REVIEW

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# Pyrrolizidine alkaloids in plants used in the traditional medicine of Madagascar and the Mascarene islands

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**Dedicated to Prof. Dr. med. Dr. rer. nat. Drs. h.c. Ernst Mutschler on the occasion of his 80th birthday**

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Pyrrolizidine alkaloids (PAs) can be hazardous to the health of humans and animals. Although their toxicity has been known for a long time, PA containing plants are still in use in many traditional medicines. Traditional healing systems have become of increasing interest as many people believe that they can be used without any risk and side effects. This also applies to the traditional medicine of Madagascar and the Mascarene island (Mauritius, Réunion, Rodriguez). Recent literature reports have recommended this traditional medicine because of its good efficacy and pharmacological properties. However, several plants are listed there which have already been described to contain toxic PAs or are suspected of containing them.

## 1. Introduction

Pyrrolizidine alkaloids (PAs) are naturally occurring compounds which are contained in about 3% of all flowering plants (Bull et al. 1968). They can mainly be found in the plant families Asteraceae (tribes: Senecioneae, Eupatorieae), Boraginaceae and Fabaceae (tribe: Crotalarieae) and Apocynaceae (tribe: Apocynoideae). They can be hazardous to humans and domestic animals in case they possess a double-bond in position 1,2 in their basic bicyclic 5-membered ring system (necine) and a free position adjacent to the bridge nitrogen atom. They are ester alkaloids and can occur as monoesters, open chain diesters and macrocyclic diesters (Stegelmeier et al. 1999; Wiedenfeld et al. 2008, 2011).

In general, PAs show either no or low acute toxicity; but they can undergo a 3-step metabolic toxication process leading to alkylating agents. This process takes place in the human or animal liver and this organ is therefore the first target organ for the intoxication. PAs can show mutagenic, genotoxic, cancerogenic and fetotoxic potential (Fu et al. 2002, 2004, 2007; Xia et al. 2004, 2006; Fig. 1).

As there is usually quite a long time between the uptake of the toxic PAs and the outbreak of the typical PA intoxication (VOD = veno-occlusive disease), the correlation between the toxic agent and the resulting toxic effects is often not seen. This is even the reason why many typical PA containing plants are still used in traditional medicines by local healers for the treatment of several diseases.

It is of major interest to report such cases and make clear that the use of such plants may constitute a serious health risk. This is even important as plant medicine is becoming more and more popular also in Western countries as people tend to believe that plant products have no or less toxic side effects compared to synthetic substances. This is also reflected in the increasing popularity of ancient medicines (Ayurveda, TCM, etc.) that play a growing role in the treatment of diseases in the form of self-medication.

In addition, increased tourism has made it possible that people come into contact with different traditional healing systems all over the world inducing them to make use of those medicines under the wrong assumption that "natural healing" can be used without any risk. This applies also to the traditional medicines of Madagascar and the Mascarene islands (Mauritius, Réunion and Rodriguez). The extraordinary flora of those islands is rich in endemic plants, which has led to a highly specialized and specific traditional medicine. However, due to the reasons mentioned before, several plants are still in use in those countries though they are known to contain toxic PAs or - on account of their botanical relation and chemotaxonomical aspects - are likely to contain them.

This paper is to list the medicinal plants which are known to contain toxic PAs (and therefore show a toxic potential) and those which can be assumed to contain them. We advise to ban those plants from the traditional medicine or use them only with exactly defined restrictions.

## 2. Plants containing pyrrolizidine alkaloids

### *2.1. Asteraceae: Tribe Eupatorieae*

#### *2.1.1. Ageratum conyzoides L.*

This plant is growing in tropical America, India, China, Madagascar, Mauritius and Rodriguez. Vernacular name in Malagasy: ahimembo, ahiboay, fotsivoana.

Vernacular name in Mauritius: herbe de bouc, herbe babouc; chin. Name: sheng hong ji.; engl. name: bill goat, billigoat weed. It is also a medicinal plant in China (Roeder 2000).

Internal use: A decoction is taken against amoebic dysentery, diarrhoea, flatulence, indigestion and haematurea.

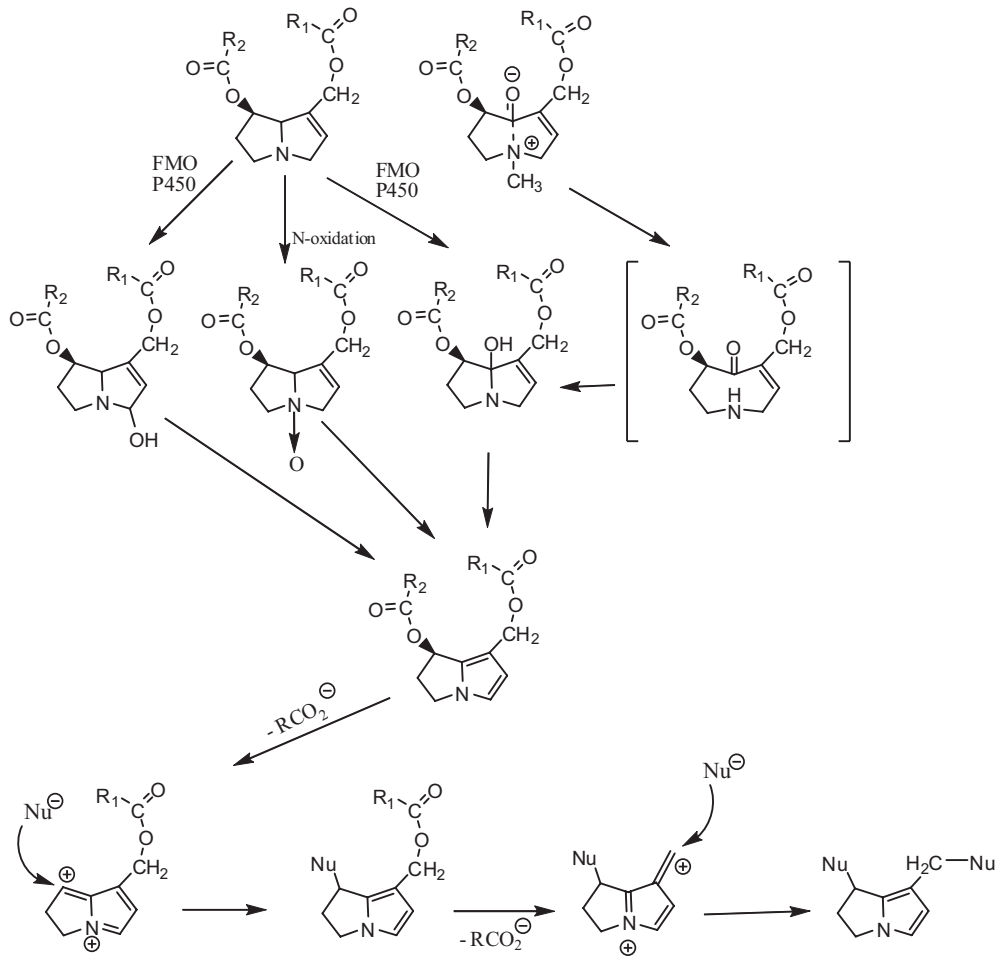



Fig. 1: Metabolic toxication process of PAs

A decoction from the leaves mixed with those of *Ayapana triplinervis* is used in case of flatulences, itches, boils. It cures diarrhoea, amoebic dysentery, indigestion, and haematurea. External use: against skin infections and abscesses. (Pernet et al. 1957; Sussman 1980; Beaujard 1988; Fakim 1990; Gurib-Fakim et al. 1993, 1994, 1995, 1996, 1997, 2004a; Novy 1997)

### *2.1.2. Ageratum riparium Regel*

Growing only in Rodrigues. Vernacular name: orthosiphon. Internal use: A decoction of four leaves is taken to treat cardiac palpitation (Gurib-Fakim et al. 1994, 1996).

Since the toxic PAs lycopsamine (**14**) and echinatine (**16**) have been found in *A. conyzoides* as well as lycopsamine (**14**), retrohoustine (**26**), heliohoustine (**27**), isoretrohoustine (**28**) in *A. houstonianum* (Wiedenfeld et al. 1990, 2001), *Ageratum* species should not be used on account of the alkaloid content and the hepatotoxic effects.

### *2.1.3. Eupatorium flexuosum Lam. (syn. Senecio flexuosus (Lam) Less., syn. Faujasiopsis flexuosa (Lam.) Baker, C. Jeffrey subspec. bourbonensis, syn. Faujasia flexuosa (Lam.) Benth. & Hook., syn. Cacalia flexuosa Wahl, syn. S. pollicaris DC (Cordemoy))*

Endemic plant in Mauritius, Reunion and Rodrigues Island. Vernacular name: bois cassant.
Internal use: leaf decoction against diabetes and dysentery. The plant is also used in cases of respiratory ailments, also against asthma, catarrh, pleurisy, and as a diuretic.

### *2.1.4. Eupatorium riparium Regel (syn. Ageratina riparia (Regel) R.M. King & H. Rob.)*

Coming from Mexico, West Indies, growing in Mauritius, Reunion and Rodrigues. Vernacular name: ortosiphon, faux ortosiphon, herbe Maurice, herbe la tension**,** engl. name: mistflower, greeping crofton weed.
Internal use: A decoction of leaves is taken to treat cardiac palpations, asthma, and gastritis, (Forgacs et al. 1981; Adsersen et al. 1997; Fakim 1990; Gurib-Fakim et al. 1994, 1995, 1996, 2004a; Fortin et al. 2002).

### *2.1.5. Eupatorium triplinerve Vahl. (syn. E. ayapana Vent., syn. Ayapana triplinervis (Vahl) R.M. King & H. Rob.)*

Coming from Brasil, in Mauritius, Réunion and Rodrigues. Vernacular name: ayapanah, apanah.
Internal use: Leaf infusion is used for burning sensations in the stomach, indigestion, diarrhoea, insomnia, nausea, ulcers and vomiting. Plant juice is also used as an adstringent and an emollient. The whole plant cures flu, fever, colds, pneumonia. (Sussman 1980; Fakim 1990; Gurib-Fakim et al. 1993, 1994, 1996, 1997, 2004a; Jelager et al. 1998; Jonville et al. 2008).

(Sussman 1980; Adsersen et al. 1997; Jelager et al. 1998; Gurib-Fakim et al. 1992, 1995, 1997, 2004a, 2005; Fortin et al. 2002; Poullain et al. 2004; Mahomoodally et al. 2010; Narod et al. 2004a).
The plant contains alkaloids with unknown structures (Vera et al 1990), probably PAs.

*E. triplinerve* Vahl contains alkaloids with unknown structures (Gurib-Fakim et al. 2004a, 2005). It can be assumed that these compounds are PAs.
*E. cannabinum* L. contains the alkaloids viridiflorine (**1**), cynaustraline (**2**)**,** supinine (**6**), intermedine (**8**), amabiline (**13**), lycopsamine (**14**)**,** echinatine (**16**) (Pedersen 1975a, 1975b; Edgar et al. 1992; Hendriks et al 1987). Most of the alkaloids are toxic. The use of *Eupatorium* species is not recommended until a possible hazardous risk is excluded.

### *2.2. Asteraceae: Tribe Senecioneae*

#### *2.2.1. Crassocephalum rubens (Jacq.) S. Moore*

Growing in Madagascar, vernacular name: anandrambo. (Beaujard 1988). Medical use: for relaxation of the childbirth. Related with *C. crepidioides* (Benth.) S. Moore. The plant contains the toxic alkaloids jacobine (**40**) and jacoline (**41**) (Asada et al. 1985).
Internal use is not recommended.

#### *2.2.2. Emilia amplexicaulis Baker*

Growing in Madagascar. Medical use: against condylomes (Pernet et al. 1957).

#### *2.2.3. Emilia citrina DC*

Growing in Madagascar, vernacular name: tsiontsio. Medical use: against scabies and syphilis (Pernet et al. 1957; Beaujard 1988).

#### *2.2.4. Emilia graminea DC*

Growing in Madagascar. Medical use: against scabies, syphilis (Pernet et al. 1957).

#### *2.2.5. Emilia sonchifolia (L.) D.C. ex Wight (syn. E. sinica Miq., syn. Senecio sonchifolius (L.) Moench, syn. Crassocephalum sonchifolium (L.), syn. Cacalia sonchifolia L. Less.)*

Common in tropical areas of India, Taiwan and China, naturalized in Mauritius and Reunion. This plant is a medicinal plant in China (Roeder 2000). Chinese name: Yang ti cao, Yi dian hong, I thien hung. Engl. name: purple emilia, purple sowthistle. Internal use: The leaves cure asthma, dysentery, influenza, colds, injuries, febrifuge, is diuretic and sudorific. (Gurib-Fakim et al. 1995, 1997).
*E. sonchifolia* contains the toxic alkaloids senkirkine (**48**), and doronine (**49**) (Cheng et al. 1986). All *Emilia* species are botanically related and the occurrence of PAs can be assumed. Internal use is not recommended.

#### *2.2.6. Gynura rubens Muscher*

Growing in Madagascar. Medical use: against backage burns (Pernet et al. 1957).

#### *2.2.7. Gynura sarcobasis DC*

Growing in Madagascar. Medical use: sgainst veneric ulcer, syphilis (Pernet et al. 1957).
The related species *G. scandens* O. Hoffm. contains the pyrrolizidine alkaloids gynuramine (**38**) and $O^{19}$-acetylgynuramine (**39**) (Wiedenfeld 1982), and *G. divaricata* DC. contains the alkaloids integerrimine (**33**), and usaramine (**34**) (Roeder et al. 1996).
All alkaloids are hepatotoxic. All the *Gynura* species are botanically related and the occurrence of PAs can be assumed. Internal use is not recommended.

#### *2.2.8. Senecio adscendens Bojer ex DC*

Growing in Madagascar. Medical use: against syphilis (Pernet et al 1957).

#### *2.2.9. Senecio ambavilla Pers (syn. Hubertia ambavilla var. ambavilla Bory)*

Endemic in Réunion and Rodrigues, introduced in Mauritius. Vernacular name: appanah, ambaville, ambaville bleu. Internal use: A decoction is drunk against dysentery, diarrhoea and stomach upsets,burning sensations in the stomach, indigestion, and stomach upsets. Leaves for hypertension, gout, rheumatism, diuretic and as a depurative. External use: The leaves are used for wounds, abscesses, eczema, scabies. (Forgacs et al. 1981; Adsersen et al. 1997; Gurib-Fakim et al. 1993, 1995, 2004a; Fortin et al. 2002; Poullain et al. 2004).

#### *2.2.10. Senecio bojeri DC*

Growing on the coast of Mauritius. Vernacular name: trezi. Medical use: A paste made from the crushed roots is applied to the childĭs forehead during a severe headache (Gurib-Fakim et al. 2004a).

#### *2.2.11. Senecio erechtitioides Bak*

Growing in Madagascar. Medical use: Against asthma, phthysis, rubeola (Pernet et al. 1957).

#### *2.2.12. Senecio hubertia Pers. (syn. Hubertia tomentosa (Bory) Pers.)*

Endemic in Réunion Island. Vernacular name: ambaville blanche. (Forgacs et al. 1981; Adsersen et al. 1997; Fortin et al. 2002; Gurib-Fakim et al. 2004a). Medical use is unknown, but it has perhaps antiviral activities (Forgacs et al. 1981) and antioxidant activities (Poullain et al. 2004).

#### *2.2.13. Senecio lamarckianus Bullock (syn. Senecio appendiculatus (Lam) DC. ex Bojer)*

Endemic plant to Mauritius. Vernacular name: bois chèvre.
Internal use: A leaf and stem decoction is administered against coughs and influenza. Decoction of parts of the whole plant is drunk against dysentery and fever.
External use: A leaf and root poultice is used against eczema (Gurib-Fakim et al. 1995, 1997, 2004a, 2004b; Brendler 2010).
Closely related to these medically used *Senecio* species is *S. madagascariense* Poir.
It is growing in the same area and under the same climatic conditions. *S. madagascariense* contains the alkaloids mucronatinine (**32**)**,** integerrimine (**33**), senecionine (**35**), retrorsine (**36**)**,** senecivernine (**37**)**,** senkirkine (**48**), $O^{12}$-acetylsenkirkine (**49**), doronine (**50**)**,** desacetyldoronine (**51**), otosenine (**52**), florosenine (**53**) (Gardner et al. 2006). All PAs are hepatotoxic. Furthermore, all *Senecio* species investigated until now contain PAs, mainly with strong hepatotoxic effects. It seems obvious that the traditionally used species contain PAs, too; on account of the strong toxic side-effects a medical use is not appropriate.

### 2.3. Boraginaceae

#### 2.3.1. *Ehretia petiolaris Lam. (syn. Hilsenbergia petiolaris (Lam.) J.D. Mill.)*

Growing in Africa, India, South East Asia, Philipines, Australia, South America, Mauritius and Réunions. Vernacular name: bois de pipe.
Internal use: as a depurative.
External use against skin infections (Gurib-Fakim et al. 1995, 1997, 2004a). Contains alkaloids with unknown structure. The closely related *E. aspera* Willd. contains the non-toxic alkaloid ehretinine (**4**) (Suri et al. 1980). There are no objections to its use as a medicinal plant.

#### 2.3.2. *Heliotropium amplexicaule M.Vahl (syn. H. anchusaefolium Poiret, syn. Cochranea anchusaefolia (Poir.), syn. Tournefortia heliotropioides Hook)*

This plant is growing in South America, Australia, naturalized in Mauritius.
Vernacular name: herbe bleu, verveine sauvage, engl. name: blue heliotrope, clasping heliotrope, purpletop, wild heliotrope.
Internal use against cough and fever (Guri-Fakim et al. 1993, 1995, 1997). It contains the toxic indicine (**11**) (Bull et al. 1968; Ketterer et al. 1987).

#### 2.3.3. *Heliotropium indicum L. (syn. H. anisophyllum P. De B., syn. H. parviflorum Blanko, syn H. cordifolium Moench, syn. Tiaridium indicum (L.) Lehm.)*

This plant is widespread in Bangladesh, India, Japan, Myanmar, Nepal, Thailand, Vietnam, China, Madagascar, Mauritius and Rodrigues. In China it is a medicinal plant (Roeder 2000).
Vernacular name: herbe papillon. Chin. name: Da wei yao. Engl. name: Indian heliotrope.
Internal use: A decoction is taken against fever and urticaria, while a decoction of the roots is indicated in cough and fevers. The decoction of the flowers is an emmenagogue in small doses and an abortifacient in large doses.
External use: A poultice of the plant is applied locally for ulcers, sores, wound, gum boils, skin affections, insect injuries, carbuncles, herpes, and rheumatism (Pernet et al. 1957; Gurib-Fakim et al. 1993, 1994, 1995, 1996, 1997, 1999; Jelager et al. 1998).
It contains strigosine (**3**), supinine (**6**), heleurine (**7**), heliotrine (**10**), indicine (**11**), $O^{3'}$-acetylindicine (**12**), lycopsamine (**14**), echinatine (**16**), europine (**17**), heliosupine (**18**), lasiocarpine (**19**), $O^{3'}$-acetyllasiocarpine (**20**), helindicine (**29**) and their *N*-oxides (Mattocks et al. 1961, 1967; Hoque et al. 1976; Kugelman et al. 1976; Pandey et al 1983, 1983, 1996; Singh et al. 2005; Souza et al. 2005).
Indicine N-oxide shows an antitumor activity. In early clinical studies the possibility of using it for the treatment of leucemia and tumors was discussed (Kugelman et al. 1976; Ohnuma et al. 1980). But severe toxic side-effects showed that a therapy with indicine-N-oxide was not justified (Cook et al. 1983; Letendre et al.1984; Winton et al. 1986). Most of the alkaloids are hepatoxic.
The internal use of *Heliotropium* species is not recommended.

#### 2.3.4. *Symphytum officinale L. (syn. S. consolidum (L.))*

This plant is widespread in Eurasia, Australia and/or USA. Introduced in Mauritius.
Common names: comfrey, liane chique, consoude. Rather rare in Mauritius but can be found in the grounds of some ashrams (Gurib-Fakim et al. 1999).
Internal use: as infusions and extracts in cases of gastrointestinal diseases and respiratory tract diseases. For vegetarians numerous recipes are offered for comfrey salad, spinach, soufflés, soups, bread, rolls and root beverages. External use: In the form of extracts, ointments, compress pastes, it is used in cases of fractures, contused injuries, sprainings, contusions, strains, thrombophlebitis, mastitis, and hematoma (Roeder 1995).
It contains the alkaloids intermedine (**8**), $O^7$-acetylintermedine (**9**), lycopsamine (**14**), $O^7$-acetyllycopsamine (**15**), symlandine (**22**), symviridine (**23**), myoscorpine (**24**), symphytine (**25**) (Furuya et al. 1968, 1971; Pedersen 1975b; Culvenor et al. 1980; Mattocks 1980; Roeder et al. 1982, 1992).
In the medicinal literature several cases of intoxication attributed to *Symphytum* are described (Huizing et al. 1981).

#### 2.3.5. *Tournefortia acuminata DC*

Endemic to Reunion Island. Vernacular name: bois de Laurent-Martin.
Internal use: against lithiase renale, as a diuretic (Adsersen et al. 1997; Gurib-Fakim et al. 2004a; Poullain et al. 2004).
Plant contains alkaloids with unknown structures (Vera et al. 1990). The related plant *T. sarmentosa* Lam. contains the low toxic alkaloid supinine (**6**) (Crowley and al.1955). The plant should not be used medically.

#### 2.3.6. *Trichodesma zeylanicum R.Br. (syn. Pollichia zeylanica F.M., syn. Borago zeylanica Burm.)*

Growing from eastern tropical Africa to India, Ceylon, western Malesia, Australia, and is naturalized in Mauritius and Rodrigues. Vernacular name: herbe cypaya, herbe cipaye, bourrache sauvage, engl name: camel bush.
Internal use: A decoction of the leaves is credited with emmollient, demulcent and diuretic properties. A decoction of the flowers is sudorific and is used as a diuretic agent.
External use: Powdered root is analgesic when applied to wounds and skin infections. (Gurib-Fakim et al. 1993, 1995, 1997).
It contains the low toxic alkaloid supinine (**6**) (O′ Kelly et al. 1961). The plant should not be used medically.

### 2.4. Fabaceae: Tribe Crotalariaceae

#### 2.4.1. *Crotalaria spec*

Growing in Mauritius and Rodrigues. Vernacular name: croton; engl. name: rattlepod (Gurib-Fakim et al. 1993).
Internal use: Root decoction is purgative. External use: A bath of a leaf decoction is used against scabies and impetigo.
This *Crotalaria* species is probably *C. retusa* L.

#### 2.4.2. *Crotalaria fulva Roxb*

Growing in Madagascar, against scabies and dermal tumor (Pernet et al. 1957).

#### 2.4.3. *2.4.3.Crotalaria retusa L. (syn. Crotalaria sericea Retz)*

This plant is growing in Africa, Australia, Brazil, India, and China, it is naturalized in Mauritius and Rodrigues. Vernacular name: cascavelle jaune. Engl. name: wedge-leaved rattlepod.

External use: A bath in the plant decoction is used to treat skin infections (Gurib-Fakim et al. 1994, 1995, 1996).
The plant contains the alkaloids retusine (**5**), monocrotaline (**30**), spectabiline (**31**), retusamine (**46**), crosemperine (**47**) (Adams et al. 1939; Culvenor et al. 1957; Han et al. 1981; Fletcher et al. 2009).

#### *2.4.4. Crotalaria spinosa Hochst*

Growing in Madagascar.
Medical use: against malaria. Contains no pyrrolizidine alkaloids, but the indolizine alkaloid tashiromine (Pernet et al. 1957; Asres et al. 2004). Toxicity of tashiromine is unknown.

#### *2.4.5. Crotalaria striata D.C*

Growing in Madagascar (Pernet et al. 1957). Medical use: against traumata.

#### *2.4.6. Crotalaria uncinella Lambk*

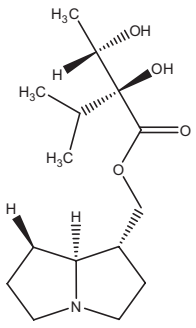
Growing in Madagascar. Medical use: against dysentery (Pernet et al. 1957).

On account of their PA content and the fact that many intoxications by *Crotalaria* species are described those plants can be assumed to be highly toxic and a medical use is not recommended.

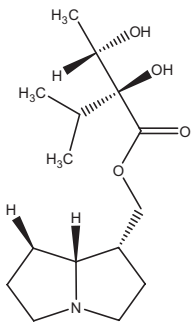
### *2.5. Apocynaceae: Tribe Apocynoideae*

*2.5.1. Parsonsia myrtifolia (Poir) Roem. & Schult. (syn. Landolphia myrtifolia (Poir.) Markgraf, syn. L. crassipes Radlk., syn. Echites myrtifolius Poiret, syn. Vahea crassipes Radlk.).*
This plant is endemic in Madagascar. Vernacular name: ditivahy, fingabary, fingizahana, robanga, vahena, voahena-mamavo, mamolava.
Internal use: An infusion of the fresh root is used for urinary incontinence and as a remedy against asthma (Gurib-Fakim et al. 2004a).
The closely related *P. laevigata* Alston contains the alkaloids parsonine (**42**), parsonsianine (**43**), parsonsianidine (**44**) and 17-metyl-parsonsianidine (**45**) (Abe et al. 1987, 1990, 1991a, 1991b). All alkaloids are toxic. An internal use is not recommended.

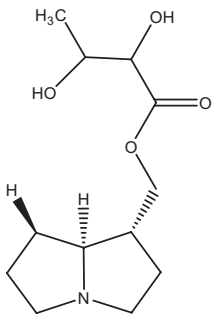
**<u>Non-toxic PAs:</u>**



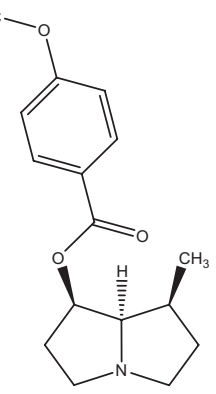
Viridiflorine (**1**)



Cynaustraline (**2**)



Strigosine (**3**)



Ehretinine (**4**)

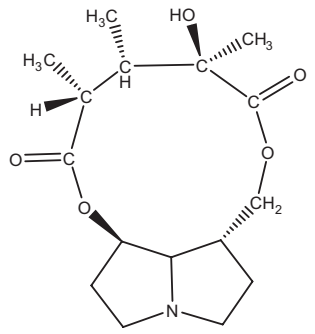
## 3. Conclusion

Within the last few years some reports were published where plants used in the traditional medicine of Madagascar and the Mascarene islands were advertised for the treatment of different diseases. As mentioned before, the flora of those islands is rich in endemics and therefore specialised. However, most of the named plants were not investigated with respect to secondary metabolites. We could show that 22 plants listed for a medical treatment can be assumed to contain toxic PAs on account of botanical and chemotaxonomical relations. These plants show therefore a serious health risk.
We advise not to use those plants and/or preparations from them before - due to a phytochemical analysis on their alcaloidal content - toxic side-effects can be excluded.

## 4. Appendix

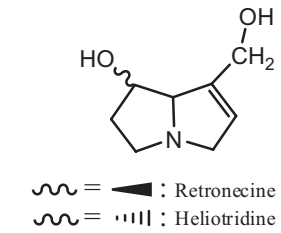
### *4.1. Structures of the PAs*

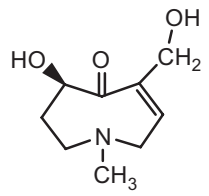
As already mentioned PAs consist of a basic 5-membered bicyclus (necine) which can show a double-bond in position 1,2 (toxic PA) or none (non-toxic PA). Further structural aspects for a possible toxicity is a free position adjacent to the bridge nitrogen atom and esterification at the hydroxy-groups of the necine. The esterifying acids (necic acids) mostly show 5 to 10 carbon atoms and are more or less branched. The combination of the different necines with the necic acids result in a great variety of possible different PA structures. More than 350 different structures are known to date.
The structures of the PA mentioned in this paper are shown in the following figures:



Retusine (**5**)

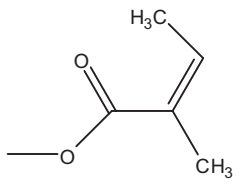
**Toxic PAs:**



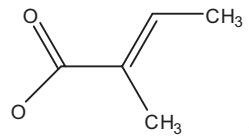




Otonecine

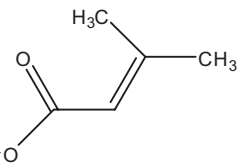
***Necines***



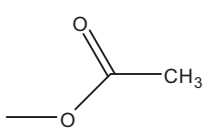

angeloyl = **ang**



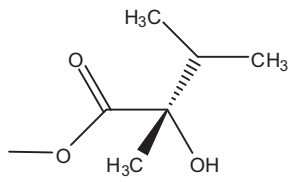

tigloyl = **tig**



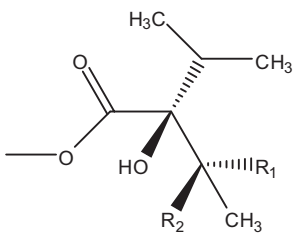

senecioyl = **sen**



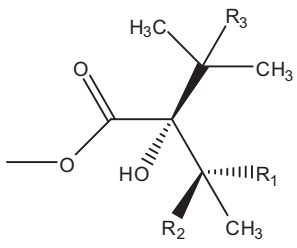

acetyl = **ac**




2*S*-2-hydroxy-2,3-dimethyl-butanoic acid = **hous**



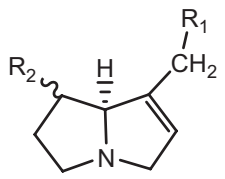

$R_1$ = H; $R_2$ = OH: (-)-viridifloroyl = **(-)-vir**
$R_1$ = OH; $R_2$ = H: (+)-trachelantoyl = **(+)-tra**




$R_1$ = H; $R_2$ = OH; $R_3$ = H: (-)-trachelantoyl= **(-)-tra**
$R_1$ = OH; $R_2$ = H; $R_3$ = H: (+)-viridifloroyl= **(+)-vir**
$R_1$ = $OCH_3$; $R_2$ = H; $R_3$ = OH: lasiocarpoyl = **las**
$R_1$ = OH; $R_2$ = H; $R_3$ = OH: echinatoyl = **ech**

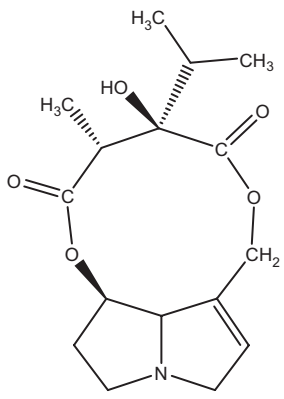
***Necic acids***

***Open-chain mono and diester PAs:***

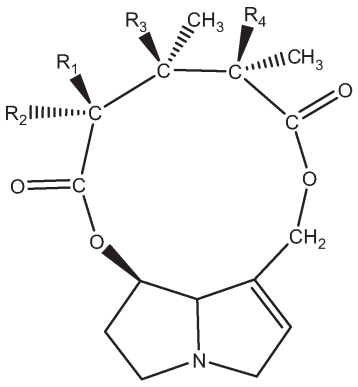



| $R_1$ | $R_2$ | Name |
|---|---|---|
| (+)-tra | H | Supinine (**6**) |
| (+)-tra,3′-$OCH_3$ | H | Heleurine (**7**) |
| (+)-tra | ◥OH | Intermedine (**8**) |
| (+)-tra | ◥ac | Acetylintermedine (**9**) |
| (+)-tra,3′-$OCH_3$ | ◥OH | Heliotrine (**10**) |
| (-)-tra | ◥OH | Indicine (**11**) |
| (-)-tra | ◥ac | Acetylindicine (**12**) |
| (-)-vir | H | Amabiline (**13**) |
| (-)-vir | ◥OH | Lycopsamine (**14**) |
| (-)-vir | ◥ac | Acetyllycopsamine (**15**) |
| (-)-vir | ┈OH | Echinatine (**16**) |
| las | ┈OH | Europine (**17**) |
| ech | ┈ang | Heliosupine (**18**) |
| las | ┈ang | Lasiocarpine (**19**) |
| las,3′ac | ┈ang | $O^3$-Acetyllasiocarpine (**20**) |
| ech | ◥ang | Echimidine (**21**) |
| (+)-vir | ◥ang | Symlandine (**22**) |
| (-)-vir | ◥sen | Symviridine (**23**) |
| (+)-tra | ◥tig | Myoscorpine (**24**) |
| (-)-vir | ◥tig | Symphytine (**25**) |
| hous | ◥OH | Retrohoustine (**26**) |
| hous | ┈OH | Heliohoustine (**27**) |
| OH | ◥hous | Isoretrohoustine (**28**) |

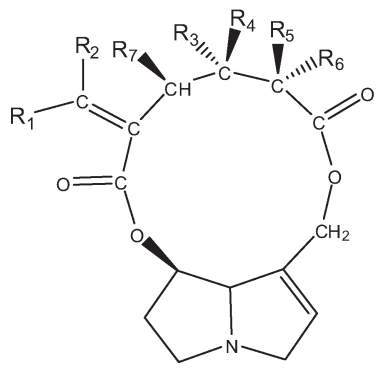
***Macrocyclic diester PAs:***




Helindicine (**29**)

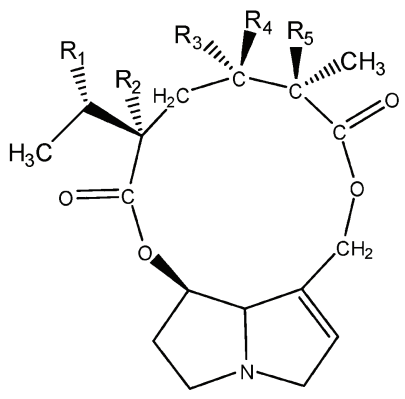


| $R_1$ | $R_2$ | $R_3$ | $R_4$ | Name |
|---|---|---|---|---|
| H | $CH_3$ | OH | OH | Monocrotaline (**30**) |
| H | $CH_3$ | ac | OH | Spectabiline (**31**) |

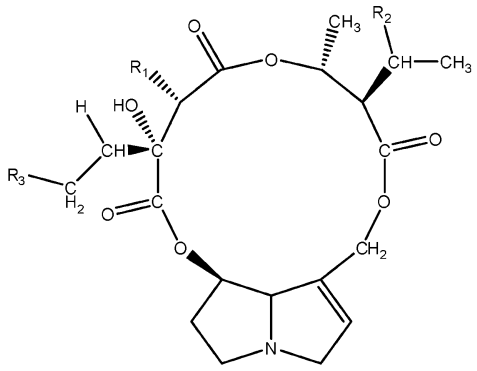


| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Name |
|---|---|---|---|---|---|---|---|
| H | $CH_3$ | H | $CH_3$ | OH | $CH_2OH$ | H | Mucronatinine (**32**) |
| H | $CH_3$ | $CH_3$ | H | OH | $CH_3$ | H | Integerrimine (**33**) |
| H | $CH_3$ | $CH_3$ | H | OH | $CH_2OH$ | H | Usaramine (**34**) |
| $CH_3$ | H | $CH_3$ | H | OH | $CH_3$ | H | Senecionine (**35**) |
| $CH_3$ | H | $CH_3$ | H | OH | $CH_2OH$ | H | Retrorsine (**36**) |
| H | H | $CH_3$ | H | OH | $CH_3$ | $CH_3$* | Senecivernine (**37**) |
| $CH_3$ | H | $CH_2OH$ | H | OH | $CH_3$ | H | Gynuramine (**38**) |
| $CH_3$ | H | $CH_2ac$ | H | OH | $CH_3$ | H | Acetylgynuramine (**39**) |

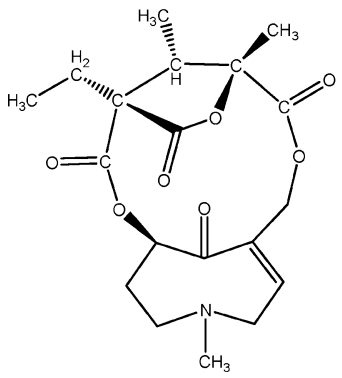
* stereochemistry estimated or unknown



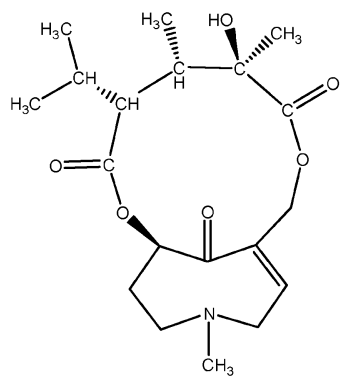
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Name |
|---|---|---|---|---|---|
| - O - | | $CH_3$ | H | OH | Jacobine (**40**) |
| OH | OH | $CH_3$ | H | OH | Jacoline (**41**) |



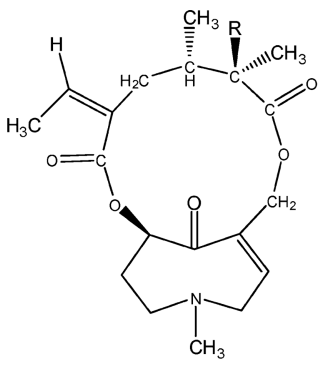
| $R_1$ | $R_2$ | $R_3$ | Name |
|---|---|---|---|
| H | $CH_3$ | H | Parsonine (**42**) |
| OH | H | H | Parsonsianine (**43**) |
| OH | H | $CH_3$ | Parsonsianidine (**44**) |
| OH | $CH_3$ | $CH_3$ | 17-Methylparsonsianidine (**45**) |



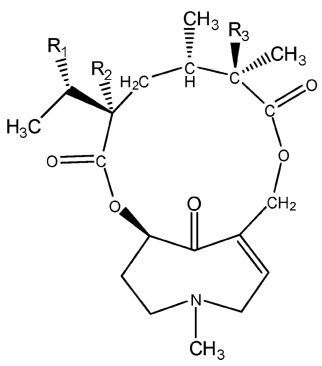
Retusamine (**46**)



Crosemperine (**47**)



| R | Name |
|---|---|
| OH | Senkirkine (**48**) |
| Ac | $O^{12}$-Acetylsenkirkine (**49**) |



| $R_1$ | $R_2$ | $R_3$ | Name |
|---|---|---|---|
| Cl | OH | ac | Doronine (**50**) |
| Cl | OH | OH | Desacetyldoronine (**51**) |
| - O - | | OH | Otosenine (**52**) |
| - O - | | ac | Florosenine (**53**) |

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