phytochemistry 65: 865–873.

Mayer-Nicolai C, Mayer G (2001) Der Wissenschaftler Leonhart Fuchs. Philologe, Mediziner und Botaniker. Z Phytother 22: 294–300.

Pedersen E (1970) Minor pyrrolizidine alkaloids from *Cynoglossum officinale* L. Dansk Tidsskr Farm 44: 287–291.

Pedersen E (1975a) Pyrrolizidine alkaloids in Danish species of the family *Boraginaceae.* Arch Pharm Chem Sci Ed 3: 55–64.

Pedersen E (1975b) Echinatine and supinine: pyrrolizidine alkaloids from *Eupatorium cannabinum.* Phytochemistry 14: 2086–2087.

Resch JF, Meinwald J (1982) A revised structure for acetylheliosupine. Phytochemistry 21: 2430–2431.

Röder E, Wiedenfeld H (1977) Isolierung und Strukturaufklärung des Alkaloids Fuchsisenecionin aus *Senecio fuchsii.* Phytochemistry 16: 1462–1463.

Rosberger DF, Resch JF, Meinwald IF (1981) The occurrence of senecionine in *Tussilago farfara.* Mitt Gebiete Lebensm Hyg 72: 432–436

Segall HJ (1978) Pyrrolizidine alkaloids derived from *Senecio jacobaea.* Toxicol Lett 1: 279–284.

Sener B, Ergun F (1996) Pyrrolizidine alkaloids from *Petasites hybridus* (L) Gaertner. J Pharm Gazi 2: 171–173.

Wiedenfeld H, Röder E (1979) Das Pyrrolizidinalkaloid Senecionin aus *Senecio fuchsii.* Phytochemistry 18: 1083–1084.

Wildi E, Langer T, Schaffner W, Berger Büter K (1998) Quantitative analysis of petasin and pyrrolizidine alkaloids in leaves and rhizomes of in situ grown *Petasites hybridus* plants. Planta Med 64: 264–267.