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Original Paper
A botanical census on pyrrolizidine alkaloid-producing species in Brazilian herbaria: data set for a potential health risk indication

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Abstract
This study accessed the informational potential of herbaria collections as a tool for establishing an indication of the distribution of species that produce pyrrolizidine alkaloids (PAs), which are considered natural toxins, in Brazil. A total of 55,480 registered exsiccates were recorded, comprising species belonging to 17 genera, including *Ipomoea* (33.2%) (Convolvulaceae), *Crotalaria* (23.8%) (Fabaceae), *Eupatorium* (16.4%), *Senecio* (13.4%), *Erechtites* (3.97%) (Asteraceae) and *Pleurothallis* (8.28%) (Orchidaceae). These records were more densely distributed in the herbaria of the southeastern (30%), southern (28%) and northeastern (24%) Brazilian states. PAs are toxic to animals in general and display high potential for contamination of human food-production chains. A qualitative relationship was evidenced when carrying out a simultaneous compilation of cases of livestock intoxicated by the ingestion of these species, evidencing risks associated with PA-contaminated foodstuffs such as cereals, meats, milks and honey. The botanical census carried out herein is aimed at supporting a prospective study on the health risk presented by PA-producing species while bringing about indicators for their distribution in Brazil. This previously unpublished approach highlights the value of multidisciplinary information incorporated into herbaria botanical collections, with possible impacts on public health.
Key words: Asteraceae, botanical census, *Crotalaria*, *Ipomoea*, pyrrolizidine alkaloids.

Resumo
Este estudo utilizou o potencial informacional das coleções dos herbários como base para estabelecer indicativos da distribuição, no Brasil, de espécies produtoras de alcaloides pirrolizidínicos (APs), que são considerados toxinas naturais. Foram detectadas 55.480 exsicatas registradas abrangendo espécies de 17 gêneros, entre os quais destacaram-se *Ipomoea* (33,2%) (Convolvulaceae), *Crolataria* (23,8%) (Fabaceae), *Eupatorium* (16,4%), *Senecio* (13,4%), *Erechtites* (3,97%) (Asteraceae) e *Pleurothallis* (8,28%) (Orchidaceae). As maiores densidades de registros foram encontradas em herbários dos estados do Sudeste (30%), Sul (28%) e Nordeste (24%). Os APs são tóxicos para animais em geral e possuem alto potencial de inserção nas cadeias produtivas de alimentos-base dos humanos. Uma relação qualitativa foi evidenciada na compilação simultânea de casos de intoxicação de diversos animais de criação pela ingestão destas espécies, deixando evidente o risco da contaminação por APs de alimentos diversos, como cereais, carnes, leites e mel. O censo botânico realizado visou alicerçar um estudo prospectivo sobre o potencial de risco sanitário representado pelas espécies com APs, pela inferência da distribuição delas no território nacional. Esta abordagem inédita ressalta valor das informações multidisciplinares incorporadas nas coleções botânicas dos herbários, com possível impacto na saúde pública.
Palavras-chave: Asteraceae, censo botânico, *Crotalaria*, *Ipomoea*, alcaloides pirrolizidínicos.

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Introduction

From the taxonomic documentation developed by European botanists from the seventeenth and nineteenth centuries, a period of eager interest regarding knowledge of the flora of new lands, herbaria gradually began to assume regional and even local importance, not only for the documentation of flora collections but also for corroborating the variability, or even the scarcity, of plant species by recording their distribution (Hicks & Hicks 1978; Resende & Guimarães 2007). By serving as a documentation center for plant categories (Peixoto & Maia 2013), as well as their characteristics and distribution areas, materials deposited in herbaria were used mainly for future comparative studies, both historical and documentary, on certain flora (Resende & Guimarães 2007; Silva 2013).

However, the 'herbarium' concept has broadened in recent times, coupled with the evolution of academic activities that now extend scientific attention to broader and multidisciplinary focuses such as plant biodiversity maintenance and efforts to implement sustainability principles (Agbogidi & Aghojare 2014), while the use of tools for the digitization of exsiccate collections and specimen records has also increased. This has contributed to the swift modernization of herbaria by modifying curatorial management and herbarium management (Peixoto & Morim 2003), greatly facilitating researcher access to collections (Costa *et al.* 2016; Willis *et al.* 2017).

The scientific boundaries of information now compiled in herbaria surpass records concerning only the floristic richness of a certain territory and its intrinsic botanical value to taxonomy, systematics and ecology, as well as research and teaching. The scenario outlined by modern scientific demands and the greater and more swift availability of information organized in herbaria have highlighted and strengthened the importance of official herbaria collections. These collections, and their incorporated information, began to subsidize the development of activities in increasingly multidisciplinary areas, with six main points, summarized in 1985 by S. A. Mori and collaborators (1985). The unfolding and peculiarities of these functions, as well as the incorporation of additional characteristics, were later systematized for the Smithsonian Institute by V. Funk, who compiled a list of 32 activities supporting various scientific and academic interests, in order to demonstrate herbaria importance (Funk 2003).

Thus, botanical knowledge added to herbaria collections has increasingly subsidized a number of different studies, as illustrated by approaches that include (i) indirectly prospecting regions potentially rich in specific minerals (inferred by soil which species displaying accumulation characteristics inhabit) (Brooks *et al.* 1977); (ii) recognizing and valuing the correct identification of species as important for forest management plans (Procópio & Secco 2008); (iii) clarifying taxonomic positions among species based on their potential to accumulate specific metals (Fernando *et al.* 2009); (iv) inferring hypotheses concerning evolutionary, ecological and conservation research using taxonomic control variables (Franz *et al.* 2016); (v) introducing new floristic analysis methods that reflect the conservation value of protected areas (Wieringa & Sosef 2011); (vi) relating floristic diversity to specific local fauna behaviors (Machado & Oliveira 2015); (vii) exploring herbaria collection potential in expanding phenological research (Willis *et al.* 2017); (viii) formulating evolutionary developmental biology hypotheses from morphometric studies (Chen *et al.* 2018); and (ix) establishing standards to relate taxonomic diversity to niche climatic conditions (Schneider *et al.* 2018), among others.

Technological research aimed at developing new products based on plant diversity is also supported by herbaria collections (Hung 2014), since the success of projects concerned with the transformation of plant diversity requires botanical origin certification and the seal of an official herbarium (Peixoto & Morim 2003; Peixoto *et al.* 2009), including sample georeferences (Siani 2003). In the research and development of phytopharmaceutical products, for example, the preservation of medicinal plants long used by traditional communities at specific locations is extremely important. In this regard, herbaria are a primary or complementary source for ethnomedical information (Fabricant & Farnsworth 2001), playing a crucial role in plant identification and authentication. Herbaria collections will help guarantee support for the correspondence between plant origin and characteristics as well as chemical and pharmacological properties established during pharmaceutical development (Ahmed & Hasan 2016).

In a similar context, the present study aimed to use the informational potential of herbaria collections as a basis for inferring the distribution of pyrrolizidine alkaloid (PA)-producing species in Brazil. PAs are nitrogenated substances known as "natural pesticides" (González-Coloma *et al.* 2002) that are present in approximately 3% of higher plants. Their main function is to act as anti-feeding compounds to halt herbivore predation (Reina *et al.* 1998; Siciliano *et al.* 2005), a property that also leads them to be sequestered by certain classes of insects in order to incorporate them into their own defensive arsenals (Hartmann *et al.* 1999; Trigo 2000). Currently, approximately 650 PAs have been identified from 6,000 plants (Stegelmeier *et al.* 2009; Ruan *et al.* 2012), mainly within the Asteraceae, Apocynaceae, Boraginaceae, Fabaceae and Orchidaceae families (Boppre 2011).

The degree of toxicity of these plants is closely related to the molecular configurations of the PAs they contain. Depending on their chemical structure, the PAs may be highly reactive towards some vital mammal proteins and DNA (Prakash *et al.* 1999). Hepatic veno-occlusive disease (VOD), hepato-splenomegaly and emaciation have been observed in chronic human PA poisoning. Mutagenicity of some PAs (monocrotaline, lasiocarpine and heliotrine) have already been demonstrated. Riddelliine and structurally related PAs are likely to be carcinogenic and cytotoxic substances (Prakash *et al.* 1999). The International Agency for Research on Cancer (IARC) has classified lasiocarpine, monocrotaline and riddelliine as possibly carcinogenic to humans (group 2B) and hydroxysenkirkine, isatidine, jacobine, retrorsine, seneciphylline, senkirkine and symphytine as not classifiable as to its carcinogenicity to humans (Group 3) (IARC-WHO 1976, 2002).

On the other hand, many plants containing these substances possess a high potential for being inserted into the production chains of basic foodstuffs. Therefore, the deleterious effects of PAs can reach humans by indirect contamination of products of animal origin.

The Codex Alimentarius, or "Food Code", in spite of having a defined quality standard for some foodstuffs, such as honey (Codex Alimentarius 2001), makes simply general statements with regard to residues and contaminants in this matrix (Codex Alimentarius 2012, 2014). No maximum levels for the naturally occurring toxicants PAs in food commodities have been recommended by the Joint FAO / WHO Expert Committee on Food Additives (JECFA), since tolerable daily intake (TDI) values could not be defined (JECFA 2009, 2015). Due to the genotoxic properties, the JECFA deemed that it was not possible to derive a health-based guidance value (e.g. TDI) and decided to use the $BMDL_{10}$ (lower 95% confidence limit on the benchmark dose for a 10% response) of 182 µg/kg body weight (bw) per day for riddelliine as the start point for estimating margins of exposure (MOEs). MOEs were calculated for exposure to 1,2-unsaturated PAs and their N-oxides from consumption of honey or tea or duplicate diets for children and adults, separately, using a range from the lowest lower-bound mean or high-percentile dietary exposure to the highest upper-bound mean or high-percentile dietary exposures. Mean and high-percentile dietary exposures, including lower-bound and upper-bound estimates, across population groups (adults and children) and individual foodstuffs (honey and tea) ranged from 0.01 to 130 ng/kg bw per day at the mean and from 5 to 260 ng/kg bw per day at the high percentile (JECFA 2017)

The European Community, through the European Food Safety Agency (EFSA) has also not established maximum levels for PAs in honey but estimated a TDI of 7 ng/kg bw per day (considering 50 kg bw), employing the MOE framework. The benchmark dose giving 10% response (BMD_{10}) of 120 µg/kg bw per day for lasiocarpine, for male rats, for the development of hemangiosarcoma in liver (the key finding in cancer studies) was used as the start point on the dose-response curve for the MOE estimation for exposure to PAs from consumption of herbal medicinal products (EMA 2016). In Brazil, Regulation RDC No 26, on 13 May 2014, lays down minimal requirements for phytomedicines (ANVISA 2014).

As it turned out, when it comes to PAs, it is clear that a specific legislation is still incipient worldwide. To date in Brazil, there are no general recommendations on risk management, except for RDC No 26/2014, besides official monitoring data.

This study aims to carry out herbaria-based research on mapping the occurrence of PA-producing plants in Brazil. Organizing data on plants containing these alkaloids constitutes the first step in guiding future health surveillance actions, which may include monitoring for the presence of these substances in diverse foodstuffs.

Material and Methods

To evaluate the distribution of PA-producing plants in Brazil, all botanical genera (or as many as possible) known to produce these alkaloids were compiled. This information was first searched in the RIKILT database. The RIKILT Institute is part of Wageningen University & Research, Netherlands, that carries out independent research into the safety and reliability of food. One of its main tasks is measuring and detecting substances in food that may have negative effects on humans and animals (WUR 2019). The RIKILT is populated with data obtained from the European Food Safety compendium of botanic genera and species, complemented with information from several other sources. A working group of experts sponsored by the EFSA Scientific Cooperation (ESCO), in order to report plants that contain toxic, addictive, psychotropic or other substances of health concern, prepares this compendium of botanicals (EFSA 2009; WUR 2019).

When the query was performed by genus, the database also returned the following information: (i) botanical family name, (ii) main classes of plant toxins present, (iii) individual components of the toxins, whenever they are previously known, (iv) species in which the toxins are present, (v) which parts of the plant contain the toxins, and (vi) the main toxic effects of the toxins.

The search by secondary metabolite class resulted in the listing of genera currently known to produce PAs at the global level. It should be noted that all database entries are properly referenced in the query itself, complementary to the botanical genera provided by RIKILT.

Once the PA-producing genera were listed, information was searched regarding the occurrence and distribution of the listed genera in Brazil. The Virtual Reflora Herbarium of the Reflora/CNPq Program at the Rio de Janeiro Botanical Garden (BFG 2020) and the Virtual Flora and Fungi Herbarium of the National Institute of Science and Technology (INCT) databases were consulted (INCT, 2017). In the case of the JBRJ, searches were based on exsiccates of specimens deposited throughout Brazil, resulting in diverse botanical information (including taxonomy) and allowing for collecting useful statistics on the geographical distribution of confirmed occurrences, such as the genera distribution by state and region. Recently, this source of information has been properly used to correlate botanical entries with geographic locales. Moreover, the INCT database is built to converge virtual data from multiple herbaria in the country. Genera consultations at the INCT Virtual Herbarium led to equally fruitful information, including exsiccate locations in herbaria. The INCT Virtual Herbarium allows for multiple genera to be queried at once. Thus, PA-producing genera were individually obtained from both herbaria. At the INCT herbarium, a search for all genera was carried out simultaneously to design the total plant distribution throughout Brazilian regions and states.

Once the most representative genera were established using their record (voucher) distribution, the five most frequent species were selected. Descriptions of toxicological events occurring in Brazil related to species belonging to the most representative genera were also obtained from the literature.

Results and Discussion

Three steps constituted the method used to assemble the data for analysis. The first step included the search in RIKILT database with the aim of establishing the AP-producing genera that occur throughout the world. The RIKILT database for plant toxins contains over 700 plant species and associated toxins.

The following step involved recognition of the genera, among those extracted from RIKILT, that occur in Brazil by checking both the Flora do Brasil and INCT databases. The final step involved using the gathered information to build Table 1. At this point, it is relevant to note that there may exist divergences between Flora do Brasil and INCT. Nevertheless, this fact has not affected the scope of the present proposition. Data were extracted from both databases and used as they were displayed, with no interferences from the authors.

Specifically, searching the INCT provided bulky data regarding genera representation and the quantitative outspread to the species records. It is quite plausible that most of this set of massive botanical data is identified with sufficient fidelity at the genus level to meet our statistical purposes. For this reason, we decided to opt for this more abundant source of data, and to consider the registers of possible PA-producing species, to more properly fit our goal of building a general risk panorama of potential toxic plants.

Thus, a quantitative scenario based on the species available from searching the INCT was built for each selected genus in the Brazilian states (Tab. 2). It is important to note that this methodology does not allow conclusions about the territorial species distribution – either by geographic coordinate or phytogeography – but rather quantifies the exsiccate records in herbaria throughout the country.

Table 1 – Geographic distribution of pyrrolizidine alkaloid-producing genera according to the RIKILT database: crossing data with registers in Flora do Brasil and INCT databases

Family[1]	Genus[1]	Species containing PAs[2]	Pyrrolizidine Alkaloid	Flora do Brasil - Genders (entries)	INCT (entries)
Asteraceae Bercht. & J.Presl	*Adenostyles* Cass.	All	Not listed	No	No
	Brachyglottis J.R.Forst. & G.Forst.	All	Senecionine	No	No
	Cineraria L.	All	Senecionine, Integerrimine, Seneciphylline, Jacobine, Jacoline, Jaconine	No	SP, RS, MT
	Erechtites L.	All	Senecionine, Seneciphylline	All states, except AP, MA, PI RO, RR, TO	All states
	Eupatorium L.	All	Supinine, Riderine	MG, GO, SC, SP	All states, except AP
	Leucanthemum Miller	*L. vulgare*	Platiphylline e Senecionine	No	ES, MG, RJ, RS, SP
	Petasites	All	Senecionine	No	SP
	Senecio L.	All	Senecionine, Riddeliine	South, Southeast, BA, GO, MS	South, Southeast, Midwest, BA, CE, PA, PB, PE, TO
	Tussilago L.	All	Senkirkine, Tussilagine, Isotussilagine	No	No
Boraginaceae Juss.	*Alkanna* Tausch	*A. tictoria*	Lycopsamine	No	No
	Anchusa L.	All	Lycopsamine, laburnine e acetyllaburnine, nontoxic PA	No	RS, SP, PE, PA
	Borago L.	All	Not listed	No	DF, MG, PE, RS, SC, SP
	Cynoglossum L.	All	Not listed	No	Sul, MG, SP
	Echium L.	All	Echimidine	No	Sul, ES, MG, MT, SP
	Heliotropium L.	All	Heliotrine, Cinoglossine, Indicine	All states, except RO	All states
	Lithospermum L.	All	Litosenine, Intermedine, Lycopsamine	No	No
	Pulmonaria L.	All	Not listed	No	RS
	Symphytum L.	All	Lycopsamine, Intermedine, Symphytine, Echimidine	No	Sul, BA, DF, GO, MG, MS, PB, PE, PI, RJ, SE, SP, TO
	Trichodesma R.Br.	*T. icanum*	Trichodesmine	No	No
Convolvulaceae Juss.	*Ipomoea* L.	All	Ipangulines	All states	All states
Fabaceae Lindl.	*CrotalariaI* L.	All	Monocrotaline	All states, except RN	All states, except MA, PI, TO
Orchidaceae A.Juss.	*Pleurothallis* R.Br.	Not listed	Not listed	AM, BA, AP, CE, MA, MG, PA, PE, RJ, RR, SC	SC
	Phalaenopsis lume	Not listed	Not listed	No	South, BA, MG, RJ, SP

[1] Discrepancies between data retrieved from both Brazilian databases are discussed in the text.

In addition to the bias inherent to the data collection, the approaches that support Table 1 and Table 2 data were also susceptible to other method limitations. The main limitation is regarding possible distortions of and inconsistencies in taxonomy and botanical aspects that would be directly transposed to our quantitative survey with no chance to be verified. Data retrieved from INCT were inserted in Table 2 and Table 3 the same way that they were generated in the search. In this sense, any possible lack in accuracy in correlating the frequency of the exsiccate records to geographical origin would be overcome by the huge amount of data generated thereof.

The amount of plant deposits varies in each state, with higher densities coinciding with areas with higher concentrations of universities and research institutes. Higher concentrations of plant deposit records were observed in southern and southeastern Brazil. This fact reflects a differentiated effort to collect samples in the states comprised in those regions (Forzza *et al.* 2016). The variable intensity of the collected records is also directly related to the number of scientific projects involving floristic surveys either executed or currently in progress throughout Brazilian states and regions. Furthermore, it is not possible to rule out the fact that a smaller number of exsiccates might have been recorded regarding collections in fields that are difficult to access. The lowest number of records was observed in the north (closed forest predominance) and central west (large flooded areas) areas. Another source of bias can occur when the voucher is sent to different states or even regions than where the material was collected. However, it is expected that this is greatly minimized because the current practice is that botanical activity remains associated with a local institution until voucher deposit - even if duplicate materials are sent to other centers, as in the case of scientific collaborations or material exchange and donation between herbaria. In this case, duplicate exsiccates would be registered more than once, possibly involving surveys from different regions or states. However, this was assumed to be insignificant for the overall aim of this study. Finally, it is also assumed that errors are minimal in the identification of botanical genera recorded through exsiccates, justifying the inclusion of specimens still under determination (c.f.).

In summary, although several biases have been recognized within our methods, a primary but plausible conclusion could be established to bring to the fore the risks of plants with PA throughout the country.

In the initial evaluation, 23 PA-producing genera belonging to five botanical families were identified from the results of the RIKILT. The geographical distribution of their records in Brazil was delineated by crossing the data with those resulting from the Flora do Brasil and INCT search. (Tab. 2).

In total, 55,480 exsiccates were found. The frequency of deposits throughout Brazilian states is variable, as displayed in Figure 1, where the distribution of total PA-producing species records is represented by color density. The number of records ranged from a minimum of 132 to a maximum of 8,126 records.

Overall, the results indicate that all Brazilian regions contain pyrrolizidine alkaloid-producing species, especially the South, Southeast and Northeast, where similar amounts of deposits were recorded (between 24% and 30% of the total). Based on the compiled specimens, the total distribution of exsiccate registers in each Brazilian state is presented in Table 1, where the predominance of records for six PA-producing genera is observed: *Ipomoea* (18,430) (Convolvulaceae) > *Crotalaria* (13,212) (Fabaceae) > *Eupatorium* (9,099) > *Senecio* (7,415) (Asteraceae) > *Pleurothallis* (4,595) (Orchidaceae) > *Erechtites* (2,202) (Asteraceae). *Symphytum* (167) and *Echium* (154) (Boraginaceae) are the most noteworthy genera

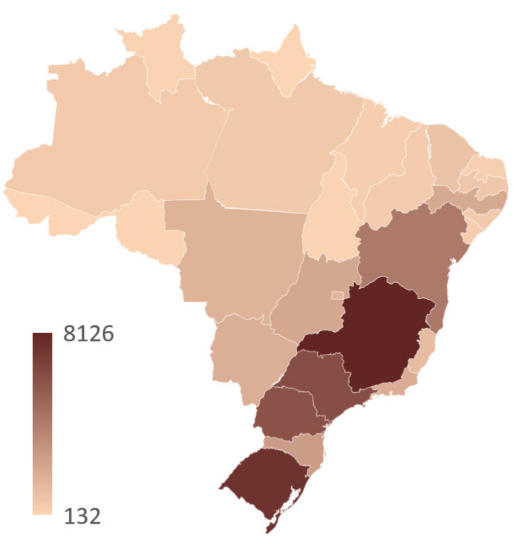

Figure 1 – Distribution density of botanical records corresponding to the pyrrolizidine alkaloids producing species in the Brazilian states

Table 2 – Total exsiccates of pyrrolizidine alkaloid-producing genera in Brazil compiled from the INCT database

Regions and states	***Ipomoea***	***Crotalaria***	***Eupatorium***	***Senecio***	***Pleurothallis***	***Erechtites***	***Symphytum***	***Echium***	***Cynoglossum***	***Borago***	***Leucanthemum***	***Anchusa***	***Phalaenopsis***	***Lithospermum***	***Cineraria***	***Petasites***	***Pulmonaria***	***Tussilago***	***Total***
North	1184	493	225	1	203	118	5	0	0	0	0	0	0	0	0	0	0	0	2229
TO	125	79	22	1	0	11	2	0	0	0	0	0	0	0	0	0	0	0	240
RR	66	130	22	0	22	1	0	0	0	0	0	0	0	0	0	0	0	0	241
RO	116	23	20	0	10	7	0	0	0	0	0	0	0	0	0	0	0	0	176
PA	434	128	51	0	28	42	0	0	0	0	0	0	0	0	0	0	0	0	683
AP	77	26	10	0	21	4	0	0	0	0	0	0	0	0	0	0	0	0	138
AM	307	76	86	0	103	45	2	0	0	0	0	0	0	0	0	0	0	0	619
AC	59	31	14	0	19	8	1	0	0	0	0	0	0	0	0	0	0	0	132
Northeast	6417	3068	463	50	327	323	15	0	1	2	1	1	2	0	0	0	0	0	10670
SE	276	118	23	0	2	19	2	0	0	0	0	0	0	0	0	0	0	0	440
RN	303	97	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	432
PI	283	219	54	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	558
PE	1368	591	71	5	38	38	3	0	0	1	1	0	1	0	0	0	0	0	2117
PB	477	247	43	6	21	17	2	0	0	0	0	1	0	0	0	0	0	0	814
MA	280	148	11	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	444
CE	685	212	18	1	22	19	2	0	0	0	0	0	0	0	0	0	0	0	959
BA	2366	1232	197	38	227	198	5	0	0	1	0	0	1	0	0	0	0	0	4265
AL	379	204	14	0	17	26	0	0	1	0	0	0	0	0	0	0	0	0	641
Midwest	3176	2414	1059	252	127	305	13	4	3	2	1	1	0	0	1	0	0	0	7358
MT	671	361	437	80	66	64	3	4	3	1	1	1	0	0	1	0	0	0	1693
MS	839	606	246	89	5	59	3	0	0	0	0	0	0	0	0	0	0	0	1847
GO	903	837	321	52	22	94	5	0	0	0	0	0	0	0	0	0	0	0	2234
DF	763	610	55	31	34	88	2	0	0	1	0	0	0	0	0	0	0	0	1584
Southeast	3903	5051	3220	2303	2154	773	54	6	28	31	6	9	1	0	1	3	2	1	17546
SP	1312	2285	922	757	615	301	31	0	20	10	2	9	0	0	1	1	1	0	6267
RJ	385	366	426	284	354	104	4	1	1	0	1	0	0	0	0	0	0	0	1926
MG	1886	2260	1834	1181	560	346	19	4	7	21	3	0	1	0	0	2	1	1	8126
ES	320	140	38	81	625	22	0	1	0	0	0	0	0	0	0	0	0	0	1227
South	3396	1916	3827	4613	1497	657	80	135	47	10	32	1	1	4	1	0	0	0	16217
SC	563	387	447	929	220	132	13	12	5	1	0	0	0	0	0	0	0	0	2709
RS	1280	615	2652	2237	199	326	36	103	4	2	30	1	0	4	1	0	0	0	7490
PR	1553	914	728	1447	1078	199	31	20	38	7	2	0	1	0	0	0	0	0	6018
Total	18076	12942	8794	7219	4308	2176	167	145	79	45	40	12	4	4	3	3	2	1	54020

among those presenting the lowest number of registered exsiccates. Considering the relative amount of species and exsiccates for the six most representative genera, graphs grouping states by region were constructed (Fig. 2).

Within the entire territory of the nation, the genus most frequently found in search results among the 17 was *Ipomoea*, represented by 33.2% of the total deposited specimens, followed by *Crotalaria* (23.8%), *Eupatorium* (16.4%), *Senecio*, (4%), *Pleurothallis* (8.28%) and *Erechtites* (3.97%). The greatest genera variation was observed for the South and Southeast regions and states. *Ipomoea* records also prevail in most Brazilian states when considered individually and, therefore, in the figures consolidated by region (Fig. 2).

Taking into account only the six most frequent genera, the number of registered *Ipomoea* specimens ranged from 45.0% to 65.9% of total occurrences in the northern states, except for Roraima, where it was superseded by Crotalaria, at 53.9%. *Ipomoea* was also listed most frequently in all northeastern states, where the recorded specimen occurrences ranged between 50.8% (Piauí) and 71.6% (Ceará). *Crotalaria* records occupy the second most abundant position in most northern and northeastern region states, rivalling *Eupatorium* which presented minimum and maximum records of specimens in northern states (7.5% in PA to 13.9% in AM). Additionally, in the northern region, the records of *Pleurothallis* were greater than or similar to *Eupatorium* in three states (9% to 16% in AC, AM, AP, RR), while in the Northeast, these two genera presented quantitative values below 10% in all states.

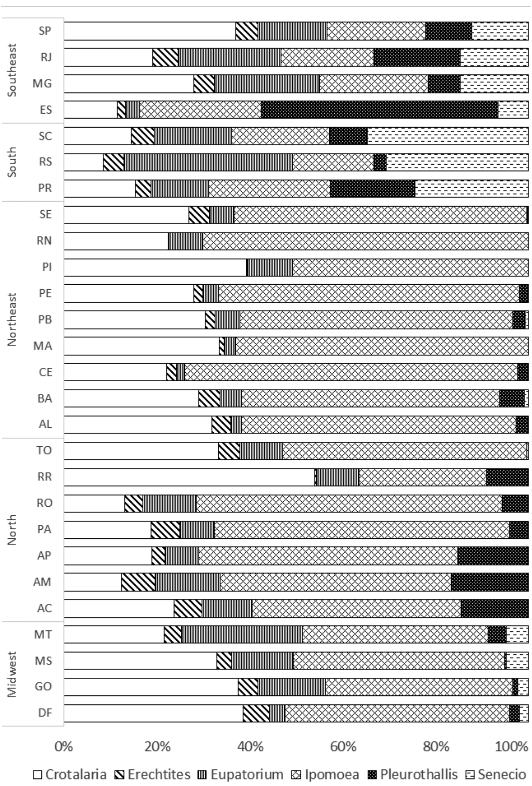

Figure 2 – Relative distributions of records of the six main genera of PA- producers in the states of Brazil

In the Central-West region, the same *Ipomoea* relation persists (40.0%-48.3%), higher than *Crotalaria* (21.5%-38.6%), with a certain relevance attributed to *Eupatorium* genus records in Goiás (14, 4%) and Mato Grosso do Sul (13.3%). A more heterogeneous distribution of genera records is observed in southeastern and southern states. Minas Gerais and São Paulo display the same relative trend: *Crotalaria* (23.4%-36.9%)> *Ipomoea* (21.2%-23.4%) > *Eupatorium* (14.9%-22.7%) > *Senecio* (12.2%-14.6%) > *Pleurothallis* (9.9%). In Rio de Janeiro, these five genera are relatively represented, with the lowest variations in the region (14.8%-22.2%), highlighting the relevance of *Pleurothallis*, at 18.4%, in addition to minor records for *Erechtites* (5.5%) surpassing the three other states. *Pleurothallis* noteworthiness is even more pronounced in Espírito Santo, where it surpasses all other genera, comprising 51.0% of the records, followed by *Ipomoea* (26.1%). Floristic surveys on Orchidaceae species in the Espírito Santo restingas probably contributed to this increase (de Fraga & Peixoto 2004).

In the southern states, the records of *Ipomoea* and *Senecio* lead the census in Paraná, comprising 26.2% and 24.9% of the total records, respectively, followed by *Pleurothallis* (18.7%), *Crotalaria* (15.4%) and *Eupatorium* (12.3%). The two leading genera switched positions in Santa Catarina and Rio Grande do Sul rankings. In the latter, an unprecedented first place was observed for *Eupatorium* records, accounting for 36.3% of the total records, followed by *Senecio* (30.6%) and *Ipomoea* (17.5%). In this case, it is interesting to note the lowest frequency of *Crotalaria* (8.4%) among all Brazilian states.

The five main species with the highest record occurrence within each of the six main genera are presented in Table 3.

Most exsiccates belonging to the *Eupatorium* and *Pleurothallis* genera still lack identification and show a clear concentration of identified species records in the South and Southeast.

The records for the genus *Ipomoea* also contained large numbers of unidentified deposits of plant samples; however, these deposits were always less abundant than the identified samples. For instance, there is a clear predominance of *I. cairica* in the South, while *I. asarifolia* and *I. bahiensis* records are relatively more abundant in the Northeast upon excluding the unidentified registers. The same is true for *I. cairica* in the Southeast, *I. asarifolia* in the North and *I. nil* in the Midwest.

Table 3 – The five most abundant records of species from the main pyrrolizidine alkaloid-producing genera found by searching the INCT database.

	Brazilian geographic region						
Genera[1]	**North**	**Northeast**	**Midwest**	**Southeast**	**South**	**Without Defined Origin**	**Total**
Ipomoea	279	2393	567	956	814	45	5054
Ipomoea sp.	131	807	391	510	260	29	2128
Ipomoea cairica	2	34	37	302	429	13	817
Ipomoea asarifolia	95	681	26	5	2	1	810
Ipomoea nil	16	332	95	134	123	1	701
Ipomoea bahiensis	35	539	18	5	0	1	598
Crotalaria	263	1762	853	1896	755	66	5595
Crotalaria sp.	72	581	359	653	212	21	1898
Crotalaria micans	63	76	241	523	233	13	1149
Crotalaria pallida	74	251	86	395	195	13	1014
Crotalaria incana	20	250	144	252	103	13	782
Crotalaria retusa	34	604	23	73	12	6	752
Eupatorium	59	184	286	1192	955	56	2732
Eupatorium sp.	43	171	177	772	515	33	1711
Eupatorium laevigatum	2	3	26	89	166	9	295
Eupatorium bupleurifolium	0	0	2	31	240	2	275
Eupatorium squalidum	14	9	76	141	13	6	259
Eupatorium vauthierianum	0	1	5	159	21	6	192
Senecio	0	17	58	995	1895	40	3005
Senecio brasiliensis	0	0	12	547	876	18	1453
Senecio sp.	0	17	41	246	308	8	620
Senecio oleosus	0	0	0	106	283	1	390
Senecio icoglossus	0	0	5	94	176	12	287
Senecio crassiflorus	0	0	0	2	252	1	255
Pleurothallis	58	124	32	573	542	86	1415
Pleurothallis sp.	51	115	26	402	165	50	809
Pleurothallis grobyi	7	6	2	81	103	23	222
Pleurothallis sonderana	0	1	3	20	134	9	167
Pleurothallis hygrophila	0	0	1	17	88	3	109
Pleurothallis saundersiana	0	2	0	53	52	1	108
Erechtites	118	320	304	764	653	20	2179
Erechtites hieraciifolius	113	213	233	344	242	8	1153
Erechtites valerianifolius	0	85	42	352	380	11	870
Erechtites sp.	5	21	12	49	27	1	115
Erechtites ignobilis	0	1	6	16	4	0	27
Erechtites goyazensis	0	0	11	3	0	0	14
Total	777	4800	2100	6376	5614	313	19980

[1]Data are displayed according to the way they emerge from searching the INCT database. Considerations on taxonomic discrepancies are commented on in the text, as exemplified by the *Eupatorium* case, in which 83 synonyms were considered distinct species by INCT.

This same scenario holds for *Crotalaria*, where a slight majority of identified species were collected from the Brazilian Northeast, and *C. retusa* was the most abundant, followed by equal amounts of *C. pallida* and *C. incana*. Excluding undetermined exsiccates, *C. micans* prevails in the South, Southeast and Midwest, which also present relatively significant amounts of records for the species listed in Table 3. The North presents the lowest number of *Crotalaria* records, with a balance between all species considered herein.

The *Senecio* genus comprises the overwhelming number of records in the South and Southeast, with a high predominance of *S. brasiliensis* but also with significant representatives of the other species listed in Table 3 (always below the number of undetermined records). The number of records for species belonging to this genus is very low in the rest of the country.

An opposite trend is observed for the *Erechtites* genus, in which most of the identified specimens originate from the South and Southeast, with *E. hieracifolia* largely predominant among all cases of exsiccates having the binomial identified.

It is known that PA production in plants is conditioned to occur based on plant phenotypes and seasonal influences, among other ecological factors (Trigo 2000). Despite this fact, the set of surveyed data allow us to conclude that a ubiquitous, if not dense, distribution of PA-producing species is observed in Brazil. This feature implies the existence of a generalized primary source of contamination by these alkaloids. Therefore, PA-producing plants exhibit high potential for being present in the productive food chains in the country by progressively contaminating food matrices such as honey (contamination carried by bees), meat, milk and eggs (animal consumption), and grain (harvesting and storage) (Stewart & Steenkamp 2001), without ruling out certain direct routes into foods, such as medicinal teas, spices and vegetables.

Studies on the contamination of the production chain of products using honey or pollen as ingredients have shown that PAs could be found in significant amounts in the products derived thereof (KEMPF *et al.* 2010; KEMPF *et al.* 2011). In some cases, the presence of pyrrolizidine alkaloids jeopardizes the health of bee colonies (REINHARD *et al.* 2009). Publications that call attention to reduced exposure (subchronic toxicity) to pyrrolizidine alkaloids that may permeate the production chain through livestock and other animal products are also found (EDGAR *et al.* 2011; KEMPF *et al.* 2011; MOLYNEUX *et al.* 2011).

Additionally, relevant information on these potential contamination events comes from the many veterinary reports that describe spontaneous intoxications of various types of farm animals. On the same hand, many *in vivo* toxicological experiments over the decades have corroborated the deleterious effects of these alkaloids on animal health since they were first observed (Pammel 1903). Circumscribing the observations to the six most common PA-producing genera detected by this census, animal intoxication is obviously related to PA presence in the spontaneous menu of grazing animals. This varies seasonally, with a relative increase in the availability of harmful species in times of drought, when the animals tolerate the poor palatability of some *Asteraceae* and *Boraginaceae* species, as they are among the most resilient species in the environment (Gazziero *et al.* 2006; Brighenti 2010). Although under specific conditions, due to the wide variety and phenological aspects, the species comprising in the genera evaluated herein - particularly *Asteraceae* - fall into the category of invasive or weedy plants, infesting pasture and ruderal environments in general.

The pantropical genus *Crotalaria* L. (family Fabaceae), comprising 600 species, is the only member of the Crotalarieae (Benth.) Hutch. tribe native to Brazil. Forty-two *Crotalaria* species occurring throughout Brazil are accepted by the Flora do Brasil database. Few phytogeographic studies on the ubiquity of the genus in the country are available (Flores & Miotto 2005). Because they belongs to the Leguminosae (Faboideae) family and display nitrogen fixation capacity, *Crotalaria* species have traditionally been used as forage in many countries (Mkiwa *et al.* 1990; Sarwatt *et al.* 1990; Arias *et al.* 2003; Mosjidis 2006), a fact that caught attention in Brazil as early as the middle of the last century, for agronomic and livestock reasons (Vandoni 1952). The production of PAs toxic to animals by species belonging to this genus has been reported since the end of the XIX century (Pammel 2017) and has directed the selection of innocuous species for exploration for the abovementioned purposes (Mosjidis & Wang 2011). For economic purposes, the present agronomic trend has suggested the domestication of certain species (even those with an exotic origin) that are, in theory, free of PAs. More recently, *Crotalaria* species have also been used in ‘green fertilization' (Rotar & Joy 1983; Agrolink 2018), displaying good results in the recovery of poor soils in Brazil (Teodoro *et al.* 2011).

Throughout investigations on the usefulness of *Crotalaria* species in agriculture, toxicity measures associated with these species have also been carried out. Even before PA chemical structures were fully clarified, experiments were performed to confirm field observations (Pammel 2017) in studies that were soon reproduced in Brazil (Vandoni 1952; Torres 1954), associated with the beginning of the modernization of livestock in the country, from the middle of the XX century (Teixeira & Hespanhol 2014). In Brazil, the effects of *Crotalaria* species ingestion, accompanied by experimental studies, have been continuously documented for cattle (Boghossian *et al.* 2007; Queiroz *et al.* 2013), sheep (Nobre *et al.* 2004; Sanchez *et al.* 2013; Borelli *et al.* 2016), pigs (Ubiali *et al.* 2011), goats (Maia *et al.* 2013), and horses (Nobre *et al.* 2004). Poultry intoxication by seed ingestion is also common (Hatayde *et al.* 1997).

The genus *Senecio* L. is included among the eight genera belonging to the Senecioneae Cass. tribe (family Asteraceae, subfamily Asteroideae) occurring in Brazil, with 60 accepted species occurring in the country (BFG 2018). Exact species number varies between 67 and 85, according to earlier authors (Matzenbacher 2009). *Senecio* species, native all over the world and widely distributed, are recognized for their high potential to invade diverse agricultural crops (Ernst 1998; Leiss & Müller-Schärer 2001).

In recent years, scientific attention to the toxic potential of *Senecio* species has intensified given the growing concern of cattle ranchers due to ingestion of the plants by herds. There is now an urgency to effectively control these pasture weeds, which pose a real risk to the rural economy (Brighenti *et al.* 2017). Livestock deaths by *Senecio* species have also been described in Brazil since the mid-XX century (Vandoni 1952; Nazário *et al.* 1988). This phenomenon is particularly seen in traditional livestock areas containing beef cattle and dairy herds (Basile *et al.* 2004; Cruz *et al.* 2010; Lucena *et al.* 2010), sheep (Ilha *et al.* 2001; Giaretta *et al.* 2014), buffalo (Corrêa *et al.* 2008) and horses (Gava & Barros 1997; Panziera *et al.* 2017a), in the latter case also reaching border countries (Micheloud *et al.* 2017). The deleterious effects of *Senecio* species ingestion have been proven via experimental intoxications conducted on calves (Panziera *et al.* 2017b), horses (Pilati & Barros 2007) and broilers (Biffi 2017). *Senecio* intoxication is estimated to account for half of all herd animal deaths that result from some type of poisoning (Damé 2009).

The genus *Eupatorium* L. (Asteraceae, Eupatorieae Cass.) is currently recognized as being represented in Brazil by the single species *Eupatorium adamantinum*, although 83 synonyms have been recognized over its main distribution in the southeastern region and part of the midwestern region (BFG 2018). Most *Eupatorium* species are perennial and highly harmful to crops in general (Agrolink, 2018). Being invasive, with a strong ruderal character, plants of these species spread in large urban agglomerations (Albuquerque 1980; de Souza & Poletto 2007; Biondi & Pedrosa-Macedo 2008).

Much of the inferences regarding *Senecio* species toxicity can be transposed to *Eupatorium* species because they belong to the same family and share similar habitats (These *et al.* 2013). However, a much lower number of reports regarding animal intoxication from foraging species belonging to this genus are available, even though cattle (Camarão *et al.* 1990; Lucioli *et al.* 2007) and other ruminants are known to ingest members of this genus, both in Brazil and in contiguous countries (Riet-Correa & Medeiros 2001; Rymer 2008).

Ipomoea L. is the largest genus in the Convolvulaceae family (Simão-Bianchini & Pirani 2005), comprising between 600 and 700 species, with a distribution concentrated in tropical and subtropical regions (Meira *et al.* 2012). In Brazil, 149 species of this genus occur, according to the Flora do Brasil database. It is an important genus for humans due to its tuberous feeding roots ('potatoes') and the aesthetic value of its flowers, in addition to containing many species used in popular medicine (Ruchi *et al.* 2009; Sharma & Bachheti 2013). Comprising a wide morphological variety (Ferreira & Miotto 2011), many species belonging to this genus also have high invasive potential (Machado & Sazima 1987) and are considered weeds in various crops (Chame 2009; Garcia *et al.* 2011). The usefulness of some *Ipomoea* species in the recovery of degraded soils in the Caatinga Brazilian biome has been tested (Montefusco *et al.* 2011).

Ipomoea species produce several other types of biologically active alkaloids besides PAs. Therefore, intoxications reported by species belonging to this genus describe a mixture of symptoms, such as visible signs of neurotoxicity (Haraguchi *et al.* 2003; Ríos *et al.* 2012). Reports on sheep intoxication (Gardiner *et al.* 1965) reaching the fetus in the case of pregnant ewes (Armién *et al.* 2011) and suckling lambs and calves have been found (Neto *et al.* 2017). In Brazil, most of the reported intoxication cases refer to goats in the Northeast (Medeiros *et al.* 2003; Barbosa *et al.* 2006; Mendonça *et al.* 2011), with some experimental intoxication also tested in goats (Barbosa *et al.* 2007; Araújo *et al.* 2008; Chaves 2009). To a lesser extent, spontaneous and experimental intoxications have been described in cattle in the Mato Grosso Pantanal (Antoniassi *et al.* 2007) and buffaloes (Barbosa *et al.* 2005). In addition, many *Ipomoea* species are visited by bees in the Caatinga (Maia-Silva *et al.* 2012).

The genus *Erechtites* Raf. (Asteraceae) contains 5 accepted species (BFG 2018) occurring in almost all Brazilian states. Intoxications resulting from consumption of species belonging to this genus are summarized as a single case described for *E. hieracifolia* (containing 0.2% PAs), affecting a herd of 1-year-old cattle (Rivero *et al.* 2011).

Several *Pleurothallis* R.Br. (Orchidaceae) species are described as containing PAs (Borba *et al.* 2001), but no reported cases of mammal or bird intoxication are available. However, this genus comprises species visited by Hymenoptera pollinators, especially *Euglossini* bees (Borba *et al.* 2001; Czervinsk *et al.* 2007; Ospina-Torres *et al.* 2015). Twelve species in Brazil are encompassed by this genus (BFG 2018).

The panorama outlined by the distribution of PA-producing species in Brazil and cases reported in the literature concerning the intoxication of farm animals show the potential risk of contamination of several foodstuffs by these natural toxins. Although this issue is of increasing concern to health authorities in many parts of the world, there are still no fully established protocols to support the control of PAs as contaminants in food matrices. Depending on the country or region, this concern has a distinct relevance, ranging from direct consumption of *in natura* plants, such as teas and medicinal infusions (Andrade *et al.* 2002), common in many places worldwide (Bosi *et al.* 2013), to contamination of basic foods (Prakash *et al.* 1999), such as cereals, meat, milk, eggs (Boppre 2011; Sandini *et al.* 2013) and, mainly, honey (Prakash *et al.* 1999). The latter is considered to be the most susceptible food substrate to PA contamination, with apicultural products being the most likely source for exposure to PA contamination (Bandini & Spisso 2017). Accurate analyses of honey produced by bees that fed on *Echium, Eupatorium* and *Senecio* species (Crews *et al.* 1997; Kast *et al.* 2018) or more diversified sources - including pollens - have indicated the presence of PAs in most of the investigated samples (Dubecke *et al.* 2011; Valese *et al.* 2016; Letsyo *et al.* 2017).

In Brazil, the three largest honey-producing states in 2015 were Paraná, Rio Grande do Sul and Bahia (Bandini & Spisso 2017). The distribution of deposited exsiccates for the PA-producing genera in these Brazilian states is displayed in Figure 3.

In these three states, locations associated with plant collection are dispersed evenly throughout. A strong hypothesis is that it is unlikely for any apicultural region to be located away from

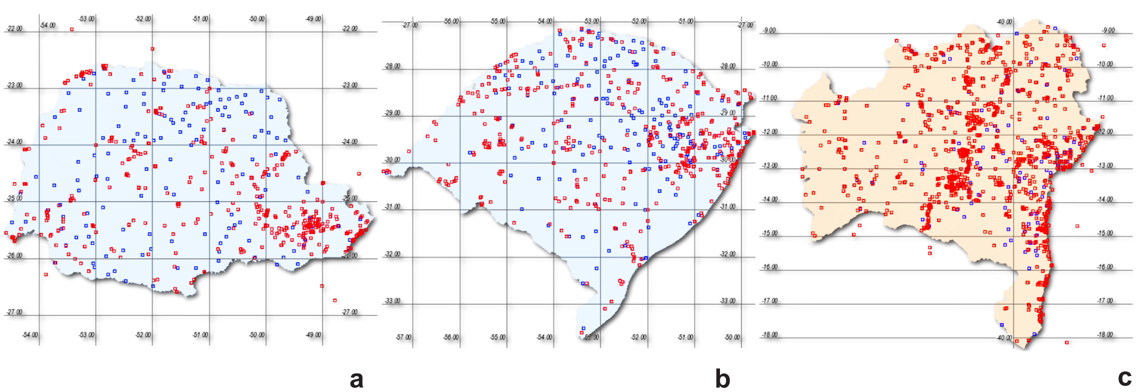

Figure 3 – a. Distribution of records of genera producing pyrrolizidine alkaloids in Paraná; b. Rio Grande do Sul; c. Bahia: red color indicates the precise coordinates of the plant collection, and blue color indicates the coordinates of the municipality where the species was collected. Source: INCT (2017)

vegetation containing PA-producing genera. This situation is similar for virtually the entire country, implying a high probability of alkaloid presence not only in honey but also in many other food matrices.

In general, the data presented herein suggest that the entire food production chain in the country is potentially exposed to PA contamination. Considering the toxic properties of these substances and the widespread occurrence of PA-producing genera potentially throughout Brazil, it is not difficult to infer how critical this situation may be. It is reasonable to assume that there is a potential risk of PA contamination in the food production chain that could lead to intoxications from cumulative underdoses or even severe acute cases. However, the direct ingestion of pyrrolizidine alkaloids could occur through the sporadic consumption of either crude plants or teas containing them (Bosi *et al.* 2013; Edgar *et al.* 2011).

At present, there is little information in Brazil about human and animal intoxications proven to be caused by the ingestion of plants containing pyrrolizidine alkaloids and contamination of food by the same substances. The absence of monitoring activities aggravates this situation because there is no historically accumulated data on the presence of these alkaloids in Brazilian foods.

Additionally, in a toxicological context, the data set compiled on the records of species that produce PAs in Brazil allows for the planning of subsequent research on the deleterious effects of PAs from Brazilian plant diversity as well as proposals regarding more incisive regulatory actions. This study demonstrates the usefulness of Brazilian herbaria for yet unexplored purposes, such as contributing to the construction of health surveillance parameters in a specific niche of basic products consumed by the population, thus seeking to solve a latent health problem not yet duly considered by authorities.

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