

Toksikovigilanca - Etnotoksikologija



Lucija Perharič

Lucija.perharic@nijz.si

SEMINAR IZ KAKOVOSTI IN VARNOSTI V ZDRAVSTVU SOCIALNE MEDICINE, HIGIENE, EPIDEMIOLOGIJE
IN ZDRAVSTVENE EKONOMIKE ZA PRIPRAVNIKE ZDRAVNIKE IN ZOBOZDRAVNIKE

9.10.2026

Toksikovigilanca

- zbiranje in analiza informacij o učinkih kemičnih snovi
 - pri akcidentalnih in namernih zastrupitvah,
 - pri poklicni izpostavljenosti,
 - pri izpostavljenosti iz okolja (zrak, voda, tla, hišni prah),
 - pri izpostavljenosti preko hrane in predmetov splošne rabe;
- ocena tveganja (presoja varnosti) kemičnih snovi;
- posredovanje informacij strokovni in laični javnosti;
- pripravo predlogov za aktivnosti, ki izboljšajo kemijsko varnost
- spremljanje učinkovitosti tovrstnih aktivnosti.

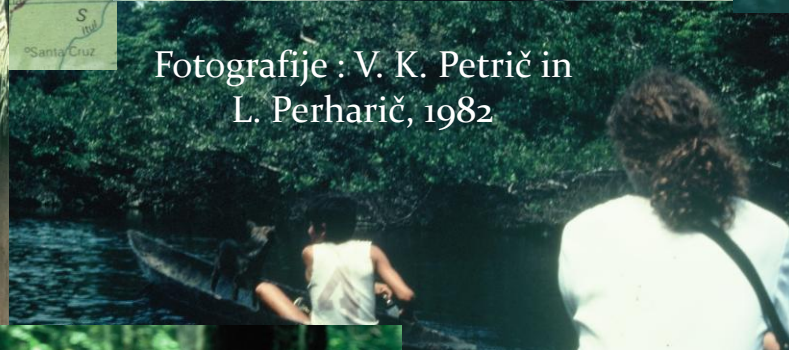
Namen

varovanje zdravja in preprečevanje bolezni, stanj in zastrupitev, ki lahko nastanejo kot posledica izpostavljenosti naravnim in umetnim kemikalijam iz različnih segmentov okolja (zrak, voda, tla, hišni prah) vključno z živali in predmeti splošne rabe

Etnofarmakologija in etnotoksikologija

- **Etnofarmakologija** proučuje ljudsko (lokalno) in tradicionalno uporabo rastlin, živali, gliv, mikroorganizmov in mineralov za preprečevanje ali zdravljenje bolezni ljudi in živali.
- **Etnotoksikologija** proučuje škodljive posledice etnofarmakoloških učinkovin in pripravkov.





Fotografije : V. K. Petrič in
L. Perharič, 1982

STUDIES ON THE TERATOGENICITY OF TEA EXTRACT POLYPHENOLS

Dr. LUCIJA PERHARIČ-WALTON, dr.med. (title equivalent to British MBBS)

A thesis submitted for the degree
of Master of Science in Toxicology
at the Department of Biochemistry
University of Surrey

Medical Research Council

Experimental Embryology &

Teratology Unit

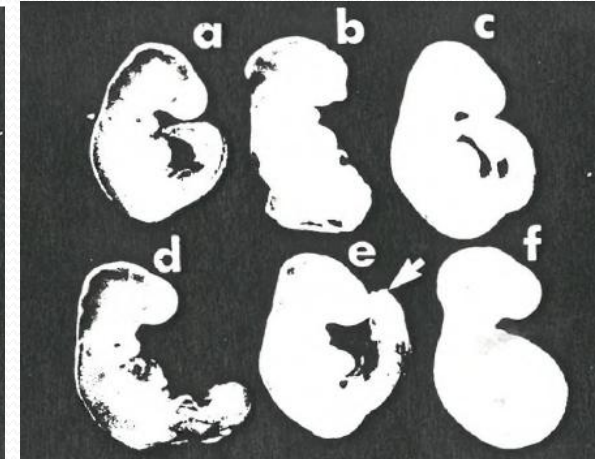
St. George's Medical School

London

September 1990



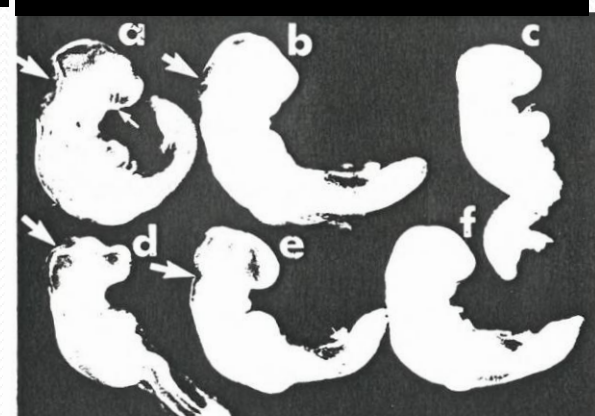
Control



1000 µM syringic acid



5 µM catechol



500 µM resorcinol

Guy's Hospital Poisons Unit: X/1990 – III/1995

Toxicity of Chinese herbal remedies

VOL 340: SEPT 12, 1992

THE LANCET

673

Čaj za zdravljenje ekcema

Cocculus trilobus Thunb

Dictamnus dasycarpus Turcz

Eurysolen gracilis Prain

Glycyrrhiza spp

Lophatherum spp

Paeonia spp

Potentilla spp

Rehmannia glutiosa Libosch

Kontaminacija z mikotoksini,
pirolizidinskimi alkaloidi,
As, Cd, Hg, Pb izključena

Toxic effects of herbal medicines and food supplements

Links between exposure and the clinical effects were found in 49 cases. Most of these were well recognised, such as heavy metal poisoning associated with exposure to Asian medicines, drowsiness and liver damage from herbal tranquillisers, thyrotoxicosis from exposure to kelp, and effects from overdosing with vitamins. Associations first identified through this study include permanent skin discolouration after the use of a tanning preparation, oesophagitis from digestive enzymes, bronchospasm from royal jelly, and death due to liver damage from Chinese herbal preparation.¹

Lucija Perharic, Debbie Shaw, Virginia Murray

National Poisons Unit, Guy's and St Thomas' Hospital Trust, London SE14 5ER, UK

¹ Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. *Lancet* 1992; 340: 674.

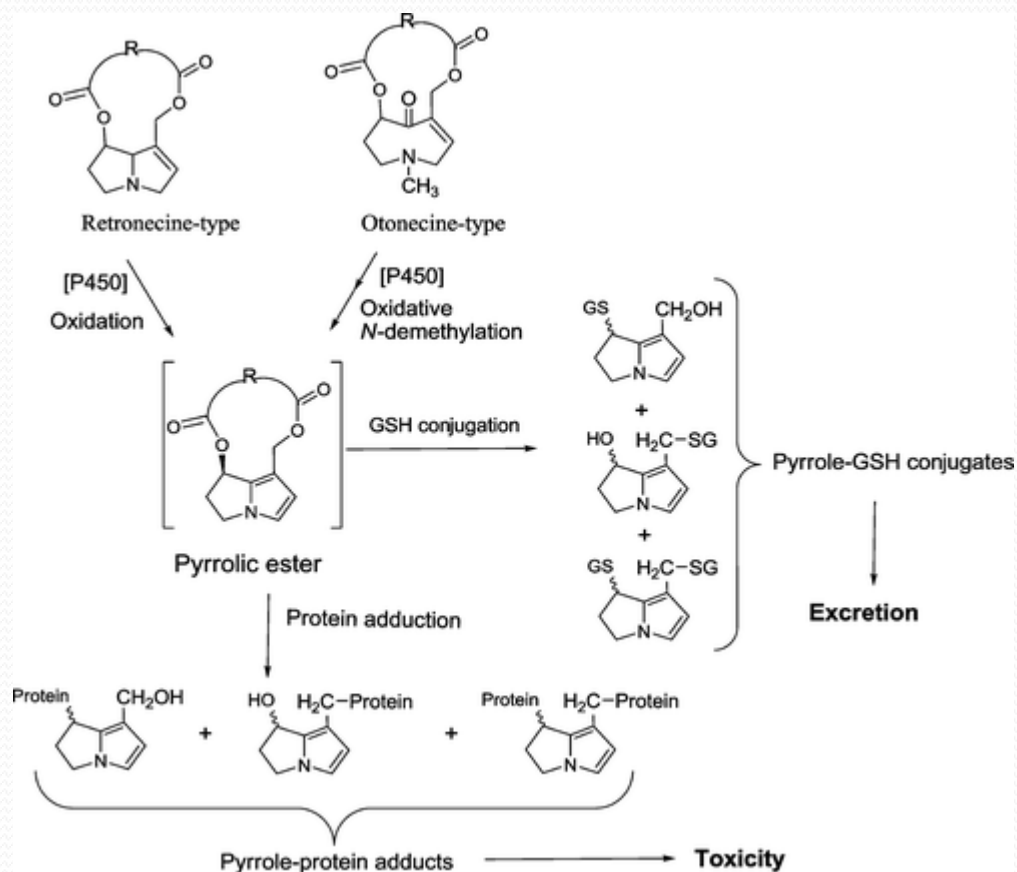
THE LANCET

Vol 342 • July 17, 1993

Navadni gabez – *Symphytum officinale*



Pirolizidinski alkaloidi, velika družina sorodnih kemikalij, v 6.000 različnih vrstah rastlin



<https://www.soin-et-nature.com/en/medicinal-plants/5341-comfrey-great-racinde-cut-iphym-herbalism-symphytum-officinale.html>

Ruan, J., Yang, M., Fu, P. P., Yang, Y., & Lin, G. -
<https://doi.org/10.1021/tx500071q>

I have recently known two patients whose vegetarian diet included much comfrey; both died of bowel cancer. Is there any known connection?

Both common comfrey (*Symphytum officinale* L) and Russian comfrey (*Symphytum x uplandicum* Nym) are known to contain numerous pyrrolizidine alkaloids, such as symphytine, symglandine, and lasiocarpine. Pyrrolizidine alkaloids have toxic properties and may cause liver veno-occlusive disease in humans and animals. Some pyrrolizidine alkaloids have been shown to be mutagenic in vitro and carcinogenic in animals. Activation to reactive dehydro pyrrolizidine alkaloids by mixed function oxidases is required for expression of toxicity. The content of pyrrolizidine alkaloids varies with the place and season of growth and age of the plant. Levels of pyrrolizidine alkaloids also vary with the type of preparation, as roots and extracts contain more than leaves. In the West the most common human exposure is ingestion of comfrey leaves, roots, and extracts as herbal remedies. There is also potential for exposure by ingestion of comfrey leaves as a staple diet and other pyrrolizidine alkaloids in honey and milk.¹

There is a theoretical possibility that pyrrolizidine alkaloids in comfrey would be activated in the gut, but the relation between the rate of metabolism and expression of

toxicity is uncertain. Furthermore, there is no correlation from epidemiological studies to suggest that long term ingestion of comfrey would result in gut cancer. It is currently believed that both environmental and genetic factors play a part in the development of colorectal cancer, and diets with high meat and low fibre contents and alcohol consumption increase the risk, with vegetarians having a lower incidence.

Although prolonged ingestion of high doses of comfrey leaves cannot be excluded as a contributory factor in the development of bowel cancer in the two cases quoted, it would be speculative to attach any degree of probability to this association.

Data on the toxicity of comfrey are not conclusive. The government believes, however, that there is sufficient information for concern, and, following the recommendation of the Committee on Toxicity and the Food Advisory Committee, it has been agreed recently to withdraw tablet and capsule preparations containing comfrey from the market. It was also proposed that labelling should be introduced to warn against the consumption of comfrey root and limit the consumption of leaves.—LUCIJA PERHARIC, *medical research fellow, National Poisons Unit, London*

¹ International Programme on Chemical Safety. *Pyrrolizidine alkaloids*. Geneva: World Health Organisation, 1988.

Ayurvedski in Unani pripravki

HEAVY METAL POISONING FROM EXPOSURE TO FOLK REMEDIES

Lucija Perharic, Ivan M. House, Debbie J. Shaw & Virginia S.G. Murray
London SE 14 5ER, U.K.



RESULTS: On clinical grounds and/or origin of traditional remedy, heavy metal poisoning was suspected in 18 patients with history of exposure to folk remedies. In 10 patients analysis of blood, urine and/or the preparation was negative. Heavy metal poisoning was diagnosed in 8 cases. Two patients suffered mercury poisoning. Blood concentrations at presentation were 24 ug/l and 400 ug/l (normal <10 µg/l); urinary concentrations 340 ug/l and 3030 ug/l (normal <10 µg/l). Lead poisoning was confirmed in five patients; blood lead concentration ranged from 460 to 1180 ug/l (normal <150 µg/l). In one patient, diagnosis of arsenic poisoning was made from the clinical presentation, history of exposure and hazardous levels of heavy metals in the remedies. This occurred because the history of folk remedy use was obtained late in the diagnostic process and arsenic would have been excreted due to its relatively short half life.

Perharic, L., Shaw, D., Colbridge, M. *et al.* Toxicological Problems Resulting from Exposure to Traditional Remedies and Food Supplements. *Drug-Safety* 11, 284–294 (1994).

<https://doi.org/10.2165/00002018-199411040-00006>

Towards the
safer use of
traditional
remedies

Friday
25 February
1994



To be held at the
Royal Botanic Gardens, Kew

ARTICLES

Pharmaceutical Journal, 1994

AN APPEAL TO PHARMACISTS TO REPORT ADVERSE EFFECTS OF HERBAL AND VITAMIN PRODUCTS

By LUCIJA PERHARIC, MB, MSc, DEBBIE SHAW, BSc, and VIRGINIA MURRAY, MB, MFoM

Possible Association of Liver Damage with the Use of Chinese Herbal Medicine for Skin Disease

Lucija Perharic MSc, Debbie Shaw BSc, Christine Leon MSc
Medical Toxicology Unit, Guy's and St Thomas Hospital Trust,
Avonley Rd, London SE14 5ER, UK

Peter AGM De Smet PhD
Drug Information Center, Royal Dutch Association for the Advancement
of Pharmacy, Alexanderstraat 11, 2514 JL The Hague, The Netherlands

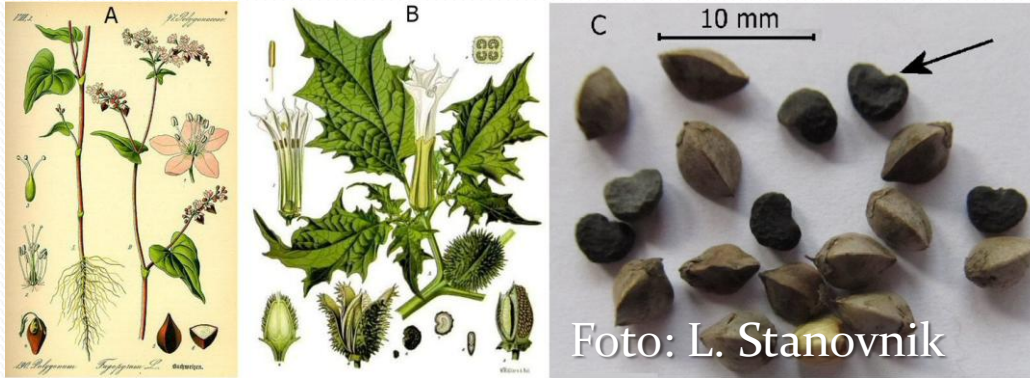
Virginia SG Murray FFOM
Medical Toxicology Unit, Guy's and St Thomas Hospital Trust,
Avonley Rd, London SE14 5ER, UK

Vet Human Toxicol 37 (6) December 1995

Dept. of Clinical Pharmacology, St. Bartholomew's and The Royal London School of Medicine and Dentistry, 1998/99

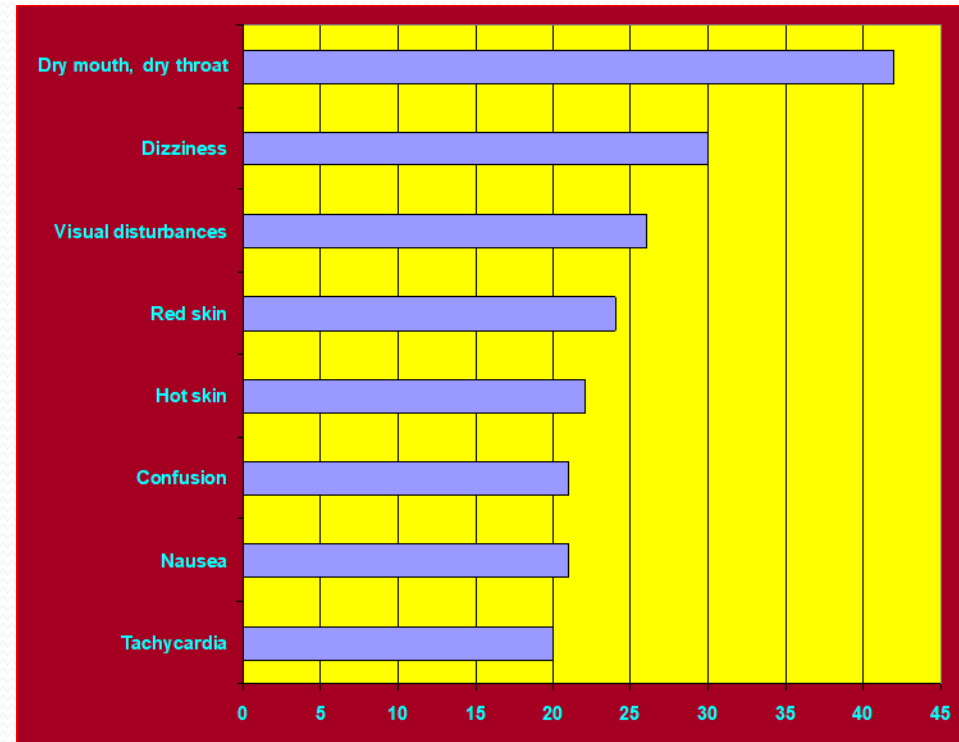
- Mednarodna klinična študija ASCOT
Anglo Scandinavian Cardiac Outcome Study
- Primerjava učinkovitost zdravil za zdravljenje arterijske hipertenzije, > 1000 hipertonikov; staroselcev in pripadnikov etničnih manjšin
- amlodipin + pp perindopril + pp doksazocin VS
atenolol + pp hidroklorotiazid + pp doksazocin
- Izzivi
Bolniki afriškega in afrokaribskega porekla se drugače ali sploh ne odzivajo na zaviralce receptorjev β oziroma inhibitorje konvertaze.
Percepcija škodljivih učinkov in interakcij zdravil verjetno etnično pogojena.

Množična zastрупitev z živili iz ajde onesnažene s semeni navadnega kristavca (*Datura stramonium* L.) - 2003



Kristavec vsebuje
tropanske alkaloide,
npr. atropin in
skopolamin
- starodavni zdravili
- starodavna strupa

Naravni halucinogen
Uporaba v obredne namene
Sporočeni simptomi in
znaki prizadetih potrošnikov
značilni za
antiholinergični sindrom



Ocena tveganja ajdove moke

- **ARfD**

- Atropin: 5 $\mu\text{g/kg tm}$
- Skopolamin: 3 $\mu\text{g/kg tm}$

- **Izpostavljenost**

- 100 g moke, otrok 10 kg

- **MRL**

- Atropin: 4 $\mu\text{g/kg moke}$
- Skopolamin: 2 $\mu\text{g/kg moke}$

- **Negotovosti**

- LOAEL namesto NOAEL
- Podatki o količini zaužite moke 2 meseca po dogodku
- Različno razmerje med atropinom in skopolaminom v vzorcih

- **Spremljanje**

- Po uvedbi spremljanja ni bilo primerov zastrupitev
 - Ocena tveganja ustrezna
 - Morebitnih simptomov ljudje niso pripisali ajdovi moki

HIPOTEZA

Trenutno sprejete najvišje dovoljene koncentracije obeh alkaloidov v živilih iz ajde (atropin 4 $\mu\text{g/kg}$, skopolamin 2 $\mu\text{g/kg}$) so dovolj nizke, da ne predstavljajo tveganja za zdravje ljudi.

METODE

Randomizirana, dvojno slepa, navzkrižna, s placebom kontrolirana raziskava

Zdravi, mladi prostovoljci so poleg placeba zaužili serijo petih odmerkov zmesi atropina in skopolamina v ajdovih žgancih. Spremljanje: telesne temperature, srčne frekvence, količine izločene sline in znoja, velikosti zenic in akomodacije, subjektivnih simptomov.

Določitev ravni obeh alkaloidov v plazmi s LS-MS/MS

Odobritev Komisije za medicinsko etiko, KME 101/05/06

Univerza
v Ljubljani
Medicinska
fakulteta



Lucija Perharič

Opredelitev odnosa med odmerkom in učinkom pri oralnem vnosu
nizkih odmerkov mešanice atropina in skopolamina v živilih

Doktorska disertacija

Risk assessment of buckwheat flour contaminated by thorn-apple (*Datura stramonium* L.) alkaloids: a case study from Slovenia

Lucija Perharič^{a*}, Gordana Koželj^b, Branko Družina^a and Lovro Stanovnik^c

^aNational Institute of Public Health, Centre for Infectious Diseases and Environmental Health, Trubarjeva 2, Ljubljana, Slovenia; ^bFaculty of Medicine, Institute of Forensic Medicine, Korytkova 2, Ljubljana, Slovenia; ^cFaculty of Medicine, Institute of Pharmacology and Experimental Toxicology, Korytkova 2, Ljubljana, Slovenia

(Received 11 April 2012; final version received 18 October 2012)

Research Article

Received: 10 May 2012,

Revised: 9 June 2012,

Accepted: 9 June 2012

Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.2797

Journal of
Applied Toxicology

Acute effects of a low-dose atropine/scopolamine mixture as a food contaminant in human volunteers

Lucija Perharič^{a*}, Katja Ažman Juvan^b and Lovro Stanovnik^c



ELSEVIER

Journal of Pharmaceutical and Biomedical
Analysis

Volume 96, 5 August 2014, Pages 197–206

Simple validated LC–MS/MS method for the determination of atropine and scopolamine in plasma for clinical and forensic toxicological purposes

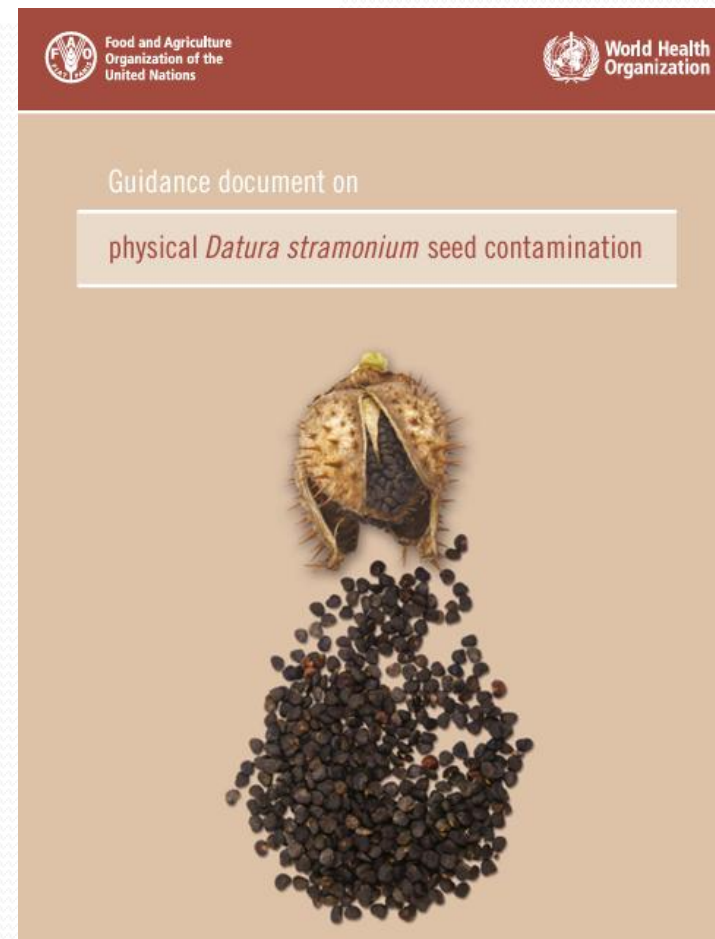
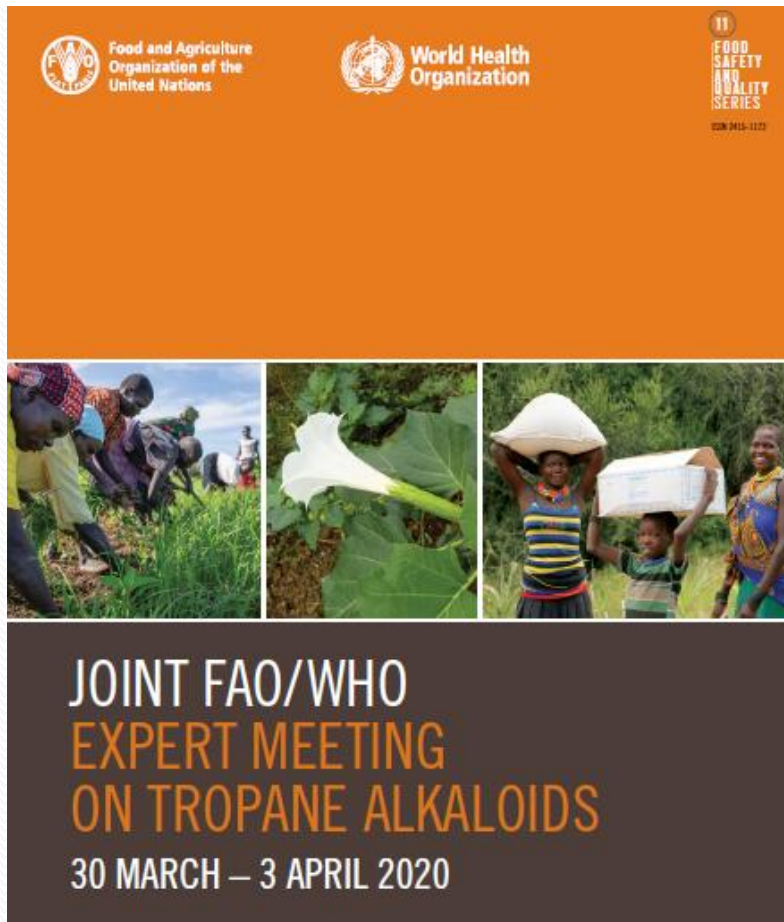
Gordana Koželj^a  , Lucija Perharič^b , Lovro Stanovnik^c ,
Helena Prosen^d 

Katarina Černe et al. Pharmacokinetics of atropine and scopolamine as food contaminants in human volunteers. Tox Lett, 2023

Scientific Opinion on Tropane alkaloids in food and feed¹

EFSA Panel on Contaminants in the Food Chain (CONTAM)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy



Nacionalna skupina za opozarjanje o novih psihoaktivnih snoveh, 2005-2015

Zloraba drog med študenti v Ljubljani*
Drug abuse among students in Ljubljana

Alenka Gosar**, Marjeta Kuzman***, Lucija Perharč****, Vesna Petrič*****,
Janez Pšenica*****

Med. Razgl., 1984



(*Banisteriopsis caapi*)

(*Psychotria viridis*)

Ayahuasca



Psilocybe sp.



Peyotl

(*Lophophora williamsi*)



Rdeča mušnica
(*Amanita muscaria* L.)



Opojna kadulja
(*Salvia divinorum*)



Kratom

(*Mitragyna speciosa*)

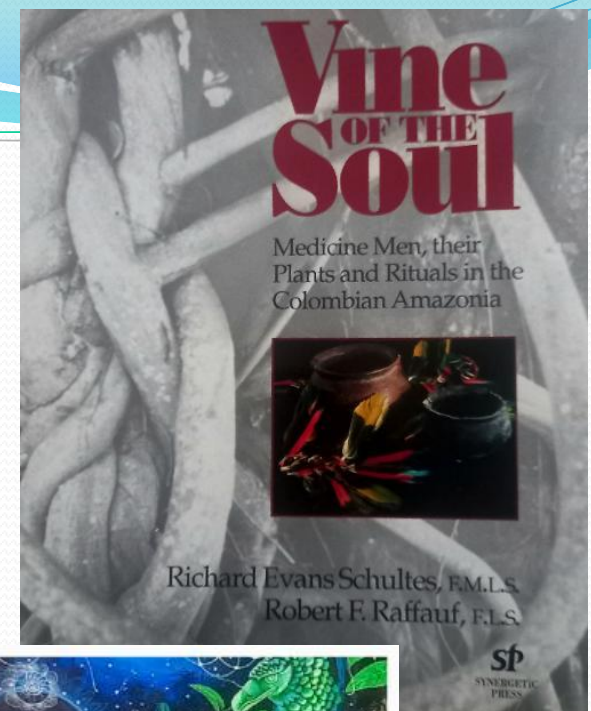


Kat (*Catha edulis*)

Three for one



Šamanizem v Amazoniji



ETNOTOKSIKOLOGIJA RDEČE MUŠNICE – ALI ZAKAJ JE BOŽIČEK OBLEČEN V RDEČO OBLEKO Z BELO OBROBO

ETHNOTOXICOLOGY OF FLY AGARIC OR WHY FATHER CHRISTMAS WEARS A RED SUIT WITH WHITE TRIMMINGS

Lucija Perharič¹

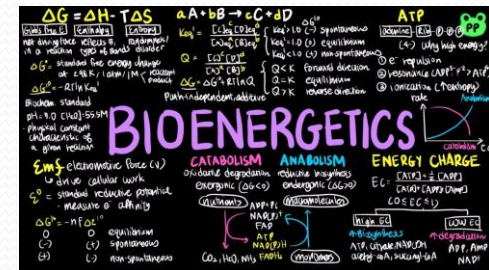


Sibirski šamani so od kamene dobe dalje uporabljali rdečo mušnico kot sredstvo za doseganje transa. Kot opisuje Furst (7), so poleg šamanov tudi drugi pripadniki ljudstev od Baltika do Kamčatke občasno uporabljali rdečo mušnico kot mamilo za zabavo. Rdeča mušnica ima osrednjo vlogo v mitologiji sibirskega plemena Korjak. Korjaki so namreč verjeli, da je z uživanjem rdeče mušnice možno pridobiti nadnaravno moč. Vedeli so tudi, da je možno doseči enake učinke tudi z uživanjem urina ljudi ali pa severnih jelenov, ki so predhodno zaužili rdečo mušnico. Z urinom se namreč v nepresnovljeni obliki izloči del ibotenske kisline, iz katere nastane psihoaktivna snov muscimol. V sibirskem šamanizmu so bili severni jeleni svete živali. Poleg tega, da radi jedo rdeče mušnice, so severni jeleni predstavljali tudi "duhovno sedlo", ki je poneslo šamana v nebo in onostranstvo. Jelenovim rogovom so pripisovali nadnaravno moč in zato so bila pokrivala šamanov pri nekaterih sibirskih plemenih okrašena z jelenovimi rogovi. Šamani so v bivališča, ki so bila zaradi nizkih temperatur pogosto v podzemnih votlinah, vstopali skozi odprtino v stropu in v vrečah nosili darilo: rdečo mušnico.

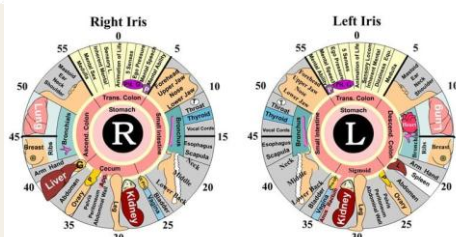
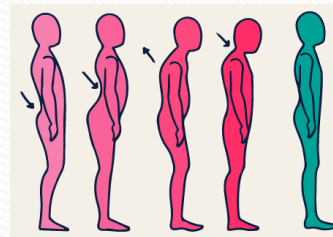
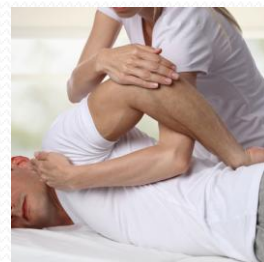
Komplementarne (alternativne) metode zdravljenja



Različne diete
presna
makrobiotska
frutarijanska itd.



shutterstock.com · 1556386601



Primer

- 2017 pri 72 letnem upokojenemu kleparju, nekdanjemu kadilcu, slučajno odkrit 13 mm tumor pljuč
- priporočena kirurška odstranitev; bolnik odkloni
- redna Rp: antihipertenzivi, zaviralci protonske črpalke
- marec 2021: hujšanje, kašelj, splošno slabo počutje
- obravnavo pri izbrani zdravnici odkloni
- april 2021: obišče zeliščarico, veščo zdravljenja konj
- Rp: tekočina z oznako A
tekočina z oznako 33
čaj korenike regrata
tablete acetil cisteina
- Junij 2021: preneha jemati zeliščaričine pripravke
- Avg . 2021: fentanil 25 µg obliži
- Sept. 2021: CT th in abd. pokažeta razširjene metastaze, bolnik umre.



Pasti

- opustitev zdravljenja
- poškodbe pri manipulativnih tehnikah
- podhranjenost pri dietah z omejenim vnosom posameznih hranil
- predoziranje z vitamini ali minerali
- stranski učinki zeliščnih preparatov kot posledica:
 - onesnaženosti s farmacevtskimi učinkovinami, kovinami, plesnimi -
 - strupenosti zeliščnih učinkovin
 - interakcij s farmacevtskimi zdravili

Ključni postulat medicine: PRIMUM NON NOCERE

Predlagamo ponovno aktivacijo dejavnosti za vzpostavitev nadzora nad komplementarnimi metodami zdravljenja.

Interakcije z zdravili

Rastlina	Zdravilo	Interakcija
Naprstec (<i>Digitalis lanata</i>) šmarnica (<i>Convallaria majalis</i>)	Lanitop [®]	Potenciranje učinka
Gladišnik (<i>Agrimonia eupatoria</i>) plešec (<i>Capsella bursa-pastoris</i>) peteršilj (<i>Petroselinum crispum</i>) regrat (<i>Taraxacum officinale</i>) rman (<i>Achillea millefolium</i>)	diuretiki Antihipertenzivi	Potenciranje učinkov, potencirana toksičnost srčnih glikozidov
divji kostanj (<i>Aesculus hippocastanum</i>), papaja (<i>Carica papaya</i>), avokado (<i>Persea gratissima</i>)	Oralni antikoagulanti (varfarin)	Povečan ali zmanjšan učinek
baldrijan (<i>Valeriana officinalis</i>), pasijonka (<i>Passiflora incarnata</i>), čeladnica (<i>Scutellaria sp.</i>)	Antihistaminiki, pomirejvala	Potenciranje pomirejvalnih učinkov
šentjanževka (<i>Hypericum perforatum</i>)	Antidepresivi	Potenciranje učinka
detelja (<i>Medicago sativa</i>), artičoka (<i>Cynara scolimus</i>) in ingver (<i>Zingiber officinale</i>)	Hipoglikemiki	Potenciranje učinka

Verjetnost povezave med izpostavljenostjo in posledicami za zdravje

- Podatke o posledicah izpostavljenosti kemikalijam pridobimo z rutinskim spremljanjem zdravstvenega stanja poklicno izpostavljenih oseb in obravnavo naključnih ali namernih zastrupljenцев.
- Presojamo z uveljavljenimi farmokoepidemiološkimi algoritmi (Jones, 2006).
- Časovna povezanost med simptomi in znaki in izpostavljenostjo?
- Ali S in Z lahko povežemo s kakšnim drugim vzrokom ?
Ali se zdravstveno stanje izboljša, ko izpostavljenost preneha?
- Ali se simptomi in znaki ponovijo pri ponovni izpostavljenosti?
- Analitska potrditev izpostavljenosti?
- Ali obstaja biološka verjetnost za povezavo?



Univerza v Mariboru

Fakulteta za zdravstvene vede

Kemijski dejavniki tveganja v prehrani

2.4 Rastlinski toksini v hrani

LUCIJA PERHARIČ

Avtorji

Sonja Šostar Turk

Urška Rozman

Urška Blaznik

Vesna Viher Hrzenjak

Viviana Golja

Ema Mivšek Mušič

Blaža Nahtigal

Lucija Perharič

Majda Pajnikihar

Dominika Vrbojnik

September 2022

Primeri uporabe zeliščnih preparatov kot dopinga

6. kongres Slovenskega toksikološkega društva Ljubljana, 26. januar 2023

Active ingredients in Chinese ginseng: mixture of triterpene saponins - ginsenosides



- Affects hypothalamic-pituitary-adrenal cortex axis,
↓ catabolic effect of cortisol,
↓ decreased lactate production
• i.e. endocrinologically active substance

- In sports to increase the intensity of exercise and/or reduce fatigue

↑ aerobic capacity
↑ cardio respiratory function
↑ muscle strength



Panax ginseng

Puncture vine, goat's-head etc (*Tribulis terrestris*)



- Extracts popular among weight lifters, sprinters and throwers,

↑ testosterone production,
↑ muscle growth,

↓ reduce inflammation
↓ oxidative damage

- i.e. endocrinologically active substance



Figure 1. Number of records on *Tribulis terrestris* in CAB abstracts since 1950s.

'Pub up Your Poison'



The birthwort (*Aristolochia clematitis*) used by ancient Egyptians and later by Greeks; ingredient in theriac, which was used as a panacea against ulcers, fevers, and snake bites. Aristolochia from áristos and lóchos - «the best» and «birth» Hildegard von Bingen: Aristolochia opens the closed female inner organs and dissolves hardened menstrual blood. Paracelsus: against cancer, treating like with like; 1981 phytotherapeutic use forbidden due to possible carcinogenic effects.

Balkan endemic nephropathy chronic renal disease, 1956

Features: endemic nature, long-incubation period, familial clustering, associated with upper urothelial cancer

Prevalence: 25 000 BEN; 100 000 people at risk

Clinical S&S: non-specific, often unrecognized for years.

Etiology: chronic poisoning with aristolochic acids constituents of *Aristolochia* sp.

Pavlović N, Clin Kidney J. 2013



Aristolochia Fangchi long history of use in TCM.

"Fang Ji" may be adulterated with *Aristolochia* sp., Lord et al. Lancet 2001

Avoid using domestic local names on the labels.

Advanced glomerular sclerosis, with interstitial sclerosis and tubular atrophy

Focal tubular atrophy with prominent interstitial sclerosis and mononuclear infiltrate

Hvala za pozornost !

