Table 13.0 Levels of Aristolochic acid-I and AA-II in *Aristolochia, Asarum* and *Saruma* herbs

It should be noted that the older literature is complicated and somewhat inconsistent in analysis. The high level of variation noted for *Aristolochia manshuriensis* is possibly due to poor species identification, differences in growing conditions or chemical variation of the species (Cheung et al. 2006). Furthermore, the analysis of Chinese patent medicine complexes is likely to show substantial variability depending on the species utilised, climatic factors, possible herb substitutions and processing methods (see Michl et al. 2017; Han et al. 2019).

There appears to be a detrimental interaction between AA-I and AA-II, with a mixture of the two reducing the liver detoxification processes with regard to AA-I. This results in higher amounts of the latter remaining in the system (liver and kidney tissues), subsequently enhancing aristolochic acid's toxic potential. This is important because individuals suffering from AA nephrotoxicity are exposed to complex plant products (i.e. variable levels of AAI/AAII mixtures) (Barta et al. (2021).

Michl and colleagues (2016) list appreciable levels of other forms of aristolochic acids and aristolactams.

AA-C and AA-D (mg/g) levels (Michl et al. 2016):

- *A. tagala* (flower): AA-C 0.408 & AA-D 0.130; and (root): AA-C 0.243 & AA-D 0.121;
- *A. albida* (root): AA-C 0.402;
- *A. debilis* (stem): AA-C 0.211;
- *A. littoralis* (root): AA-C 0.260;
- *A. indica* (stem): AA-D 0.192;
- *A. manshuriensis* (flower): AA-C 0.171 & AA-D 0.217.

Aristolactam-I (AL-I mg/g):

- *A. guentheri* (leaf): 0.212;
- *A. trilobata* (leaf): 0.190.

Aristolactam-I is also known to be a kidney toxin and may well contribute to AA nephrotoxicity, which may be further complicated by iron overload (Li et al. 2004; Deng et al. 2020). Interestingly aristolactam -AII has been isolated from the Australian rainforest plant *Goniothalamus australis* (Annonaceae; Levrier 2013). Overall, the contributory/synergistic effect of these components to the toxicity of AA-containing plants remains unclear.

The role of toxic food contaminants (eg. ochratoxin, citrinin), heavy metals and environmental pollutants, as well as nutritional deficiencies eg. selenium (and, possibly, magnesium), are among the factors that are likely to compound the situation. Indeed, recent studies have shown a co-carcinogenic effect with arsenic, which is present in high levels in soils in parts of the world where unexplained forms of kidney disease occur. There is also a potential additive effect of other environmental renal toxins such as cadmium and fluoride, the latter being a potential groundwater contaminant that can be found in unusually high levels when water levels are low (Maksimovic 1991 and 1997; Ezgi et al.2020; Oztas et al. 2020; Veljkovićc et al. 2020; Wimalawansa and Dissanayake 2020; Chen et al. 2021).

Species	AA-I	AA-II	Reference
Aristolochia			
A. albida	1.151 mg/g (leaf); 1.346 mg/g (root); 0.721 mg/g (stem)	0.077 mg/g (leaf); 1.413 mg/g (root); 0.081 mg/g (stem)	Michl et al. (2016)
A. argentina	0.085 mg/g (stem	0.156 mg/gm	Michl et al. (2016)
A. austroszechuanic	1.050 (root/root tuber)		Zhou et al. (2008); Han et al. (2019)

a			
A. baetica	0.086 mg/g (leaf)	0.073 mg/g (leaf)	Michl et al. (2016)
A. bracteolata	12.98 gm/kg	49.03 gm/kg	Abdelgadir et al. (2011)
A. californica	0.802 mg/g (stem)	0.070 mg/g (stem)	Michl et al. (2016)
A. chamissonis	0.682 mg/g (leaf)		Michl et al. (2016)
A. cinnabarina	0.887–12.098 (root)	0.659–5.076 mg/g (root)	Zhou et al. (2008); Han et al. (2019)
A. clematitis	1.322 mg/g (leaf); 1.496 mg/g (roots); 1.313 mg/g (flower); 1.219 mg/g (stem); 1.813 mg/g (seeds)	1.494 mg/g (leaf); 2.557 mg/g (roots); 1.066 mg/g (flower); 1.419 mg/g (stem); 0.876 mg/g (seeds)	Michl et al. (2016)
A. contorta	not detected	1–115 ppm	IARC Monograph (2002)
	0.08–0.8 mg/g	0.07–0.7 mg/g	Wu et al. (2007)
	195 ppm	33ppm	Cheung et al. (2006)
	0.034–4.695 mg/g (fruit)	0.010–0.574 mg/g (fruit)	Han et al. (2019)
	0.840–2.293 mg/g (seed)	0.014–0.132 mg/g (seed)	Mao et al. (2017); Han et al. (2019)
	0.511–6.421 mg/g (root)	0.029–6.108 mg/g (root)	Mohamed et al. (1999); Han et al. (2019)
	0.127–10.460 mg/g (herb)	0.034–6.325 mg/g (herb)	Han et al. (2019)
	0.364 mg/g (leaf)		Michl et al. (2016)
A. cucurbitifolia	1.107 mg/g	0.122 mg/g	Michl et al. (2016)
A. cymbifera	0.016 mg/g (stem)	0.127 mg/g (stem)	Michl et al. (2016)
A. debilis	various samples: 568 and 790–1080 mg/kg	various samples: 80–180 and 208 mg/kg	IARC Monograph (2002)
	0.012 and 0.035 mg/g (stem)		Michl et al. (2016)
	0.299–1.532 mg/g (fruit)	0.064–0.524 mg/g (fruit)	Han et al. (2019)
	0.078–2.610 mg/g (root)	0.013–0.875 mg/g (root)	Han et al. (2019)
	0.175 mg/g (herb)	0.039 mg/g (herb)	Han et al. (2019)
A. fangchi (*A. fangchi*)	various samples: 480–612 and 1030–2220 mg/kg; 437–668ppm	various samples: 40–220 and 315 mg/kg	IARC Monograph (2002)
	0.07 mg/g	0.04–0.4 mg/g	Wu et al. (2007)
	943ppm	59ppm	Cheung et al. (2006)

	0.609 mg/g		Michl et al. (2016)
A. fimbriata	0.180 mg/g (stem)		Michl et al. (2016)
A. fontanesii	0.855 mg/g (leaf)	0.102 mg/g (leaf)	MIchl et al. (2016)
A. gibertii	0.050 mg/g (leaf)	1.875 mg/g (leaf)	Michl et al. (2016)
A. grandiflora	0.003 mg/g (leaf); 0.066 mg/g (root)		Michl et al. (2016)
A. guentheri	0.002–0.005 mg/g (stem)		Michl et al. (2016)
	0.001 mg/g (leaf)		
A. heterophylla	0.2–0.4 mg/g	0.07–0.17 mg/g	Wu et al. (2007)
	1.640–3.260 mg/g (stem + roots)		Mohamed et al. (1999); Zhou et al. (2008); Han et al. (2019)
	1.320–4.450 mg/g (root/root tuber)		Zhou et al. (2008); Han et al. (2019)
A. indica	0.334, 0.382, 0.454 and 0.913 mg/g (leaf); 0.818 mg/g (root); 1.368 mg/g (stem)	0.239 mg/g (root)	Michl et al. (2016)
A. kaempferi	0.001 mg/g (leaf); 1.202 mg/g (stem)	1.261 mg/g (stem)	Michl et al. (2016)
A. labiata	0.003 mg/g (leaf)		Michl et al. (2016)
A. lagesiana	0.008 mg/g (stem)		Michl et al. (2016)
A. littoralis	0 and 0.117 mg/g (leaf); 0.070 mg/g (root); 2.186 mg/g (seed)	0.048 mg/g (root); 0.189 mg/g (seed)	Michl et al. (2016)
A. liukiensis	0.708 mg/g (stem)	0.176 mg/g (stem)	Michl et al. (2016)
A. macrophylla	0.014 mg/g (stem)	0.000 mg/g (stem)	Michl et al. (2016)
A. manshuriensis	1690–8820 mg/kg	140–1000 mg/kg	IARC Monograph (2002)
	41ppm		Cheung et al. (2006)
	2.85 mg/g extract	0.5 mg/g extract	Hwang et al. (2012)
	0.28–0.62 mg/g		Sim et al. (2013)
	0.938, 1.109 mg/g (leaf); 0.001, 0.122, 0.650, 1.094 and 1.660 mg/g (root); 0.551 mg/g (flower)	1.317 & 1.673 mg/g (leaf); 0.044, 0.268 and 1.227 mg/g (root); 0.125 mg/g (flower)	Michl et al. (2016)
	0.310–10.850 mg/g (stem)	0.130–2.977 mg/g (stem)	Han et al. (2019)
A. maurorum	0.140 mg/g (leaf)		Michl et al. (2016)
A. maxima	0.032 and 0.034 mg/g (leaf); 2.151, 2.289 & 2.467 mg/g (root);	0.54, 0.617 and 1.438 mg/g (root); 0.242 mg/g (flower)	Michl et al. (2016)

	0.971 mg/g (flower)		
A. mollissima	0.03–0.4 mg/g	not detected	Wu et al. (2007)
	1.234 mg/g (leaf)		Michl et al. (2016)
	0.06–2.650 mg/g (herb)	0.022–0.038 mg/g (herb)	Han et al. (2019)
	0.050 mg/g (aerial part)		Zhou et al. (2008); Han et al. (2019)
	0.465 mg/g (stem and root)		Mohamed et al. (1999); Han et al. (2019)
A. moupinensis	1.164 mg/g (leaf)	0.14 mg/g (leaf)	Michl et al. (2016)
	0.540–2.780 mg/g (root/root tuber)		Zhou et al. (2008); Han et al. (2019)
	0.540–2.150 mg/g (stem)		Han et al. (2019)
	AA-I & AA-II: 412–1279 ppm		Wu et al. (2007)
A. odoratissima	0.054 mg/g (leaf)		Michl et al. (2016)
A. ovalifolia	0.419 mg/g (leaf)		Michl et al. (2016)
A. paucinervis	1.597 mg/g (fruit); 0.756 mg/g (seed)	0.931 mg/g (fruit); 0.130 mg/g (seed)	Michl et al. (2016)
A. ringens	0.668 mg/g (root)	0.138 mg/g (root)	Michl et al. (2016)
	0.003 mg/g (root)		Aigbe et al. (2019)
A. rotunda	1.629 mg/g (root)	1.518 mg/g (root)	Michl et al. (2016)
A. sempervirens	0.676 mg/g (leaf)	0.073 mg/g (leaf)	Michl et al. (2016)
A. serpentaria	1.207 mg/g (leaf); 0.992 mg/g (fruit)	0.546 mg/g (leaf); 0.077 mg/g (fruit)	Michl et al. (2016)
A. tagala	0.907 and 1.2 mg/g (leaf) 1.347 mgg (root); 0.937 mg/g (stem); 1.125mg/g (flower)	0.311 and 2.502 mg/g (leaf); 0.090 mg/g (root); 0.737 mg/g (stem); 2.246 mg/g (flower)	Michl et al. (2016)
A. taliscana	0.010 mg/g (stem)		Michl et al. (2016)
A. tomentosa	1.047 mg/g (stem)	0.370 mg/g (stem)	MIchl et al. (2016)
A. triangularis	0.025 mg/g (stem); 0.082 mg/g (leaf); 0.633 mg/g (leaf)	0.157 mg/g (leaf)	Michl et al. (2016)
	0.000 mg/g	0.000 mg/g	Oliveira et al. (2019)
A. trilobata	0.582, 0.750 and 0.891 mg/g (leaf); 0.435 mg/g (stem); 1.484 mg/g (flower)	0.223, 0.491 and 0.520 mg/g (leaf); 0.157 mg/g (stem); 1.480 mg/g (flower)	Michl et al. (2016)
A. tubiflora	0.04–0.4 mg/g	0.2–1.0 mg/g	Wu et al. (2007)
A. westlandii	0.001 mg/g (stem)		Michl et al. (2016)
A. zollingeriana	0.945, 1.088 and 1.189 mg/g (leaf)	1.745, 1.833 and 2.289 mg/g (leaf)	Michl et al. (2016)
Asarum			
As. caudigelellum	0.150–0.220 mg/g (not reported)		Han et al. (2008); Han et al. (2019)
As. crispulatum	3376.9 ng/mg		Michl et al. (2017)

As. heterotropides	0.040–0.110 mg/g (herb)	0.025 mg/g (herb)	Zhou et al. (2008); Han et al. (2019)
	0.008 mg/g (root + rhizome)		Han et al. (2019)
A. himalaicum	0.440 mg/g (herb)		Zhou et al. (2008); Han et al. (2019)
As. sagittarioides	0.070–0.180 mg/g (not reported)		Zhou et al. (2008); Han et al. (2008); Han et al. (2008); Han et al. (2019)
	0.016 mg/g (root + rhizome)	0.020 mg/g (root + rhizome)	Han et al. (2019)
Saruma			
S. henryi	0.184–1.995 mg/g (root)		Zhao & Jiang et al. (2009); Zhang et al. (2011); Han et al. (2019)
	0.116 mg/g (stem)		Zhang et al. (2011)

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