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Common Toxic Plants Poisoning in Serbia: The Experience of the National Poison Control Centre

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ABSTRACT

Introduction: The Republic of Serbia has a number of plants, contact with which can lead to poisoning, affecting different organ systems. The National Poison Control Centre (NPCC) is responsible for treatment of acute poisonings and providing information regarding the severity and treatment of toxic exposures.

Materials and Methods: Retrospective analysis of medical histories of patients with plant poisoning, treated at the NPCC during 2011-2021, and recorded calls regarding toxic plant exposure during that period.

Results: In the eleven-year period 46,061 patients with acute poisoning were treated at the NPCC, out of them 476 with suspected plant and mushroom poisonings. The main cause of poisoning were mushrooms with 279 cases (58.61%), followed by 46 cases of poisoning by Jimson Weed (*Datura stramonium*), Black Henbane (*Hyoscyamus niger*) and Deadly Nightshade (*Atropa belladonna*), while other toxic plants were the cause of only a small number of poisonings.

Conclusion: While mushroom poisonings were accidental, plants with anticholinergic effects were mainly abused due to their hallucinogenic effect. Other accidental plant poisonings occurred due to misidentification of edible plants with poisonous ones. The most severe poisonings were caused by Autumn Crocus (*Colchicum autumnale*) and White Hellebore (*Veratrum album*).

INTRODUCTION

Approximately 7,500 plant species have been registered in the Balkan region, which is about 70% of the total European flora. Data refer to 7,500 vascular plants compared to the total number of European flora consisted of 11,000 plant species [1]. Fortunately, only a small number of plant species lead to serious poisoning. They contain highly toxic compounds, which, when taken in small quantities, lead to severe poisoning or even death. Among wild plants are Autumn Crocus (*Colchicum autumnale L.,* Liliaceae), Black Henbane *(Hyoscyamus niger L., Solanaceae*), Deadly Nightshade (*Atropa belladonna L.* Solanaceae), Jimson Weed (*Datura stramonium L., Solanaceae*), Cuckoo Pint (*Arum maculatum L.,* Araceae) and Wild Hemlock (*Conium maculatum L., Apiaceae*). This review would be incomplete if it did not mention poisonous mushoorms, which, strictly speaking, do not belong to plants, but the largest number of severe poisonings with lethal outcome belongs to this system category. Among them, the most severe poisonings are caused by the mushroom *Amanita phalloides*. One of the most poisonous plants in Serbia and Europe is Monkshood (*Aconitum napellus L., Ranunculaceae*), but considering that it grows in high mountainous areas that are not

easily accessible and cannot be replaced with edible plants, the poisonings are rare. A much larger group of plants consists of species that are considered poisonous because they contain ingredients with a strong physiological effect, but lower toxicity. These plants can lead to poisoning, although severe poisoning occurs only exceptionally. In this group of plants White Hellebore (*Veratrum album L., Liliaceae*), Common Yew (*Taxus baccata L., Taxaceae*), Black Locust (*Robinia pseudoacacia L., Fabaceae)*, Greater Celandine (*Chelidonium majus L., Papaveraceae*), Lily of the valley (*Convallaria majalis L., Liliaceae*) [1].

Localization of toxic ingredients

Body systems and organs most prominently affected by plants include the digestive tract, liver, kidneys, and nervous system, heart and blood, skin, reproductive tract and its functioning. However, it is important to realize, that toxic plants rarely affect only one body system or organ and thus may generate a complex pattern of effects.

Active principles of strong physiological action (toxic substances) arise in plants through complex biochemical processes. The content of active ingredients is not uniform in the plant. Toxic ingredients are usually localized in some parts of the plant. For example, the Common Yew tree (*Taxus baccata*) is poisonous, except for the fleshy part of the seed (*arilus*) [2]. The whole Black Locust (*Robinia pseudoacacia*) is toxic, but only the flower is not toxic [3]. Inquiry to the National Poison Control Centre, regarding the poisoning of children who ate Black Locust bark was recorded.

Common Holly (*Ilex aquifolium, Aquifoliaceae*), a beautiful ornamental plant from which Christmas wreaths are made, contains poisonous compounds in the fruit. Symptoms of poisoning appear after ingestion of two berries. The lethal dose for children is 20-30 berries [3,4].

Plants with alkaloid compounds

Until the beginning of the 20th century, herbal extracts, tinctures or tea mixtures, made from herbal drugs containing alkaloids, could be bought in pharmacies. The most important representatives of alkaloids with condensed pyrrolidine and piperidine rings, which by pharmacological action belong to the mydriatic Solanaceae, are Deadly Nightshade (*Atropa belladonna*), Jimson Weed (*Datura stramonium*), Black Henbane (*Hyocyamus niger*), along with Henbane Bell (*Scopolia carnioli ca Jacq.*) and Mandrake (*Mandragora officinarium L.*) (Figure 1).

Figure 1: Deadly Nightshade (*Atropa belladonna L.*) (left). The leaves contain the alkaloid (-)-hyoscyamine. The forest of mountain Goc, Serbia. Jimson Weed (*Datura stramonium L.*) (in the midle). The leaves contain the alkaloids (-)-hyoscyamine and scopolamine. The territory of Belgrade (Kumodraz), Serbia. Black Henbane (*Hyocyamus niger L.*) (right). The leaves contain the alkaloid (-)-hyoscyamine. East Serbia (around Knjazevac). Photographs by G. Fodulovic.

These plants belong to the *Solanaceae* family. They contain tropane alkaloids, the most important of which are atropine, scopolamine and hyoscyamine [4-6].

Plants with heteroside compounds

Plants with cardiotonic glycosides are Foxgloves, Squil bulb (*Urginea maritime L., Liliaceae*), pheasant's eye (*Adonis vernalis L., Ranunculaceae*), Lily of the valley (*Convallaria majalis L., Liliaceae*), Black Hellebore (*Helleborus odorus L., Ranunculaceae*) and Oleander (*Nerium oleander L., Apocynaceae*) (Figure 2).

Figure 2: Lily of the valley (*Convallaria majalis L., Liliaceae*) contains about 20 cardiac glycosides. Convallotoxin, a digitalis-like cardioactive steroid, and irritant saponins are two of the main components. The whole plant is poisonous, as is the water in which flowers have been kept. The territory of Belgrade (Zvezdara). Photograph by Dmitar Lakusic.

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Foxgloves (*Digitalis purpurea L., Scrophulariaceae*) is a plant with bell-shaped white, pink or purple flowers. This plant, due to its beautiful appearance, is often an ornament in gardens. Foxgloves contains cardiotonic glycosides: purpurea glycoside, gitoxin and digitoxin. These glycosides, applied in a therapeutic dose, have a beneficial effect on heart, increase the contraction of the heart muscle and normalize the work of the heart in the case of heart failure [4,7,8].

MATERIALS AND METHODS

The NPCC is the only reference institution in the country (referral population was 6,945,235 on October 2019) for the management of acute poisonings and information support for medical professionals and general public with 24/7 service. It has two main organizational units: The Clinic of Emergency and Clinical Toxicology and The Institute of Toxicology and Pharmacology, which provide management of acute poisonings, information support and toxicological analyses. Retrospective analysis of medical histories and NPCC annual reports of patients with plant poisoning, treated at the NPCC during 2011-2021, and telephone calls from throughout the country, regarding toxic plant exposure in the same period, was performed. Recorded data included demographic data, the intent of exposures, exposure routes, clinical findings and treatment measures. Due to the technical capacity of the Toxicological Chemistry Department of the NPCC, results of toxicological analysis were available only for cases of poisonings by several plants, such as those with anticholinergic and mitosis-inhibiting properties. The Poisoning Severity Score grades severity as (0) none, (1) minor, (2) moderate, (3) severe, and (4) fatal poisoning were used for an overall evaluation of cases, taking into account the most severe clinical features.

Statistical analysis

Data on PSS score distribution were checked by Kolmogorov-Smirnov test. In the case of normal data distribution, ANOVA followed with the post hok Tukey test was used for testing significance. In the case of non-normal data distribution Kruskal-Wallis followed with the Mann-Whitney was used for testing significance. P value for both tests was set at 95% i.e. $p < 0.005$. Chi square test was used for testing significance in frequency of values. P value was also set at 95% i.e. $p < 0.005$, for this test. Statistica 10.0 was used.

Alkaloid colchicine was determined by liquid chromatography coupled with Diode-Array Detection (DAD) and confirmed by Liquid Chromatography with Mass Spectrometry (LC-MS), where data are collected either in full-scan ES+ mode at m/z 100-450. Colchicine was isolated from plasma or urine using a liquid- liquid extraction with chloroform at pH 9.6 with satisfactory extraction recoveries. Separation was achieved on the Symmetry® C8 column with mobile phase acetonitril: dihidrogen sodium phosphate 50 mM pH 3.6 in the gradient mode, and XTerra ® RP18 column with a mobile phase: 5 mM ammonium acetate (pH 3.5): acetonitril with 0, 1% acetic acid. The method is validated blood and linear in the range of 20-1000 ng/mL (r2> 0.99). Limit of detection was 10 ng/mL and limit of quantification was 20 ng/mL. Because of its good sensitivity HPLC-PDA-MS is a reliable technique. Alkaloids atropine, hyoscyamine, scopolamine and veratridine were determined by liquid chromatography coupled with Diode-Array Detection (DAD) and column Symmetry® C8 4,6 x 250mm Waters. Alkaloids were isolated from urine using a liquid- liquid extraction with chloroform (alkaline) (Figure 3).

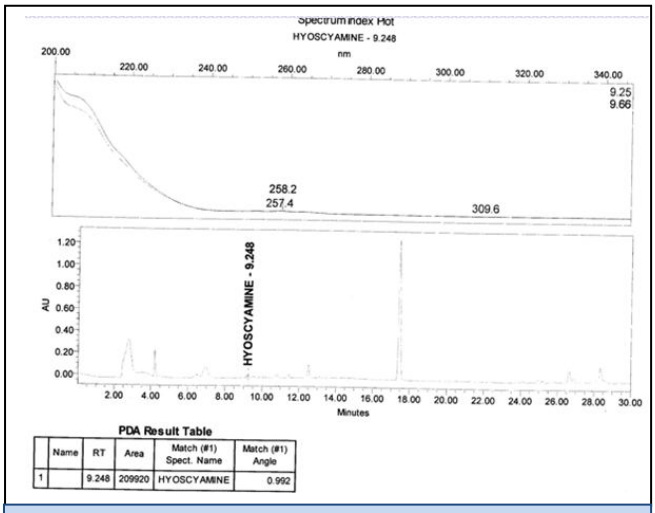

Figure 3: HPLC-PDA chromatogram hyoscyamine in urine and UV spectra hyoscyamine in urine and Waters Toxicology library.

Cases with phytomedicines and cannabis sativa were excluded as the clear distinction between various products (marijuana plant, processed product, and hashish) was not possible.

Ethical clearance was received from the Ethical Board of the Military Medical Academy.

RESULTS

The National Poison Control Centre (NPCC) Database analysis showed that in the eleven-year period from 2011 to 2021 (the

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territory of Belgrade and its wider surroundings, as well as other hospitals in Serbia in case of moderate and severe poisonings), the total number of patients treated due to acute poisoning was 46,061, out of it 476 (1.03%) with suspected mushroom and plant poisonings. Mushroom poisoning was confirmed in 279 (58.61%), plant poisoning in 81 (17.02%) patient, while 116 (24.36%) patients, who were examined as mushroom and plant poisonings, had alimentary intoxication. Similar distribution between men (51.5%) and women (48.5%) was noted. Regarding age distribution, poisoning was most frequent in group of patients of 19-65 years (81.3%), followed by >65 years (11.7%) and 5.6% were in the group of 14-18 years. Plant poisonings were predominantly caused by Jimson Weed (*Datura stramonium*), Black Henbane (*Hyoscyamus niger*) and Deadly Nightshade (*Atropa b elladonna*) that were noted in 46 patients (56%) (Table 1).

Table 1: Toxic plants involved in acute poisoning treated at the NPCC (2011-2021).

Year	Total number (n=81)	Plant Species	Plants Accidental	Plants Abuse	PSS 1	PSS 2	PSS 3	PSS 4
2011	3	*Datura stramonium*	-	3		2	1	
2012	19	*Datura stramonium*	-	11	6	5		
		Hyoscyamus niger	-	1			1	
		Atropa belladonna	-	4	3	1		
		Ricinus communis	1	-	1			
		Tamus communis	1	-	1			
		Unknown	1	-	1			
2013	7	*Datura stramonium*		2		2		
		Colchicum automnale	2	-	1	1		
		Ricinus communis	1		1			
		Hyoscyamus niger		1		1		
		Atropa belladonna	1	-		1		
2014	7	*Datura stramonium*	-	5	3	2		
		Colchicum automnale	2	-		1	1	
2015	8	*Datura stramonium*	-	5	2	3		
		Unknown	2	-	2			
		Papaver somniferum	-	1	1			
2016	7	*Datura stramonium*	-	3	1	2		
		Arum maculatum	1	-	1			
		Papaver somniferum + THC + Heroin	-	3	3			
2017	14	*Colchicum automnale*	1	-				1
		Datura stramonium	-	5	3	1	1	
		Nerium oleander	1			1		
		Argyrea nervosa	-	1	1			
		Unknown	5	-	5			
		Papaver somniferum	-	1	1			
2018	12	*Datura stramonium*	-	4	2	2		
		Veratrum album	2	-		2		
		Ricinus communis	1	-		1		
		Eucalyptus globulus	1	-	1			
		Pelargonium spp.	1	-	1			
		Atropa belladonna	-	1	1			
		Ricinus communis	1	-	1			
		Cheledonium majus	1	-	1			
2019	1	*Sempervivum tectorum*		1(smoking)	1			
2020	-		-	-				
January-November 2021	3	*Papaver somniferum*	-	2	2			
		Euphorbia trigona rubra	1	-	1			

*PSS 0: no signs; PSS 1: minor; PSS 2: moderate; PSS 3: severe; PSS 4: fatal

Except in one case, when the patient used *Sempervivum tectorum* for smoking, in all hospitalized patients poisonings were peroral. In the analyzed group of patients during this period, lethal outcome was registered in only one (1.2%) patient who ingested the plant with mitosis-inhibiting properties (*Colchicum autumnale*). Mild poisoning was registered in 48 (59.2%), moderate in 28 (34.5%) and severe in 4 (4.9%) patients who ingested poisonous plants.

The ANOVA test indicates that there is no significant difference among PSS scores among groups, however ANOVA test with post hoc Tukey test showed significantly higher number of PSS 1 - minor poisonings comparing with PSS 2, PSS 3 and PSS 4, respectively; $p = 0.00000121$.

Plants with anticholinergic effects were mainly abused due to their hallucinogenic effect. Other accidental plant poisonings occurred by replacing edible with poisonous plants. Anticholinergic effects, such as dry mouth, burning skin, dilated pupils, rapid heartbeat, hallucinations were predominant in poisonings caused by Jimson Weed (*Datura stramonium*), Black Henbane (*Hyocyamus niger*) and Deadly Nightshade (*Atropa belladonna*). Toxico-chemical analysis of biological material (blood and urine) confirmed the presence of atropine and hyoscyamine, and in some cases the presence of alcohol and other psychoactive substances, most often THC-carboxylic acid (derived from marijuana), was proven (Table 2).

Table 2: Effects of poisonus plants and toxic compounds.

Plant genus	Toxic compound	Toxicity of the plant	Clinical picture
Datura stramonium	Hyoscyamine, atropine and scopolamine	whole plant during the whole vegetation period	dry skin, flushing, mydriasis, tachycardia, hyperpyrexia, disorientation, confusion, hallucinations, psychosis, agitated delirium, seizures, coma, decreased bowel activity, urinary retention and neurological disorders with ataxia.
Hyoscyamus niger	Hyoscyamine, atropine and scopolamine	whole plant during the whole vegetation period	dry skin, flushing, mydriasis, tachycardia, hyperpyrexia, disorientation, confusion, hallucinations, psychosis, agitated delirium, seizures, coma, decreased bowel activity, urinary retention and neurological disorders with ataxia.
Atropa belladonna	atropine, hyoscyamine and scopolamine, a then pyridine and methyl proline	whole plant during the whole vegetation period	dry skin, flushing, mydriasis, tachycardia, hyperpyrexia, disorientation, confusion, hallucinations, psychosis, agitated delirium, seizures, coma, decreased bowel activity, urinary retention and neurological disorders with ataxia.
Ricinus communis	ricin	all parts of the plant, especially	Abdominal pain, emesis, diarrhoea, dehidration, circulatory collapse, muscle pain, dyspnoea, increase in leucocytes, BUN, AST, ALT.
Colchicum autumnale	colchicine	all parts of the plant but especially the seeds and bulb	Nausea, vomiting, diarrhoea, arrhythmia, renalfailure, bone marrow depletion, leucopoenia, hepatic lesion, acute respiratory insufficiency, leucocytosis, scock, organ faliure, death.
Papaver somniferum – poppy capsules	alkaloids (morphine)	poppy capsules	somnolence, coma, respiratory depression
Nerium oleander	cardiac glycosides (oleandrin, oleandrigenin, and then digitoxigenin and diginoside)	all parts of the plant	Nausea, headache, vomiting, disrrhythmias, tachyarrhythmias, bradycardia, heart block, confusion, dizziness, drowsiness, visual distrubances, mydrasis.
Eucalyptus globulus	monoterpens	leaves and oil	Nausea, vomiting, diarrhea, stomach pain, dizzines, muscle weakness, drowsiness, hallucinations, seizures, coma in severe poisonings
Arum maculatum	aroine, aronin, aroidin, oxalates	leaves, berries and flowers	irritation of skin, mouth, tongue and throat, swelling of throat, difficulty breathing, burning pain, upset stomach.

The most common problems in other poisonings were nausea, stomach pain, vomiting, after which, due to the expulsion of the contents. Five patients with *Colchicum automnale* poisoning were treated, four of them with mild poisoning and only gastrointestinal complaints. Single lethal outcome was registered in one patient, 40 years old, who accidentally ingested two whole plants of Autumn Crocus, believing that it is *Allium ursinum*. Seven hours later he had nausea, vomiting (20-30 times per day), diarrhea, tachycardia (130/min), hypertension (180/110 mmHg), leucocytosis (19.76), signs of

hepatic (AST 280, ALT 84) and acute renal failure. Colchicine was confrimed in following concentrations: 0.011 mg/L (blood sample) and 0.051 mg/L (urine) [9]. On Day 2 day cardiorespiratory insufficiency developed, and despite all therapeutic measures lethal outcome was registered. Colchicine concentrations in body fluids and organs (method HPLC-PDA and LC-MS): blood (0.011 mg/L), urine (0.051 mg/L), gastric - content not found, brain - not found, kidney (0.008 mg/kg) and liver with gallbladder (0.007 mg/kg) (Figure 4,5).

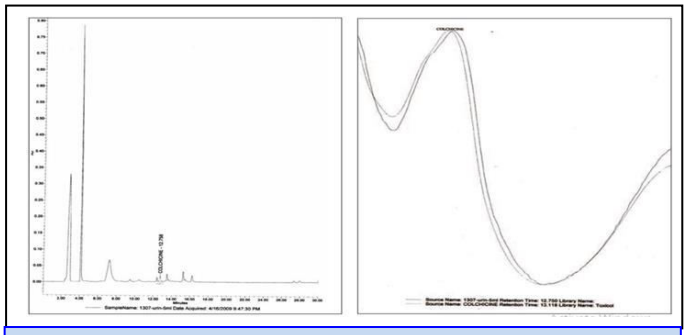

Figure 4: HPLC-PDA chromatogram colchicine in urine and UV spectra colchicine in urine and Waters Toxicology library.

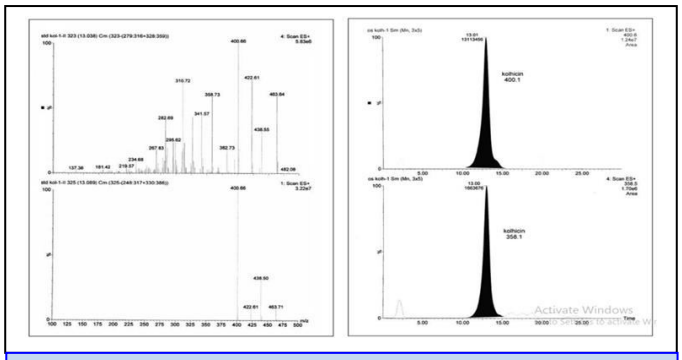

Figure 5: LC-MS chromatogram and mass spectrum of colchicine in urine.

A man aged 57 years, from the interior of the country, drank one sip of brandy which contained White Hellebore root (*Veratrum album L, Liliaceae*). Half an hour later he had nausea, vomiting, drowsiness, dizziness, trembling, gait instability and according to his wife, he shortly lost consciousness. At the admission to the NPCC, three hours later, he was alert, with hypotension (70/30 mmHg), bradycardia (40/min), SpO2 98%, pale skin, mydriasis and leucocytosis (17.29 x 10^9 per L). Toxico-chemical analysis of biological material (blood sample) confirmed the presence of veratridine (2 mg/L) and ethyl alcohol (0.04‰). The treatment included supportive and symptomatic measures, fluid replacement, vasopressors during 7 hours, resulting in full recovery.

A man aged 38 years, from the interior of the country, 20 hours before transfer from the local hospital, ingested castor bean (10-15 seeds) (*Ricinus communis, Euphorbiaceae*) in order to reduce bloating in the stomach. Two hours after ingestion he had nausea, vomiting (> 20 times), diarrhea (>10 times), hypotension (80/40 mmHg). Besides gastric lavage, supportive and symptomatic treatment and in spite of consultation of clinical toxicologyst from the NPCC, patient was transferred to the NPCC. At the admission he was alert, communicative, hypertensive (150/90 mmHg), tachycardic (105/min), while all laboratory analysis were within normale range. The treatment was continued with fluid replacement, probiotics and proton pump inhibitors. On Day 3 patient was discharged fully recovered.

Expected signs and symptoms of plant poisoning are presented in Table 2.

Besides medical treatment of acute poisonings, the NPCC provides continuous information support to medical professionals and general public throughout the year. The structure of calls to the Toxicological Information Department of the NPCC, for the period 2011-2020, shows that out of 132 inquiries related to toxic plant exposures, calls from pediatricians about toxic effects of decoration plants predominated (Table 3).

The Chi square test indicates that the number of calls is significantly higher for pediatric population, p = 0.00002164.

DISCUSSION

Despite the wide diversity of toxic plants in Serbia, acute plant poisonings are represented with 0.17% of all cases, while in 2019, the 55 U.S. poison control centers provided telephone guidance for over 2.1 million human poison exposures. Plant poisonings accounted for 26,417 (2.8%) cases [10].

During the eleven year period, at the NPCC, the total number of patients treated due to acute poisoning was 46,061, and out of it 81 poisonings with toxic plants were registered. Plant poisonings were predominatly caused by Jimson Weed (*Datura stramonium*), Black Henbane (*Hyocyamus niger*) and Deadly Nightshade (*Atropa belladonna*) that were noted in 46 patients (56.7%).

Black Henbane and Jimson Weed, which grow in neglected places, along roads and settlements, are extremely widespread in Serbia [11], especially Jimson Weed that

thrives easily in urban areas (teritory of Belgrade). Deadly Nightshade thrives in beech forests of the hilly and mountainous belt, while the Henbane Bell (*Scopolia carniolica L.*) is very rare (Kučajske mountains, around Majdanpek), so it is protected by law. Mandrake grows in bright forests along the roads of northern Italy and on the Adriatic coast. Anticholinergic effects, such as dry mouth, burning skin, dilated pupils, rapid heartbeat, hallucinations were predominant [12,13].

Table 3: The structure of calls at the Toxicological Information Department (2011-2020).

Year	Poisoning cases	Plant species	Pediatrician	General practitioner	Public
2011	12	Jimson Weed (***Datura stramonium*** *L, Solanaceae)*		1	
		Deadly Nightshade (***Atropa belladonna*** *L, Solanaceae)*		1	
		Fragrant Elephant's Ear (***Alocasia odora***, *Araceae)*	5		
		Castor Bean (***Ricinus communis*** *L, Euphorbiaceae)*	1	1	
		Lily of the valley (***Convallaria majalis*** *L, Liliaceae)*	1		
		Blackberry Nightshde (***Solanum nigrum*** *L, Solanaceae)*	1		
		Wisteria (***Wisteria sinensis*** (Sims) Sweet, *Fabaceae*)		1	
2012	14	Deadly Nightshade (***Atropa belladonna*** *L, Solanaceae*)		1	
		Mother-in-Law's Tongue ***Dieffenbachia seguine*** *(Jacq.) Schott,* Araceae)	4		
		Opium Poppy (***Papaver somniferum*** *L, Papaveraceae)*			1
		Castor Bean (***Ricinus communis*** *L, Euphorbiaceae)*		1	
		Oleander (***Nerium oleander*** *L, Apocynaceae)*	1		
		Fragrant Elephant's Ear (***Alocasia odora***, Araceae*)*	1		
		Philodendron (***Philodendron*** *spp. Araceae)*	1		
		Japanese Lantern Plant (***Physalis alkekengi***, *Solanaceae)*	1		
		Coontie (***Zamia integrifolia*** Aiton, *Zamiaceae*)	1		
		Unknown		2	
2013	17	Anthurium (***Anthurium anderanum***, *Araceae)*	1		
		Poison Hemlock (***Conium maculatum*** *L, Apiaceae*)		1	
		Holly (***Ilex aquifolium*** *L, Aquifoliaceae*)	1		
		Fragrant Elephant's Ear (***Alocasia odora***, *Araceae)*	1		
		Weeping Fig ***(Ficus benjamina*** *L, Moraceae)*	1		
		Azalea, Rhododendron ***(Rhododendron spp***, *Ericaceae)*	1		
		Heart-leaved bergenia	1		

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		(***Bergenia crassifolia***, *Saxifragaceae)*			
		Castor Bean (***Ricinus communis*** *L, Euphorbiaceae)*	1		1
		Black Locust (***Robinia pseudoacia*** *L, Fabaceae)*	1		
		Unknown	7		
2014	10	Jimson Weed (***Datura stramonium*** *L, Solanaceae)*		2	
		Fragrant Elephant's Ear (***Alocasia odora***, *Araceae)*	5		
		Heart-leaved bergenia (***Bergenia crassifolia***, Saxifragaceae)	1		
		Italian Arum (***Arum italicum*** *Mill.* Araceae)	1		
		Mother-in-Law's Tongue ***Dieffenbachia seguine*** *(Jacq.) Schott , Araceae)*	1		
2015	6	Fragrant Elephant's Ear (***Alocasia odora***, Araceae)	1		
		Italian Arum (***Arum italicum*** *Mill. Araceae*)	1		
		Garden hyacinth (***Hyacinthus orientalis***, *Asparagaceae)*	1		
		Hedge bindweed ***Calystegia sepium,*** *Convolvulaceae)*	1		
		Uknown	1		
		Castor Bean (***Ricinus communis*** *L, Euphorbiaceae)*	1		
2016	20	Fragrant Elephant's Ear (***Alocasia odora***, *Araceae)*	4		1
		European yew (***Taxus baccata***, *Taxaceae)*	1		
		Oleander (***Nerium oleander*** *L, Apocynaceae)*	1		
		Deadly Nightshade (***Atropa belladonna*** *L, Solanaceae)*		2	
		Chrysanthemum (***Chrysanthemum sp***, *Asteraceae)*			1
		Mother-in-Law's Tongue ***Dieffenbachia seguine*** *(Jacq.) Schott , Araceae*)	1		
		Meadow saffron ***Colchicum autumnale*** *L, Colchicaceae)*		2	
		Unknown	5		
		Coontie ***(Zamia integrifolia*** *Aiton, Zamiaceae)*	1		
		Tulip (***Tulipa spp.*** *Liliaceae)*			1
2017	16	*Oleander* (***Nerium oleander*** *L, Apocynaceae)*	2		
		Japanese Privet (***Ligustrum japonicum*** *Thunb.. Oleaceae)*	2		
		Cuckoopint (***Arum maculatum*** *L. Araceae)*	1		
		Jimson Weed ***(Datura stramonium*** *L, Solanaceae)*	1		
		Mother-in-Law's Tongue	3		

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		Dieffenbachia seguine *(Jacq.) Schott , Araceae)*			
		Calla Lily (***Zantedeschia aethiopica*** *L) Spreng., Araceae*)	1		
		Iris (***Iiris germanica***, *Iridaceae)*	1		
		Western Redcedar (***Thuja plicata***, *Cupressaceae)*	1		
		Lady orchid (***Orchis purpurea,*** *Orchidaceae)*	1		
		Uknown	2		
		Meadow saffron ***Colchicum autumnale*** *L, Colchicaceae*)		1	
2018	10	Castor Bean (***Ricinus communis*** *L, Euphorbiaceae)*	2		
		Fragrant Elephant's Ear (***Alocasia odora***, *Araceae*)	3		
		Calathea (***Calathea crotalifera***, *Marantaceae*)	1		
		Virginia creeper ***Parthenocissus quinquefelia***, *Vitaceae*)	1		
		Grat yellow gentian (***Gentiana lutea*** *L, Gentianaceae)*		1	
		Turmeric (***Curcuma longa***, *Zingiberaceae*)	1		
		Uknown	1		
2019	9	Ivy (***Hedera helix***, *Araliaceae*)	1		
		Peace Lily (***Spathiphyllum spp.,*** *Araceae*)	1		
		Daffodil ***Narcissus poeticus***, Amaryllidaceae)		1	
		Meadow saffron ***Colchicum autumnale*** *L, Liliaceae*)		1	
		Fragrant Elephant's Ear (***Alocasia odora***, *Araceae)*	3		
		Weeping Fig (***Ficus benjamin*** *L, Moraceae*)	1		
		Henbane (***Hyosciamus niger*** *L,* Solanaceae)	1		
2020	18	Hydrangea (***Hydrangea macrophylla*** *(Thunb.) Ser.,* Saxifragaceae)			1
		Meadow saffron ***Colchicum autumnale*** *L,* Liliaceae)		2	1
		Black Locust ***Robinia pseudoacacia,*** *L,* Fabaceae*)*			1
		Sage (***Salvia spp***. Lamiaceae)	1		
		Fragrant Elephant's Ear (***Alocasia odora***, Araceae)	1		
		Uknown	1		2
		Deadly Nightshade (***Atropa belladonna*** *L,* Solanaceae*)*		1	1
		Italian Arum	1		

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		(***Arum italicum*** *Mill.* Araceae)			
		Aetheroleum origani			1
		Henbane (***Hyosciamus niger*** *L,* Solanaceae)		2	
		Pokeweed (***Phytolacca americana*** *L,* Phytolaccaceae)			1
		Ivy (***Hedera helix***, Araliaceae)			1

Autumn Crocus (*Colchicum autumnale L., Liliaceae*) - usually found in wet medows. Three species of the genus *Colchicum L.* [14] are registered in Serbia. *Colchicum autumnale L.* is the most widespread species with two varieties: *var.autumnale* (West Serbia - Zlatar, Tara, Cer) and *var.pannonicum* (Southeast Serbia – Knjazevac area, South Serbia - Vranje area). *C.arenarium* W.K. dominates in Northeast Serbia and Vojvodina (Deliblato Sands and Banat). *C.visianii* Parl. is spread on Apennine and Balkan peninsulas. It grows in Kosovo (near Peja). All species contain colchicine and related alkaloids. Autumn Crocus has a bulb from which the stem grows in autumn, when it usually blooms with a single light purple saffron-like flower. All parts of the plant are poisonous, and the seed is the most poisonous because it contains the alkaloid colchicine. The lethal dose is 20 mg of colchicine (5 g of seeds) for adults and 5 mg (1.25 g of seeds) for children. Colchicine is a cellular poison and antimitotic. Clinical manifestations of poisoning go through three phases, after a latent period lasting from 3 to 12 hours after ingestion. In the first phase, there is a characteristic itching in the throat and difficulty swallowing, followed by nausea, vomiting, bloody diarrhea, abdominal pain. In the second phase of poisoning, 1 to 3 days after ingestion, bone marrow dysfunction, leukopenia and thrombocytopenia, acute hepatic lesion, rhabdomyolysis, acute renal failure and cardiorespiratory failure occur. In the third phase, after 5-7 days, there is an increase in the number of leukocytes and gradual recovery of the patient [15,16]. If the patient is not provided with medical assistance, death occurs in 2-3 days. Poisoning most often occurs in the spring, as a result of replacing Ramsons, or bear, wild onion (*Allium ursinum L.*), the plant is used as a spice and has a smell similar to garlic) with Autumn Crocus (which has no odor and is bitter has a bulb from which the stem grows in autumn, when it usually blooms with a single light purple saffron-like flower (Figure 6).

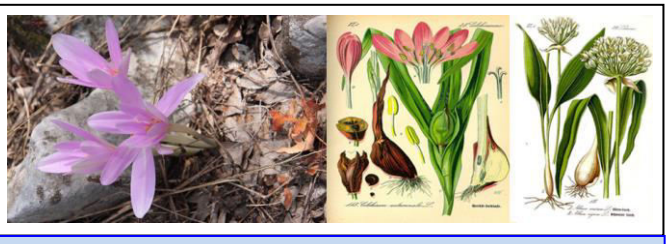

Figure 6: Autumn Crocus (*Colchicum autumnale L, Liliaceae*). The mountain Goc, from field, Serbia. Photograph by G. Fodulovic. The name of the genus Colchicum comes from the name of the ancient Colchicum (today's Georgia) after which Carl Line chose the name of the genus, as delicate light purple flowers appear straight from the ground. In the spring, poisoning occurs due to the replacement with *Allium ursinum* (bear onion), which can be found in the same habitats and apparently has similar leaves, frost does not bloom at that time. Bear onion has white flowers. (https://en.wikipedia.org/wiki/Colchicum_autumnale#/media/File:Illustration_Colchicum_autumnale0.jpg) (https://www.wikiwand.com/en/Allium_ursinum)

Five patients with colchicine poisoning were treated at the National Center for Poison Control. These poisonings were due to the misidentification of the edible plant with a poisonous one. There was a fatal poisoning at the NPCC in 2010, when person used honey mixed with Ramsons, which was replaced by Autumn Crocus, for the purpose of treatment. In the Department of Toxicological Chemistry, NPCC, the presence of colchicine was confirmed in all blood and urine samples of poisoned persons. Colchicine is also toxic to animals. The most sensitive domestic animals are horses, pigs and cows. However, it is interesting that the goat can tolerate a larger amount of colchicine without consequences. Poisonings of a large number of people with milk from goats that consumed Autumn Crocus have been reported [1].

Wild arum (*Arum maculatum L., Aracaceae*) – Two species of genus Arum are represented in Serbia: *A. maculatum* and *A. italicum Mill.* [17]. *A.maculatum* grows on soils rich in humus. It is

found in deciduous and coniferous forests from the lowlands to the subalpine zone. It is a very widesprad species in Serbia (found in forests around Belgrade). *A.italicum* is widespread in Mediterranean, while in Serbia it is sporadic. Both species are poisonous.

Wild arum has poisonous alkaloids aroine and coniine in all parts of the plant (as in the already described hemlock). After consuming beautiful orange-red berries, there is pain and burning sensation, then a feeling of insensibility in the mouth, strong thirst, difficulty swallowing, vomiting, diarrhea, lowering of the body temperature and in death in severe poisonings. The berries have an attractive appearance, but the taste of the plant is sharp, and the spindle blooms (cob) has an unpleasant odor of rotten flesh, but still poses a great danger to children and animals [8,18,19] (Figure 7).

Figure 7: Wild arum (*Arum maculatum* L, *Aracaceae*) has poisonous alkaloids aroine and coniine in all parts of the plant. Most exposures occur because of ingestion of the colorful fruit that attracts children. Previously thought to contain calcium oxalates; this has not been clearly established The territory of Belgrade (forest Kosutnjak), Serbia. Photograph by G. Fodulovic.

Since 2011, two poisonings with plants belonging to this family have been recorded at the NPCC (some plant species are grown as ornamentals, e.g. Adam (Fragrant Elephant,s Ear - *Alocasia odora*). In contrast to the poisonous parts of the plant, Wild arum's rhizome contains about 70% starch in the dried state, so it has been used in the diet during the past wars. It is known that Serbian soldiers used boiled and baked rice of this plant during their retreat through Albania [1,8,18].

White hellebore (*Veratrum album L., Liliaceae*) is a perennial plant. It grows on moist meadows, bright forests, especially in the mountain area. Two species of the genus *Veratrum L.* (*V.nigrum L.*, and *V. album L.*) are represented in Serbia [14]. *V.nigrum* grows in forests in mountainous areas in Balkans (such as Kosovo). In terms of chemical composition, Black Hellebore is similar to White Hellebore. *V.album* is a very widespread species in the mountainous regions of Serbia.

The whole plant is poisonous and contains the alkaloids protoveratrine A and B. In addition to human poisoning, frequent livestock poisoning has been reported. The powdered root causes a strong irritation for sneezing (hence the Latin name of the genus of this plant is “verere” – “to speak truthfully”, sneezing is considered a reliable sign that the truth is being told) [20]. Clinical picture of poisoning includes nausea, vomiting, diarrhea, hypotension, bradycardia, abdominal pain, dizziness and drowziness. In case of a more severe poisoning, there is muscle weakness and difficult and unstable gait, as well as a disorder in the coordination of movements. Loss of consciousness may occur. At the NPCC, accidental poisonings with hellebore root were recorded, which was replaced by the Yellow Gentian root (*Gentiana lutea L., Gentianaceae*) in alcoholic beverages, added as a bitter remedy. Both plants grow in the same habitats, have sessile leaves that are similar, with parallel nervation. The entire rim of hellebore (Yellow Gentian) has lower leaves on a short stalk, the upper ones are sessile, but hellebore rhizome is brown on the outside, densely overgrown with pale yellow roots, while the Yellow Gentian has a light yellow rhizome that forks into long thick roots [8,21-23] (Figure 8).

Figure 8: White Hellebore (*Veratrum album* L, *Liliaceae*). The mountain Stara planina, Serbia. Photograph by D. Stojanovic and Yellow Gentian (*Gentiana lutea* L, *Gentianaceae*) The mountain Tara, Serbia. Photograph by G. Fodulovic. White Hellebore and Yellow Gentian the mountain Goc, Serbia. Photograph by G. Fodulovic.

Monk's Hood (*Aconitum napellus L., Ranunculaceae*) - a perennial plant that has the deadly alkaloid aconitine in all parts, especially in the root. The lethal dose for an adult is 2-5 mg. It is considered the most poisonous plant in Europe, which usually grows in mountain areas. In Serbia it is known as "wolf's death" (before hunting, arrows were dipped in the extract of

the edible tuber). Poisoning can occur during picking, because the juice causes a rash on the skin, so it is necessary to use gloves. Some species of plants are grown as ornamental plants in gardens around the world. If a part of the plant is eaten, after a few minutes fever, sweating, a feeling of coldness and numbness (especially of the tongue) occur, followed by vomiting and diarrhea, poor vision and hearing, and within hours respiratory and cardiac arrest and death may occur.

According to the data of the American Association of Poison Control Centres, a case of poisoning with a lethal outcome was recorded in a 62-year-old man, after drinking a tea from Kazakhstan. Death occurred within hours despite all applied treatment [15].

Plants with cardiotonic glycosides are Foxgloves, Squil bulb (*Urginea maritime L.*), pheasant's eye (*Adonis vernalis L.*), Lily of the valley (*Convallaria majalis L.*), Black Hellebore (*Helleborus odorus L.*) and Oleander (*Nerium oleander L.*). Oleander (*Nerium oleander L., Apocinaceae*), one of the five most poisonous plants in the world contains cardiotonic glycosides (oleandrin). The leaves are the most poisonous due to the highest amount of cardiac glycosides [24,25]. The first signs of poisoning are nausea and headache, followed by vomiting, abdominal pain, mydriasis and arrhythmia. After ingestion of the lethal dose, heart failure and death occur after 2-3 hours. One poisoning of an elderly person who drank tea from the leaves of this plant for the purpose of suicide has been recorded at the National Poison Control Center since 2011.

Poisoning with ornamental plant species, which were mostly mild, occurs sporadically. Compared to the reports of other poison control centers in the world, as well as in Serbia, the most frequent contact with plants was accidental, and patients remained asymptomatic or developed mild symptoms, which completely resolved in a short time [26].

English Yew (*Taxus baccata L., Taxaceae*) is a tree about 15 m high. It is widespread in northern and central Europe. In Serbia, it grows in beech forests. In West Serbia it is found on Zlatibor and Kopaonik, while in East Serbia it grows in Resava gorge, Djerdap gorge on steep limestone cliffs that descend to Danube (Figure 9). In Serbia, it is ofthen found as an ornamental and cultivated species in parks and gardens [27,28].

Figure 9: Common Yew (*Taxus baccata* L, *Taxaceae*). The whole plant is poisonous except for the arilus. The leaves are a source of 10-deacetyl-baccatin III which is a raw material for the semi-synthesis of paclitaxel (antineoplastic drag). East Serbia (Djerdap gorge). Photograph by G. Fodulovic.

The whole plant is poisonous except for the arilus. It contains the alkaloid taxine (more than 30 toxin derivatives have been isolated) and small amounts of ephedrine and hydrocyanic acid. Severe poisoning with fatal outcome was noted after taking seeds and needles. After an hour or two, abdominal pains, fainting, mydriasis, bradycardia, arrhythmia, coma and death due to circulatory collapse and respiratory paralysis occur.

Proteins are an integral part of all cells of a living organism. In plants, they are mostly present in seeds as reserve substances. Certain plant proteins (toxalbumins) are the cause of severe poisoning, often fatal. Toxalbumin ricin is found in the seedlings of castor seeds (*Ricinus communis L, Euphorbiaceae*) (Figure 10). It is an extremely strong toxin, so many authors compare it with cyanide, nerve agents and cobra and rattlesnake toxins [4,20]. Six seeds can lead to fatal poisoning of an adult. The severity of the clinical picture depends on the mode of exposure.

Ricin in the form of an aerosol leads to acute lung damage, pulmonary edema and acute respiratory distress syndrome and acute respiratory insufficiency, and death occurs after 36 to 72 hours. Taken intramuscularly, it leads to local tissue extinction,

internal bleeding, hepato-renal insufficiency and death occurs after four days. The most notorious crime committed by ricin is "umbrella murder" (Georgi Markov, a Bulgarian dissident killed in London in 1978) [4].

Figure 10: *Ricinus communis* L, *Euphorbiaceae*, plant is quite decorative. In thrives in Serbia, and it is most often cultivated in Banat and Backa. (https://agroekonomija.files.wordpress.com/2012/12/ricinus.jpg)

Ricin, ingested with food, leads to gastrointestinal problems, including bubrnih sensation in mouth and throat, abdominal pain, vomiting and diarrhea, severe dehidration, hypotension and a decrease in urine. If untreated, death may occur after 3 to 5 days. All poisonings, treated at the NPCC, had favourable outcome.

One should not waste time with the analysis of the plant in question, but immediately induce vomiting, unless there is a disturbance of consciousness when intubation should be performed first. Then continue with symptomatic and supportive treatment. According to the German Poison Control Centre, there were 42,344 confirmed contacts with various plant species. Of these, 39,346 (93%) cases were characterized as asymptomatic, while only 3 (0.007%) had severe symptoms of poisoning. Twenty-six plant genera were responsible for 70% of all registered cases. Accidental poisonings of children aged 6 months to 5 years occurred mainly (98%) due to peroral intake (60%) [16].

Swiss Toxicology Information Center, between January 1995 and December 2009, reported 42,193 cases of exposure to various plant species were analyzed. Of these, 255 acute poisonings with moderate, severe and lethal outcomes were reported. Severe and fatal intoxications were extremely rare and were caused by plants with cardiotoxic properties (Yew - *Taxus baccata*) or *Colchicum autumnale* [26].

According to the American Association of Toxicology Centers, 44,731 cases of exposure to various plant species have been reported. Of that, for 12.2% (5,466 / 44,731) it was not possible, for various reasons, to make an accurate identification of these species. The most common positive identification exposures to plants are the following: species containing amygdalin and cyanogenic glycosides (1,158 cases), *Phytolacca americana L.* (1,135 cases with gastrointestinal symptoms), *Philodendron* (621 cases with oxalates as the cause of poisoning), *Zantedeschia aethiopica* (500 cases with oxalates as the cause of poisoning) and fewer number of other cases of poisoning [9,15].

CONCLUSIONS

Despite the wide diversity of toxic plants in Serbia, this type of poisoning is rare. Accidental poisoning in adults occurs due to misidentification of edible plants with poisonous one, while abuse of plants with anticholinergic effect is registered in adolescents. Timely information about toxic plants effects is crucial for pediatric service. Taking into account that epidemiology of plant poisonings is geographically specific, the awareness of clinicians of local poisonous plants and their toxicities should be improved.

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