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Plant Poisons in the Garden: A Human Risk Assessment

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Abstract: A study of the plants, and their associated poisons, in the Poison Garden at The Alnwick Garden was undertaken across a calendar year. By selecting 25 plants in the Poison Garden, we have been able to develop a single chromatographic method for the determination and quantification of 15 plant toxins by liquid chromatography mass spectrometry (LC-MS). Chromatographic separation was achieved on a C18 column (3.5 µm, 100 × 4.6 mm) with a gradient method using water +0.1% formic acid and methanol +0.1% formic acid. The developed method was validated for precision, linearity, limits of detection and quantification and extraction recoveries. The method showed good linearity with a R^2 value of >0.995 for all 15 compounds with good precision of 10.7%, 6.7% and 0.3% for the low, medium and high calibration points, respectively. The LC-MS method was used to analyse 25 plant species, as well as their respective parts (i.e., bulb, flower, fruit, leaf, pollen, seed, stem and root), to assess the human risk assessment to children (aged 1 to <2 years) in relation to the plant toxin and its respective LD_{50}. The analysis found that the greatest potential health risks were due to the ingestion of *Colchicum autumnale* and *Atropa belladonna.* As a caution, all identified plants should be handled with care with additional precautionary steps to ensure nil contact by children because of the potential likelihood of hand-to-mouth ingestion.

Keywords: liquid chromatography-mass spectrometry; plant toxins; solid liquid extraction; LD_{50}

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1. Introduction

Toxins are produced by some plants as a form of protection against threats from insects, bacteria, and fungi. Exposure to plant toxins can be via intentional (i.e., intending to do harm) or an unintentional (as a result of contact) act. It is therefore important to consider the potential exposure pathways that can lead to harm from plants and their toxins. For example, oral ingestion (e.g., by hand-to-mouth), dermal absorption and inhalation can all occur after contact or exposure with the different parts of a plant whilst, for example, undertaking gardening activities (pruning, planting, transferring). In this situation unintentional exposure can be commonplace with the outcomes ranging from itching skin and rashes to potentially a lethal toxic dose. Intentional exposure, often by oral ingestion, has been reported both historically [1–11] and more recently [12–18] where plants and/or their toxins have been used for assassination [14,15]. A compounds toxicity can be reported as the median lethal dose (LD_{50}) referring to the concentration required to kill half the test population [19–21].

Alternatively, many plants (and their) toxins have dose dependent useful effects in humans, for example, *Aconitum* root is used in traditional Chinese medicine for the treatment of joint pain, rheumatic fever, asthma and diarrhoea [4,22]. Colchicine from *Colchicum* sp. is used in pharmaceutical preparations for its anti-inflammatory properties and is commonly used to prevent flare-ups of familial Mediterranean fever and gout [23]. Digitoxin and digoxin from *Digitalis* sp. are clinically approved for the treatment of heart failure and arrhythmia for humans and in veterinary medicine and has been used as a treatment for congestive heart failure for more than a century [10,24–28]. Furocoumarins (e.g., psoralen) are used in photo ultra-violet A (PUVA) therapy for treatment of conditions

such as eczema, psoriasis, vitiligo and skin conditions linked to certain lymphomas [29–34]. *Veratrum album* was previously used during the 19th century as a treatment for hypertension however significant side effects limited its clinical use [35].

In the treatment of suspected poisoning the determination of the plant toxin is often critical in the successful treatment and recovery of the intended victim. However, most methods focus on the analysis of specific groups of toxins, or a specific plant family, depending on the individual circumstances [7,24,36–43]. A more recent article included 12 compounds but similarly focuses on distinct group, namely *Amaryllidaceae* alkaloids, *Veratrum* alkaloids and glycoalkaloids [44]. As liquid chromatography mass spectrometry (LC-MS) instrumentation has become more common place over recent years in clinical biochemistry and toxicology laboratories the analytical technique lends itself to the simultaneous analysis of plant toxins [45]. This significant development in its use and application allows for a faster and more reliable identification, and quantitation, of the toxin present and therefore aids in the treatment of the patient by the clinician. This paper is the first to report a multi-residue method for the analysis of the 15 compounds in plant material in a single chromatographic run. In addition, and also for the first time, the ingestion risk from consuming poisonous plants is assessed in terms of an exposure risk factor.

Alnwick Garden, Alnwick, Northumberland was opened to the public in 2001 and resulted from the foresight of the Duchess of Northumberland. Subsequent developments and additions meant that the Poison Garden was opened in 2005. Access to the Poison Garden is only via trained wardens and contains around 100 poisonous plants. The Poison Garden Wardens reward visitors with information on the history, uses and misuses as well as their own informed anecdotes on the plants therein. In addition, four story boards within the Poison Garden inform visitors about infamous murderers: the Teacup Poisoner (also known as the St. Albans Poisoner) Graham Young who used the poison from *Atropa belladonna* (also known as deadly nightshade) to poison members of his family and up to 70 other people, two of whom died [18], The Curry Killer, Lakhvir Singh, who used *Aconitum ferox* (commonly known as Monk's Hood) to poison her lover by adding the plant to a curry [12,13]; Doctor Death, Harold Shipman, a GP, who was found guilty of murdering fifteen patients, using the poison from *Papaver somniferum* (or the opium poppy) [16,17] and, finally, The Umbrella Murder, in which the poison from *Ricinus communis* (or the Castor bean plant) was used to murder Georgi Markov via injection of ricin into his leg from an umbrella [14,15].

This paper investigates the simultaneous analysis by LC-MS/MS of 15 plant toxins found within 25 varieties of plants located within the Poison Garden at The Alnwick Garden, Northumberland. However, many of the plants are common ornamental plants and available for purchase in garden centres and via online nurseries. Depending upon the plants, samples were extracted from the bulb, flower, fruit, leaf, pollen, root, seed and stem prior to analysis using LC-MS/MS. The concentrations obtained were then used to calculate the exposure risk factor by ingestion, by a child aged between 1 and <2 year, and the values compared to the LD_{50} of each compound to determine their risk to human health.

2. Experimental

2.1. Chemicals and Reagents

Standards of aconitine, atropine, (-)-scopolamine, veratridine, colchicine, coumarin, psoralen, 8-methoxypsoralen, 5-methoxypsoralen, α-solanine, digitoxin, digoxin, (-)-α-thujone, and S(-)-cathinone were purchased from Sigma Aldrich (Dorset, UK) with a purity of ≥95%. A hellebrin standard was purchased from Enzo Life sciences (Exeter, UK) with a purity of <99%. Organic LC-MS grade solvents; methanol, acetic acid and formic acid were purchased from Fisher Scientific (Loughborough, UK). Nylon 0.2 µm syringe filters were purchased from Thames Restek (High Wycombe, UK). A number of plants were selected, namely; *Heracleum mantegazzianum*, *Artemisia absinthium*, *Catha edulis*, *Colchicum autumnale*, *Fritillaria imperialis*, *Fritillaria meleagris*, *Veratrum album*, *Digitalis ferruginea*, *Digitalis purpurea*,

Helleborous sp., *Aconitum lycoctonum*, *Aconitum napellus*, *Aquilegia alpina*, *Aquilegia atrata*, *Ruta graveolens*, *Atropa belladona*, *Brugmansia suaveolens*, *Hyoscyamus niger*, *Solanum dulcamara* and *Daphne laureola.* These plants were chosen based on availability to purchase in garden centers, availability in nature and toxicological importance. All plant materials were obtained from the Poison Garden within Alnwick Gardens (Northumberland, UK).

2.2. Instrumentation

For LC-MS analysis a Thermo Surveyor LC (Thermo Scientific, Hemel Hempsted, UK) consisted of a quaternary MS pump, vacuum degasser, a thermostated autosampler (set to 5 °C), a thermostated column oven (set to 25 °C) coupled to a LTQ XL ion trap mass spectrometer was used. Chromatographic separation was achieved on a reversed phase Eclipse™ Plus C18 column (3.5 µm, 100 × 4.6 mm) from Agilent (Stockport, UK). Sample aliquots of 10 µL were introduced onto the column at a flow rate of 300 µL/min. The analytes were separated using 0.1% formic acid in water (A) and 0.1% formic acid in methanol (B) as the mobile phase. The specific LC and MS parameters are show in Table 1 and the collision energies and monitored ions in Table 2. Mass spectra, and their respective compound fragmentation, are shown in the Supplementary Materials for all compounds investigated.

Table 1. LC-MS instrument parameters.

Parameter	Plant Poison Analysis		
Mobile Phase	A: 0.1% Formic acid in water B: 0.1% Formic acid in methanol		
Pump program	Time (min)	% A	% B
	0.00	60	40
	10.00	10	90
	20.00	10	90
	20.10	60	40
	25.00	60	40
HESI temperature	Ambient		
Ion source voltage	4.50 kV		
Capillary voltage (V)	25, 45, 15, 14		
Transfer capillary temperature	350 °C		
Auxiliary Gas (arb)	10		
Sweep Gas (arb)	5		
Sheath gas (arb)	10		
Ion Mode	Positive		
Scan mode	SRM		

2.3. Preparation of Stock Solutions and Samples

Stock solutions of each compound were prepared at a concentration of 1.0 mg/mL in methanol, except for hellebrin which was prepared at 0.5 mg/mL and cathinone which were provided as a 1 mg/mL solution and stored at −20 °C. Calibration standards were prepared daily for each analysis from the stock solution by diluting in mobile phase. Calibration standards were prepared over a concentration range of 0–100 ng/mL for 5-methoxypsoralen, 8-methoxypsoralen, aconitine, cathinone, colchicine, digitoxin, psoralen, scopolamine, thujone and veratridine; a concentration range of 0–400 ng/mL for hellebrin; a concentration range of 0–300 ng/mL for digoxin and a concentration range of 0–5000 ng/mL for coumarin. A full set of calibration standards were run at both the start and end of each chromatographic run cycle. In addition, a quality control standard was prepared at

a mid-calibration point by diluting stock standard solutions in mobile phase and analysed at points throughout the run to ensure there was no deviation throughout the run.

Table 2. Collison energies and fragmentation ions for LC-MS/MS.

Compound	Collison Energy (eV)	Fragmentation Ion Observed (*m*/*z*)	Fragmentation
5-methoxypsoralen	30.0	217, 202 *, 173	$[M + H]^+$, $[M + H\text{-}CH_3]^+$, $[M + H\text{-}CO_2]^+$
8-methoxypsoralen	30.0	217, 202 *, 173	$[M + H]^+$, $[M + H\text{-}CH_3]^+$, $[M + H\text{-}CO_2]^+$
Aconitine	24.0	647, 597, 587 *	$[M + H]^+$, $[M + H\text{-}HO_3]^+$, $[M + H\text{-}C_2H_4O_2]^+$
Atropine	24.0	290, 260, 124 *	$[M + H]^+$, $[M + H\text{-}OH]^+$, $[M + H\text{-}C_8H_7O_2]^+$
Cathinone	30.0	150, 133 *, 105	$[M + H]^+$, $[M + H\text{-}NH_3]^+$, $[M + H\text{-}C_2H_7N]^+$
Colchicine	23.0	400, 382 *, 358	$[M + H]^+$, $[M + H\text{-}H_2O]^+$, $[M + H\text{-}C_2H_2O]^+$
Coumarin	30.0	147, 119, 103 *	$[M + H]^+$, $[M + H\text{-}CO]^+$, $[M + H\text{-}CO_2]^+$
Digitoxin	28.0	788, 743, 387 *	$[M + Na]^+$, $[M + Na\text{-}CO_2]^+$, $[M + Na\text{-}C_{17}H_{36}O_{10}]^+$
Digoxin	29.0	804, 786, 387 *	$[M + Na]^+$, $[M + Na\text{-}H_2O]^+$, $[M + Na\text{-}C_{17}H_{36}O_{11}]^+$
Hellebrin	32.0	747, 701, 585 *	$[M + Na]^+$, $[M + Na\text{-}CH_2O_2]^+$, $[M + Na\text{-}C_6H_{10}O_5]^+$
Psoralen	30.0	187, 159, 143 *	$[M + H]^+$, $[M + H\text{-}CO]^+$, $[M + H\text{-}CO_2]^+$
Scopolamine	23.5	304, 156, 138 *	$[M + H]^+$, $[M + H\text{-}C_9H_8O_2]^+$, $[M + H\text{-}C_9H_{10}O_3]^+$
Solanine	40.0	869, 723, 707 *	$[M + H]^+$, $[M + H\text{-}C_6H_{10}O_4]^+$, $[M + H\text{-}C_6H_{10}O_5]^+$
Thujone	28.0	175, 133, 119 *	$[M + Na]^+$, $[M + Na\text{-}C_3H_6]^+$, $[M + Na\text{-}C_4H_8]^+$
Veratridine	25.0	674, 656, 492 *	$[M + H]^+$, $[M + H\text{-}H_2O]^+$, $[M + H\text{-}C_9H_{10}O_4]^+$

* Quantification ion.

For plant toxin analysis approximately 0.1 g of plant material was removed using a scalpel, which was cleaned with water and methanol between each collection, from various parts of the bulb, flower, fruit, leaf, pollen, root, seed and stem, was macerated and sonicated for 15 min in 10 mL of methanol. The solution was filtered through a 0.22 µm nylon syringe filter and diluted to within the calibration range with mobile phase before transferring to an autosampler vial.

2.4. Data Mining

R statistical computing software v. 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) with "lattice" package was used for data mining and visualisation.

3. Results and Discussion

Chromatographic separation was achieved using an Eclipse Plus™ (Agilent, Stockport, UK) C18, 3.5 µm, 100 × 4.6 mm column using acidified methanol and water as the mobile phase over a gradient pump program (Table 1) over a total of 25 min including re-equilibration of the column as shown in Supplementary Materials Figure S15. LC-MS parameters were optimised using the in-built tuning parameters and manual gas adjustments. The MS/MS fragmentation parameters (see, Supplementary Materials) were optimised by direct infusion of each standard diluted in methanol and the parameters were adjusted until a precursor ion of approximately 10% relative abundance and 2 stable product ions were obtained. Due to number of compounds being analysed a combination of segments and scan events were utilised to allow for the use of different tune parameters during the run with the breakdown of each segment and corresponding tune file is shown in Table 3. Dandelion extract was used to determine specificity and extraction recoveries by spiking compounds onto the plant material prior to extraction. Dandelion samples were used as they were readily available and are a common plant found in gardens and most importantly contain none of the compounds of interest [46–48]. Typical recoveries ranged from 71 to

99%. No interfering peaks were observed at the same retention time as the compounds of interest. Verifying that the method was selective for the detection and quantification of the 15 plant toxins.

Table 3. Breakdown of MS/MS method per segment.

Segment Number	Time Window (min)	Compounds	Tune File Used
1	0–6	atropine, cathinone, scopolamine	Atropine
2	6–10	aconitine, coumarin, hellebrin, solanine, veratridine, colchicine	Hellebrin
3	10–14.5	digoxin, 5- and 8-methoxypsoralen, psoralen, thujone	Psoralen
4	14.5–20	digitoxin	Digitoxin

The calibration curves showed a linear response across the standard ranges shown in Table 4 with an R^2 of greater than 0.995 for all 15 compounds. The methods also shown good precision with % CVs of 10.7%, 6.7% and 0.3% for the low, medium and high calibration points, respectively. Matrix matched calibration standards were analysed by diluting standard in dandelion extract and linearity and precision accessed. Minimal variation was observed in matrix matched standards. The limit of detection (LOD) and limit of quantitation (LOQ), both in solution and in the matrix matched standards, were determined. This was based on the calibration using the following equations, 3.3 δ/S and 10 δ/S for LOD and LOQ, respectively. Where δ is the standard deviation of the y intercept and s is the average of the slope. The LODs in solution ranged from 0.2 ng/mL for veratridine to 92 ng/mL for coumarin, with corresponding LOQs of 0.8 ng/mL and 308 ng/mL, respectively. In matrix data for LODs ranged from 8 ng/g for veratridine to 6.4 µg/g for coumarin, with corresponding LOQs of 24 ng/g and 21.3 µg/g, respectively. In assessing the concentration of the plant toxins in their matrices the LOQ, as determined in the matrix matched standards, was used. The stability of each compound, when stored at 2–8 °C, was assessed when stored in solution, in glass storage vials, by measurement of the analytical standard (at a concentration of 100 ng/mL for all, except coumarin which was at 5000 ng/mL) against the calibration data. This was initially done on a weekly based for the first 4 weeks, then on a 2-week basis for a further 8 weeks, and finally on a 4-week basis for the remainder of the study (Figure 1). It was noted that the majority of the compounds are stable when stored in methanol between 2–8 °C. However, some influence of storage conditions is noted for cathinone and thujone (Figure 1). A reduction in % nominal concentration was observed after a period of around 30 weeks and 25 weeks for cathinone and thujone, respectively. While this was not investigated further, fresh solutions were prepared on a 3 monthly basis to eliminate the possibility of degradation by storage conditions.

The developed method was applied to the analysis of plant materials obtained from Alnwick Poison Garden for the presence of the toxins (Table 5a). Due to the unknown stability of the plant material once collected all extractions were performed within 24 hrs by maceration followed by solid liquid extraction in methanol. As a family, *Solanaceae*, contained the overall highest concentrations of plant toxins. Specifically, *Atropa belladona* fruit were found to contain the highest concentration of toxins, specifically atropine 63 mg/g and scopolamine 44 mg/g. Additionally, notably high levels of psoralen (1.4–1.7 mg/g), 5-methoxypsoralen (0.9–1.3 mg/g) and 8-methoxypsoralen (0.7–0.5 mg/g) were found in the family, *Apiaceae*, and specifically *Heracleum mantegazzianum*, in both the flower and leaf. Similarly, the presence of these compounds (psoralen, 5-methoxypsoralen and 8-methoxypsoralen) were noted in the family, *Rutaceae*, in the leaf and fruit of *Ruta graveolens*

but at lower concentrations (typically ranging from 0.004 to 0.3 mg/g). The family, *Plantaginaceae*, in the genus *Digitalis*, contained levels of digoxin (from 0.08 mg/g to 0.03 mg/g) and digitoxin (from 0.2 mg/g to 0.07 mg/g) in the flower, leaf and seed of *D. ferruginea* while the leaf of *D. purpurea* contained 0.2 mg/g digitoxin and 0.001 mg/g digoxin. Finally, of note, is the concentration of colchicine in the bulb (0.6 m/g) and leaf (0.1 mg/g) of *Colchicum autumnale*.

Table 4. Analytical figures of merit for developed method.

Compound	Calibration Range (ng/mL)	No of Data Points	Linearity (y=)	R^2 Value	Precision (%CV) (Low, Mid, High)	LOD (in Solution) (ng/mL)	LOQ (in Solution) (ng/mL)	LOD (in Matrix) (ng/g)	LOQ (in Matrix) (ng/g)
5-methoxypsoralen	0–100	7	1325.5x + 2893	0.9964	10, 4.6, 2.3	2.0	6.7	128	389
8-methoxypsoralen	0–100	7	1315.3x − 1107.7	0.9984	9.3, 2.2, 2.9	0.7	2.3	56	169
Aconitine	0–100	7	7001.2x −6390.8	0.9991	1.5, 0.9, 2.9	1.0	3.3	500	1515
Atropine	0–100	7	4227.2x − 5294.6	0.9994	2.8, 2.6, 6.9	3.7	12	259	784
Cathinone	0–100	7	7116.8x − 36,698	0.9957	1.4, 3.2, 2.4	6.3	20.1	488	1478
Colchicine	0–100	7	267.94x + 115.8	0.9985	3.5, 4.1, 4.0	0.3	1.1	27	82
Coumarin	0–5000	10	4.1771x − 158.54	0.9990	0.6, 2.3, 1.7	92	308	6450	21,276
Digitoxin	0–100	7	108.28x +258.93	0.9959	2.9, 5.0, 2.9	1.1	3.5	94	286
Digoxin	0–300	7	30.352x − 47.162	0.9988	2.8, 5.2, 4.1	5.5	18.2	134	407
Hellebrin	0–400	10	195.98x + 1686.6	0.9981	6.0, 6.7, 6.5	7.5	25	527	1597
Psoralen	0–100	7	198.35x − 491.57	0.9952	10.7, 2.7, 3.3	1.2	4.1	79	238
Scopolamine	0–100	7	720.56x + 142.49	0.9993	0.8, 5.5, 5.4	1.0	3.3	177	536
Solanine	0–100	7	2478.2x + 959.64	0.9996	1.8, 1.4, 1.6	2.4	7.9	103	311
Thujone	0–100	7	73.474x + 180.44	0.9969	3.4, 2.8, 2.1	2.7	8.5	101	305
Veratridine	0–100	7	6533.4x − 814.27	0.9979	2.1, 1.0, 0.3	0.2	0.8	8	24

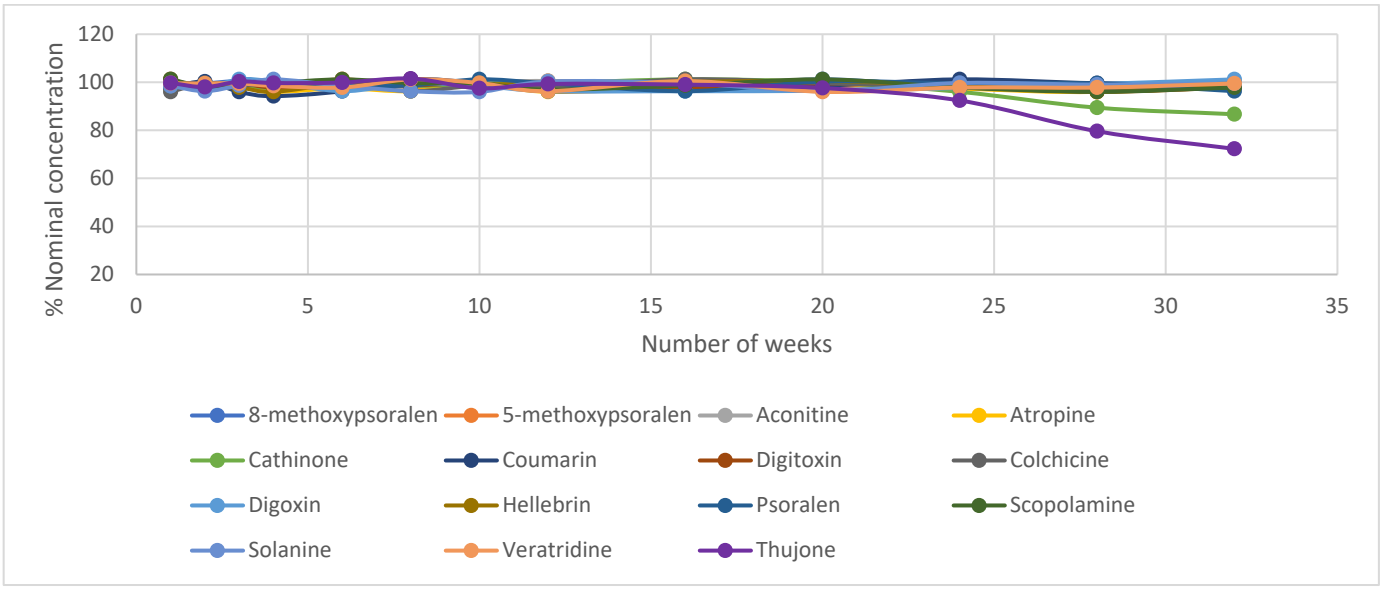


Figure 1. Stability of analytical standards, stored in methanol, at 2–8 °C.

Table 5. Summary of plant toxin data (a) actual concentration, and (b) calculated human health risk.

Family	Genus	Species	Common Name	Part of Plant	Ground Position	Compound	(a)	(b)		
							Concentration (μg/g) ± SD (n = 3)	Exposure Factor (μg/kg-day)	Compound LD_{50} (mg/kg)	Days (Years) to Reach LD_{50}
Apiaceae	*Heracleum*	*H. mantegazzianum*	Giant hogweed	Flower	above	Psoralen	1428 ± 30	9000	1700	190
					above	5-Methoxypsoralen	920 ± 15	5800	>3000	519 (>1)
					above	8-Methoxypsoralen	672 ± 10	4200	791	188
				Leaf	above	Psoralen	1703 ± 14	11,000	1700	159
					above	5-Methoxypsoralen	1298 ± 17	8100	>3000	368 (>1)
					above	8-Methoxypsoralen	499 ± 21	3100	791	252
Asteraceae	*Artemisia*	A. absinthium	Common wormwood	Leaf	above	Thujone	322 ± 9.7	2000	500	247
				Stem	above	Thujone	110 ± 3.5	688	500	727 (>2)
Celastraceae	*Catha*	*C. edulis*	Khat	Leaf	above	Cathinone	ND	ND	379.7	ND
Colchicaceae	*Colchicum*	*C. autumnale*	Autumn crocus	Bulb	below	Colchicine	578 ± 3	3,600,000	5.87	0.002
				Leaf	above	Colchicine	127 ± 1	800,000	5.87	0.007
Liliaceae	*Fritillaria*	*F. imperialis*	Crown imperial	Leaf	above	Veratridine	0.44 ± 0.01	2.8	1.35	489 (>1)
				Stem	above	Veratridine	ND	ND	1.35	ND
		F. meleagris	Snake's head	Leaf	above	Veratridine	0.04 ± 0.001	0.3	1.35	5400 (>14)
				Stem	above	Veratridine	ND	ND	1.35	ND
Melanthiaceae	*Veratrum*	*V. album*	White hellebore	Flower	above	Veratridine	1.3 ± 0.02	8.3	1.35	163
				Seed	above	Veratridine	ND	ND	1.35	ND
Plantaginaceae	*Digitalis*	*D. ferruginea*	Rusty foxglove	Flower	above	Digitoxin	184 ± 2	1200	3527	3000 (>8)
					above	Digoxin	81 ± 1	506	28.27	56 (<1)
				Leaf	above	Digitoxin	70 ± 0.6	440	3527	8000 (>21)
					above	Digoxin	ND	ND	28.27	ND
				Seed	above	Digitoxin	244 ± 3	1500	3527	2300 (>6)
					above	Digoxin	26 ± 0.6	160	28.27	176
		D. purpurea	Foxglove	Leaf	above	Digitoxin	256 ± 4	1600	3527	2200 (>6)
					above	Digoxin	1.1 ± 0.1	6.7	28.27	4200 (>11)

Table 5. *Cont.*

Family	Genus	Species	Common Name	Part of Plant	Ground Position	Compound	(a)		(b)	
							Concentration (μg/g) ± SD (n = 3)	Exposure Factor (μg/kg-day)	Compound LD_{50} (mg/kg)	Days (Years) to Reach LD_{50}
Ranunculaceae	*Helleborous*	*H. argutifolis*	Holly-leaved hellebore	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	1.6 ± 0.03	1.1	8.4	7800 (>25)
		H. niger	Christmas rose	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	ND	ND	8.4	ND
		H. orientalis	Lenten rose	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	18.1 ± 1.2	12.5	8.4	669 (>1)
		H. cyclophyllus	-	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	ND	ND	8.4	ND
		H. early purple	-	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	10.8 ± 1	7.5	8.4	1100 (>3)
		H. viridis	Green hellebore	Flower	above	Hellebrin	ND	ND	8.4	ND
				Leaf	above	Hellebrin	ND	ND	8.4	ND
				Root	below	Hellebrin	55.6 ± 2.9	38.4	8.4	218
	Aconitum	*A. lycoctonum*	Wolf's-bane	Leaf	above	Aconitine	ND	ND	1	ND
				Stem	above	Aconitine	ND	ND	1	ND
		A. napellus	Monk's-hood	Leaf	above	Aconitine	1.7 ± 0.02	10.9	1	92
				Stem	above	Aconitine	ND	ND	1	ND
	Aquilegia	*A. alpina*	Breath of God	Flower	above	Aconitine	ND	ND	1	ND
				Seed	above	Aconitine	ND	ND	1	ND
				Stem	above	Aconitine	ND	ND	1	ND
		A. atrata	Dark columbine	Flower	above	Aconitine	ND	ND	1	ND
				Leaf	above	Aconitine	ND	ND	1	ND
				Stem	above	Aconitine	ND	ND	1	ND
				Seed	above	Aconitine	ND	ND	1	ND

Table 5. *Cont.*

Family	Genus	Species	Common Name	Part of Plant	Ground Position	Compound	(a)		(b)	
							Concentration (μg/g) ± SD (n = 3)	Exposure Factor (μg/kg-day)	Compound LD_{50} (mg/kg)	Days (Years) to Reach LD_{50}
Rutaceae	*Ruta*	*R. graveolens*	Rue	Leaf	above	Psoralen	343 ± 5	2200	1700	790 (>2)
					above	5-Methoxypsoralen	335 ± 5	2100	>3000	1400 (>3)
					above	8-Methoxypsoralen	139 ± 4	873	791	905 (>2)
				Fruit	above	Psoralen	42 ± 0.5	265	1700	6400 (>17)
					above	5-Methoxypsoralen	ND	ND	>3000	ND
					above	8-Methoxypsoralen	4.1 ± 0.04	25	791	31,000 (>85)
Solanaceae	*Atropa*	*A. belladonna*	Deadly nightshade	Fruit	above	Atropine	63,146 ± 126	400,000	75	0.19
					above	Scopolamine	44,498 ± 1201	280,000	1300	4.7
				Leaf	above	Atropine	2117 ± 176	13,000	75	5.6
					above	Scopolamine	388 ± 2	2400	1300	534 (>1)
	Brugmansia	*B. suaveolens*	Angel's trumpet	Flower	above	Atropine	31 ± 0.8	197	75	380 (>1)
					above	Scopolamine	29 ± 3	185	1300	7000 (>19)
				Pollen	above	Atropine	79 ± 1	494	75	152
					above	Scopolamine	69 ± 0.5	433	1300	3000 (>8)
				Stem	above	Atropine	100 ± 2	625	75	120
					above	Scopolamine	5257 ± 37	33,000	1300	39
	Hyoscyamus	*H. niger*	Henbane	Flower	above	Atropine	61 ± 1.2	385	75	195
					above	Scopolamine	2755 ± 58	17,000	1300	75
				Root	below	Atropine	6.9 ± 0.2	4.8	75	16,000 (>43)
					below	Scopolamine	36 ± 1	25	1300	52,000 (>100)
				Seed	above	Atropine	91 ± 6	574	75	131
					above	Scopolamine	3907 ± 176	25,000	1300	53
	Solanum	*S. dulcamara*	Bittersweet	Flower	above	Solanine	ND	ND	590	ND
				Leaf	above	Solanine	0.73 ± 0.01	4600	590	129
				Stem	above	Solanine	0.93 ± 0.01	5800	590	101
				Root	below	Solanine	ND	ND	590	ND
Thymelaeceae	*Daphne*	*D. laureola*	Spurge laurel	Leaf	above	Coumarin	98 ± 0.2	612	359.5	587 (>1)

ND = <LOQ in the matrix (see Table 4).

To assess the risk of exposure to young children (aged from 1 to <2 years old) from the plants in the Poison Garden, the exposure factors for ingestion were calculated. This can be done using the following equation [49–52]:

$$\text{Ingestion exposure risk (ADD)} = C_{medium} \times \text{IngR} \times \text{EF} \times \text{ED/BW} \times \text{AT} \quad (1)$$

where:

ADD = Average daily potential dose (mg/kg-day).

C_{medium} = Concentration of contaminant (mg/g).

IngR = Ingestion rate (mg/day); calculated for plants above ($IngR_a$) and below ($IngR_b$) ground.

EF = Exposure frequency (0.088 days/year).

ED = Exposure duration (5 years).

BW = Body weight (11.4 kg).

AT = Average time of exposure (5 days).

However, some assumptions are required and are noted in Table 6. For the $IngR_a$ for the plant material located above the ground the ingestion rate for fruit and vegetables was used [49] whereas for the ingestion rate for plant material below ground the ingestion rate via soil and dust was used [49] as it is unlikely that roots would be accidentally eaten. The determined exposure factors (Table 5b) were then compared to the compound's LD_{50} and an estimate made of the amount of exposure required to reach the LD_{50} was done, using the data from the exposure factor (Table 5b) [53–67]. From the calculated durations ingestion of *Colchicum autumnale* from either its leaves or the bulb poses the greatest risk with <1 day exposure required to reach the LD_{50} of 5.87 mg/kg [57]. Many of the plants investigated have exposure durations, assessed against their $LD_{50's}$, in days that mean accidental poisoning is possible, particularly for young children.

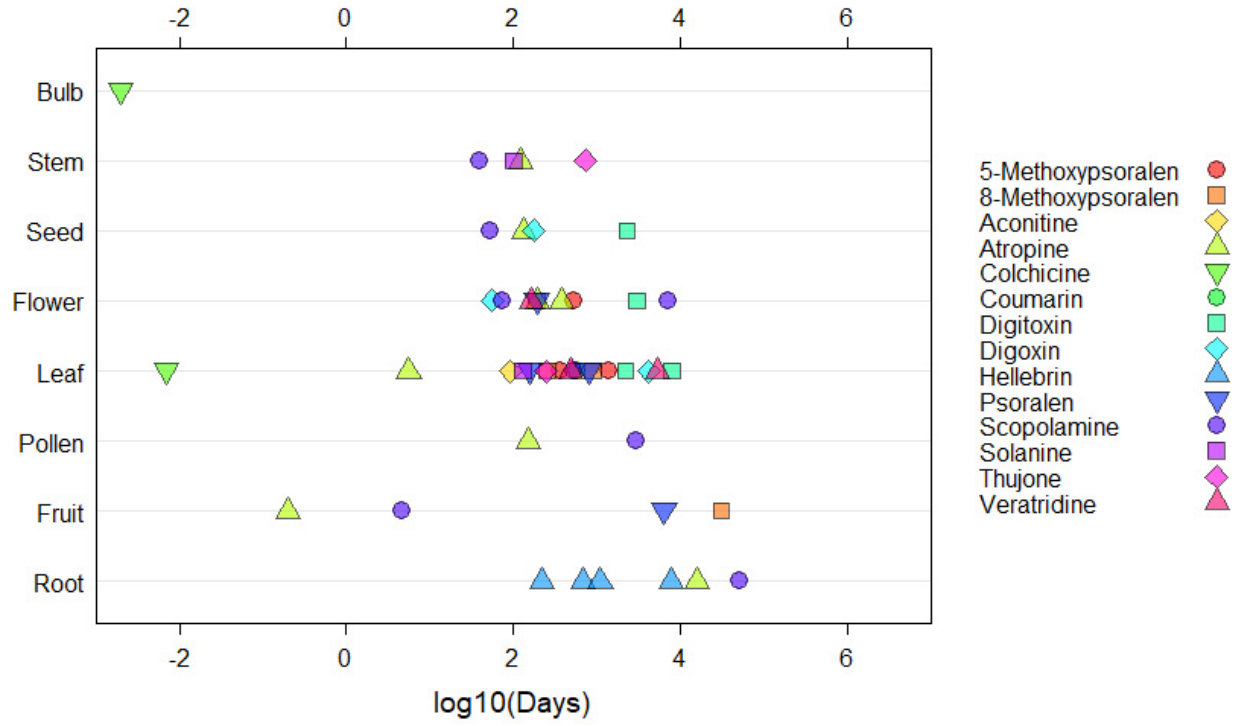
Table 6. Values used in risk factor calculations for a child (1–<2 years old).

Parameter	Abbreviation	Value (Units)
Exposure frequency	EF	0.088 (days/year)
Exposure duration	ED	5 (years)
Average time of exposure	AT	5 (days)
Body weight	BW	11.4 (kg)
Ingestion rate (above ground)	$IngR_a$	816 (mg/day)
Ingestion rate (below ground)	$IngR_b$	90 (mg/day)

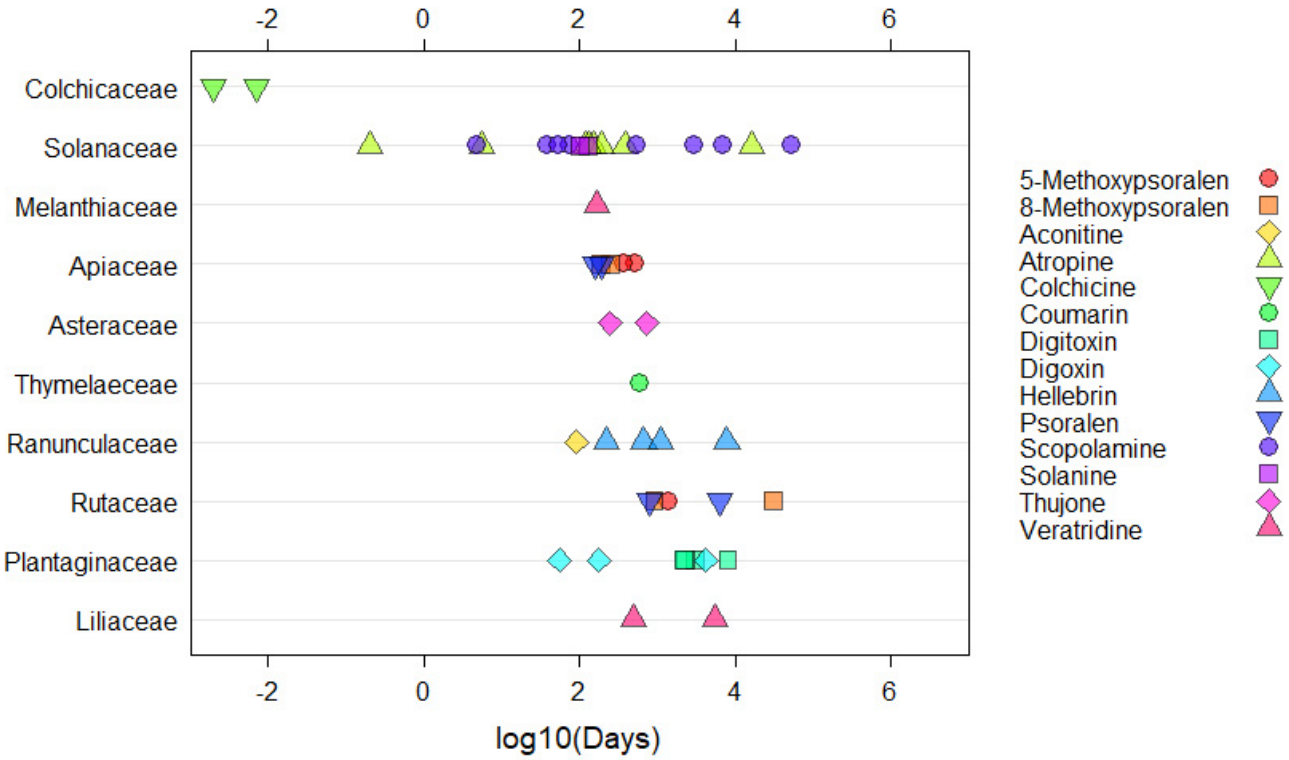
Note: The following presumptions were made: EF = Exposure frequency was estimated at 8 days per month over a period of four months while the plant is actively growing; ED = Exposure Duration was estimated at 5 years based, i.e., based on perennial plants staying in the garden for this duration; AT = the average time of exposure was estimated based on the likely average number of days of exposure; BW = body weight of a child aged 1 to <2 years [46]. $IngR_a$ = Ingestion rate for a child aged 1 to <2 years for the mean intake of fruit and vegetables. The EPA recommended value [47] for 2-day average intake of 9.3 g/kg-day, was converted to an Ingestion rate of 816 mg/day, based on the body weight. $IngR_b$ = Ingestion rate for a child aged 1 to <2 years for the average central tendency value. The EPA recommended for soil and dust for the general population was an ingestion rate of 90 mg/day [48]. N/A = not applicable.

Dot plots have been used to highlight the most important aspects of the results. It can be seen in Figure 2a that the highest risk from colchicine is from the bulb and leaf, whilst also noting that the fruit and leaf present the highest risk for atropine. Figure 2b highlights the effect of plant family and their human health risks. This plot reinforces the high risks associated with the family of *Colchicaceae* and *Solanaceae*. Some of the parts of the plants are accessible either above (flower, fruit, leaf, pollen, seed and stem), or below (bulb and root) ground (Figure 2c). It is observed that the highest risk is from colchicine below ground,

closely followed by its above ground presence. Of lower risk is the presence of atropine in above ground plant parts.

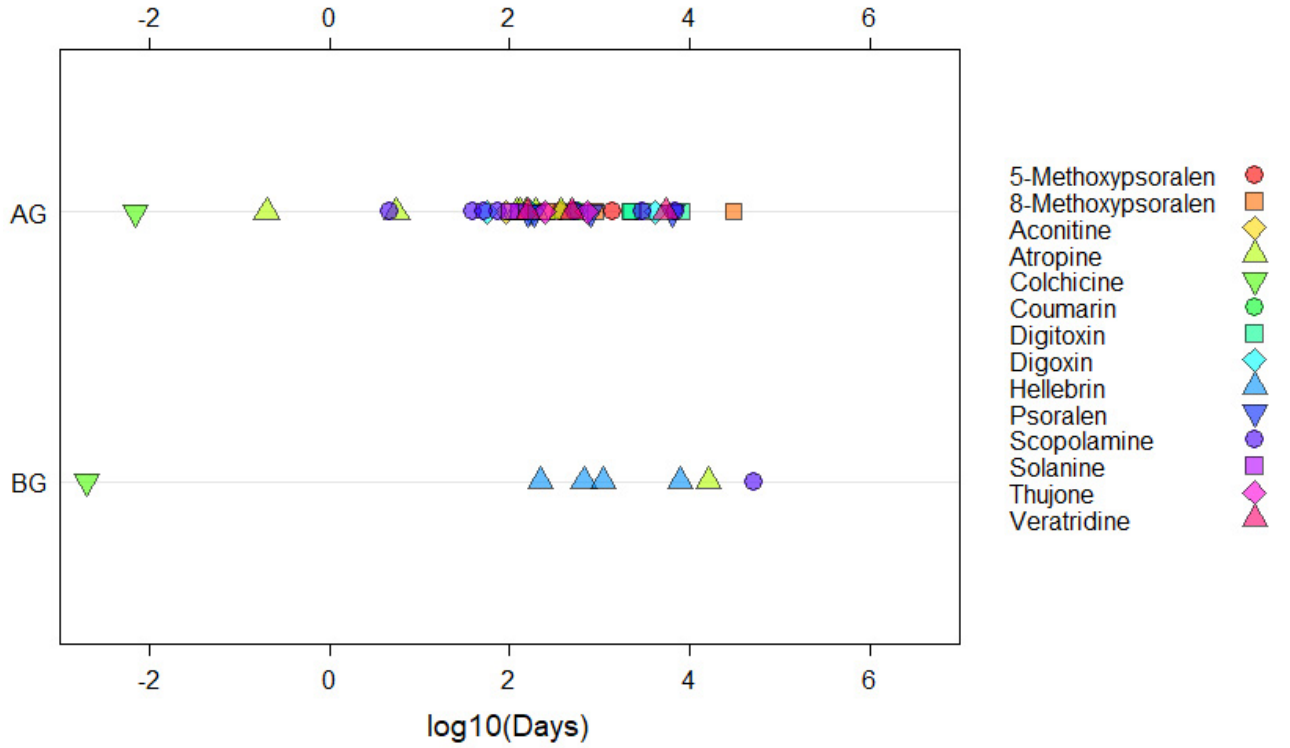


(**a**)



(**b**)

Figure 2. *Cont.*



(**c**)

Figure 2. Dot plots investigating the human health risk based on the number of days exposure to reach the compound LD50, as expressed as toxicity (**a**) Influence of plant anatomy, (**b**) Effect of plant family, and (**c**) Positioning of plant anatomy (above or below ground).

4. Conclusions

This research highlights the importance of assessing the human health risk to children (and adults) from commonly occurring plants. While the plants in this study were selected from the Poison Garden at Alnwick Gardens, many of them are found (and hence accessible) within public gardens, household gardens and woodlands and can be purchased from gardens centres. Therefore, better public awareness and information is required into the potential impact of toxins within plants to prevent the misidentification, miss-use and potentially fatal consequences associated with them.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/separations9100308/s1, Figure S1. Full scan MS/MS spectrum for (a) 5-methoxypsoralen, (b) 8-methoxypsoralen and (c) compound fragmentation; Figure S2. Full scan MS/MS for (a) aconitine and (b) compound fragmentation; Figure S3. Full scan MS/MS for (a) atropine and (b) compound fragmentation; Figure S4. Full scan MS/MS for (a) cathinone and (b) compound fragmentation; Figure S5. Full scan MS/MS for (a) colchicine and (b) compound fragmentation; Figure S6. Full scan MS/MS for (a) coumarin and (b) compound fragmentation; Figure S7. Full scan MS/MS spectrum for (a) digitoxin and (b) compound fragmentation; Figure S8. Full scan MS/MS spectrum for (a) digoxin and (b) compound fragmentation; Figure S9. Full scan MS/MS spectrum for (a) hellebrin and (b) compound fragmentation; Figure S10. Full scan MS/MS spectrum for (a) psoralen and (b) compound fragmentation; Figure S11. Full scan MS/MS spectrum for (a) scopolamine and (b) compound fragmentation; Figure S12. Full scan MS/MS spectrum for (a) α-solanine and (b) compound fragmentation; Figure S13. Full scan MS/MS spectrum for (a) α-thujone and (b) compound fragmentation; Figure S14. Full scan MS/MS spectrum for (a) veratridine and (b) compound fragmentation. Figure S15. Standard extracted ion chromatograms for (a) 5- and 8-methoxypsoralen, (b) aconitine, (c) atropine, (d) cathinone, (e) colchicine, (f) coumarin, (g) digitoxin,

(h) digoxin, (i) hellebrin, (j) psoralen, (k) scopolamine, (l) solanine, (m) thujone and (n) veratridine. References [68–74] are cited in the supplementary materials.

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