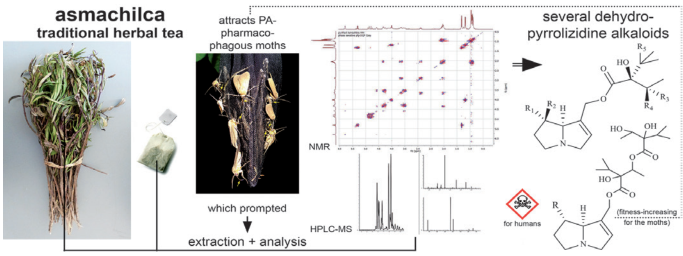
Asmachilca – an Andean herbal medicine with harmful but hidden side-effects *

Steven M. Colegate[1,2], Michael Boppré[3], Julio Monzón[3], Joseph M. Betz[4]

[1] USDA, Poisonous Plant Research Laboratory, Logan, UT, USA; [2] Department of Animal, Dairy & Veterinary Sciences, Utah State University, Logan, UT, USA;
[3] Chair of Forestzoology and Entomology, Albert-Ludwigs-Universität, Freiburg, Germany; [4] Office of Dietary Supplements, NIH, Bethesda, MD 20892, USA

Background

• Asmachilca is a Peruvian medicinal herb preparation ostensibly derived from *Aristeguietia gayana* (Wedd.) R.M. King & H. Rob. (Asteraceae: Eupatorieae). Decoctions of the plant have a reported bronchodilation effect that is purported to be useful in the treatment of respiratory allergies, the common cold and bronchial asthma.



Graphical abstract

• During field work in Peru, asmachilca was observed to attract pyrrolizidine alkaloid-pharmacophagous moths (cf. Boppré 2011). 1,2-Dehydropyrrolizidine alkaloids (dehydroPAs) are hepatotoxic, pneumotoxic and are genotoxic carcinogens. They can be rationally implicated in the etiology of chronically-developing disease in humans (Edgar et al. 2015).

• This study was undertaken to determine if commercial asmachilca samples, including fully processed herbal teas, contain potentially toxic dehydroPAs that may impact adversely on the health of consumers.

Methods

• Commercial samples of asmachilca plant material (Table 1) were examined morphologically and extracted for qualitative, quantitative and structural analysis using HPLC-esi(+)MS and MS/MS, high resolution MS, and 1D and 2D NMR experiments.

• As a preliminary indicator of possible human exposure, hot water infusions of commercial asmachilca herbal tea bags were also analyzed for the presence of dehydroPAs.

Sample	Description	Source
I	powdered plant material, not labelled	Paraguay, via German internet vendor
II	~ 60 g crushed plant material in a cellophane bag, labeled "Pulmonaria"	Peru, Lima market
III	~ 60 g crushed plant material in a cellophane bag, labelled "Asmachilca (*Eupatorium gayanum* wedd.)" [sic]	
IV	Herbal tea bags, 1.5 g labelled "Infusion Asmachilca"	
V	Bundle of freshly cut plant material (stems with leaves), called "asmachilca" by the vendor	
VI	Herbal tea bags, 1.2 g labelled "Asmachilca" (Eucalyptus, Asmachilca, Scorzonera, Borage, Cinnamon and Cloves)	Peru, via USA internet vendor

Table 1 Asmachilca-related samples investigated in this study. Names of suppliers are withheld intentionally.

Results

• Morphological evidence showed that the purchased asmachilca samples II and III, and sample V (Table 1) were sourced from at least two different plant species (Fig. 1).

• HPLC-esi(+)MS and MS/MS revealed a qualitative similarity of the asmachilca samples comprising two distinct suites of dehydroPAs including the major presence of the dehydroPA monoesters rinderine (**4**) and supinine (**6**) and their *N*-oxides (Figs 2, 3).

• Sample V did not contain supinine or its *N*-oxide. This is consistent with morphological distinctiveness and confirms that it is a different plant species.

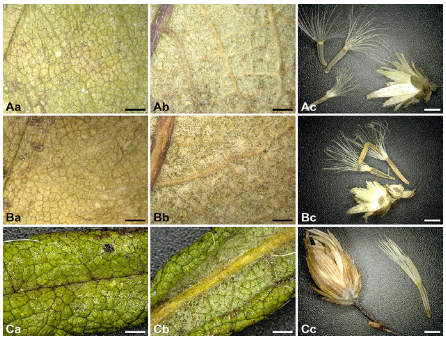


Fig. 1 Leaf surfaces (a upper, b lower), perianths and achenes (c) of: **A** Sample II; **B** Sample III; and **C** Sample V. Scale bars: a, b 1 mm, c 2 mm.

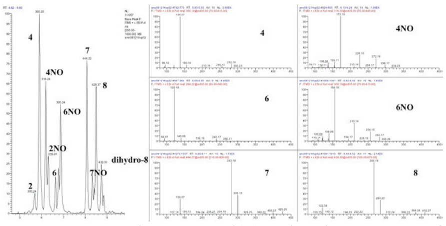
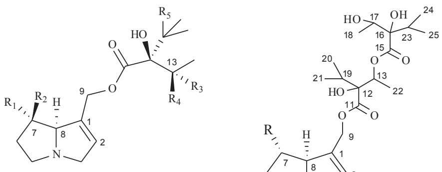


Fig. 2 Representative HPLC-esi(+)MS ion chromatogram of an extract of asmachilca material. Also shown are examples of MS/MS profiles used for dehydroPA identification. See Fig. 3 for structure numbers.



R1 = R4 = R5 = H; R2 = R3 = OH: lycopsamine (**1**)
R1 = R3 = R5 = H; R2 = R4 = OH: intermedine (**2**)
R2 = R4 = R5 = H; R1 = R3 = OH: echinatine (**3**)
R2 = R3 = R5 = H; R1 = R4 = OH: rinderine (**4**)
As above with R3 or R4 = $OCOCH_3$: 13-O-acetyl lycopsamine/intermedine/rinderine/echinatine (**5**)
R1 = R2 = R3 = R5 = H; R4 = OH: supinine (**6**)
R = OH: asmachilcadine (**7**)
R = H: asmachilcadinine (**8**)

Fig. 3 Structures of dehydropyrrolizidine alkaloids identified in extracts of asmachilca plant material and in asmachilca-derived tisanes.

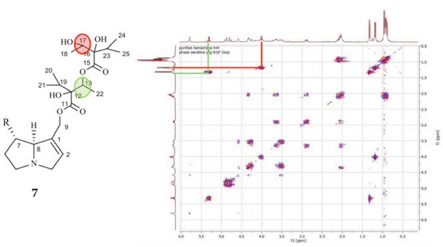


Fig. 4 1D 1H and 13C, and 2D COSY, HSQC and HMBC NMR structure elucidation. For example: 2D COSY spectrum of asmachilcadine (**7**) showing two distinct CH_3CH--O entities.

• Two major, previously undescribed alkaloids, asmachilcadine (**7**) and asmachilcadinine (**8**), were isolated and identified as dehydroPA monoesters with two ‚head-to-tail‘-linked viridifloric and/or trachelanthic acids (Figs 3, 4).

• The concentrations of dehydroPAs in asmachilca plant material (Table 2) were assessed as lycopsamine-equivalents of methanol extracts using HPLC-esi(+)MS.

• Mean pyrrolizidine alkaloid content of a hot water infusion of a commercial asmachilca herbal tea bag was 2.2 ± 0.5 mg (Table 2).

Estimated total PA and PA-*N*-oxide	Sample #					
	I	II	III	IV	V	VI
content (w/dw)	0.7 %	0.9 %	0.4 %	0.4 %	N/A	0.16 %
content/cup (hot water infusion)	N/A					2.2 mg

Table 2 PA content of asmachilca-related investigated samples.

Conclusions

• The pharmacophagous moths proved to be a reliable bioindicator of the presence of toxic 1,2-dehydropyrrolizidine alkaloids.

• Asmachilca preparations lack standardization, and recipes for utilization of the plant vary.

• Exposures to high doses of dehydroPAs are known to cause diagnostic hepatic sinusoidal obstruction syndrome (hepatic veno-occlusive disease) while diseases such as cirrhosis, pulmonary arterial hypertension and various cancers associated with chronic low level exposures are generally not apparent without epidemiological studies (Edgar et al. 2015).

• The unequivocal determination of potentially toxic dehydroPAs in dried and fresh plant material sold as asmachilca, and in Asmachilca herbal teas indicates a potential health risk to consumers.

• Tisanes made using asmachilca expose consumers to amounts of dehydroPA in excess of existing regulations and/or recommendations in various countries (e.g., 0.1 µg/day (Germany); 0.007 µg/kg BW/day (UK); 0.1 µg/kg BW/day (Netherlands); and 1 µg/kg BW/day (Australia/New Zealand) (EMA 2014).

Future research needs

• Plant species used to prepare asmachilca need to be unambiguously identified and complete phytochemical characterization needs to identify beneficial bioactives (if any).

• Asmachilca use patterns and epidemiological studies needed to determine risks and benefits.

References

Boppré M (2011) The ecological context of pyrrolizidine alkaloids in food, feed and forage: an overview. Food Addit Contam A 28:260–281

* Colegate SM, Boppré M, Monzón J, Betz JM (2015) Pro-toxic pyrrolizidine alkaloids in the traditional Andean herbal medicine „asmachilca“. J Ethnopharmacol 172:197–194

Edgar JA, Molyneux RJ, Colegate SM (2015) Pyrrolizidine alkaloids: potential role in the etiology of cancers, pulmonary hypertension, congenital anomalies, and liver disease. Chem Res Toxicol 28:4–20

EMA (European Medicines Agency) (2014) Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs). http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2014/12/WC500179559.pdf