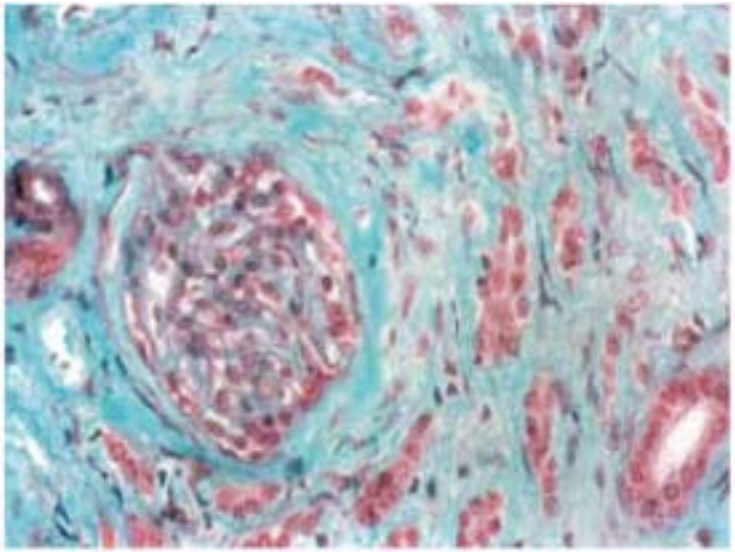
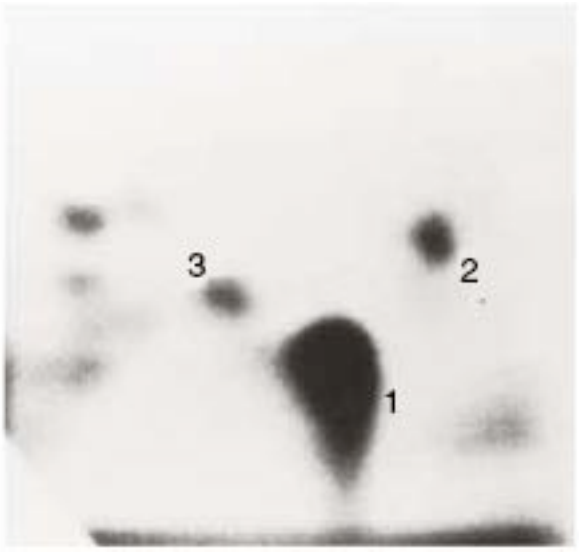
Herbs and chronic kidney disease in Asia





Vivekanand Jha

Postgraduate Medical Institute, Chandigarh

Secretary, Indian Society of Nephrology

http://www.isn-india.org

Herbal Medicines Worldwide

- Represent an estimated **$60 billion a year** global market, some **20%** of the overall drug market (U.N. agency)

- Only China, Japan and the European Union **have regulations** for medicinal plants.

Herbal Medicines Worldwide

- Europe, North America: **> 50% use complementary or alternative** medicine at least once (WHO report)
- **Africa: Up to 80 %** population depends on traditional medicine for primary health care
- China: herbal preparations account for up to **50 % of total consumption**.
- **India: 60% lives in rural areas**, and depend upon local practitioners.

Plant Remedies in Medicine

- **Western Medicine has derived benefit** from botanical derivatives

- Digitalis (heart) and Artemisia (malaria)
- These drugs have undergone safety and efficacy testing

Regulation of herbal remedies

- Numerous products have toxic substances.
- 2003: **WHO issued guidelines** for ensuring the safety and efficacy
- The guidelines, **intended for national regulatory** bodies, lay out the best techniques for growing and harvesting, as well as the clear labeling of the contents of any product.
- **Multi-billion dollar** herbal medicines market
  "….. traditional medicines are being shipped from various exporting countries to many other countries. **Somebody has to regulate that, at least their safety**…….. "

Reason for taking herbal medicines

- **Dissatisfaction** with Western Medicine
- Traditional medicines believed to be **good and innocuous** [Larrey, J Hepatol 1997]
- Strong **placebo effect** from ritual ingestion of herbal medicines [De Met, J Ethnopharmacol 1991]
- Psychosomatic **complaints may improve** and where resources are restricted this is a **saving to the patient and health service** [Chan, Drug Safety 1997]

Why the use of these substances?

- Many cultures believe that disease reflects disharmony between person and their ancestors
- Zulu: the traditional healer consults the spirits to find this disharmony in order to cure the problem
- This theme of 'Ancestral appeasement' is common amongst many African cultures
- **Toxic herbal substances or chemical substances are intrinsic to many cultures**

Traditional Remedies: Facts

- Many people use them
- **Secrecy!**
- Potentially life-threatening complications

BUT

- **Most "patients" do not get complications!**

Diagnosis is a problem

- Many doctors are not aware of these medicines.
- History often not sought.
- May be denied despite specific enquiry!!
- Relationship more obvious in acute renal injury.
- Presentation may yield a clue: e.g. combination of liver and kidney failure, neurological abnormalities, etc.
- Over-the-counter medications

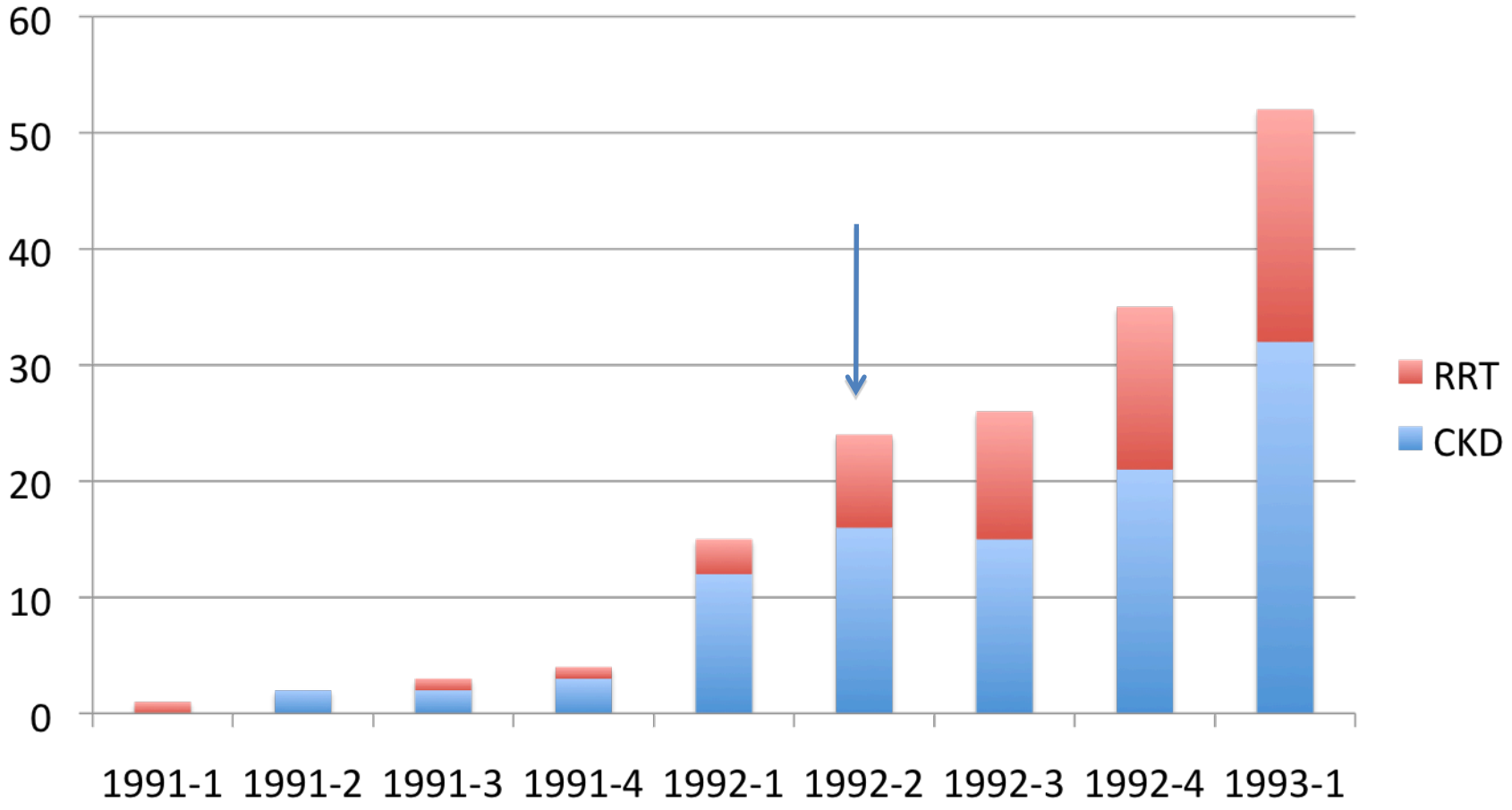
Unusual ways of administration : enemas

- Zulus receive 3 enemas/week
- Swazi infants : upto 50 enemas/year
- Baragwanath Hospital, Soweto : 63% of all patients frequent enema users.
- Constituents: herbs, barks, roots, leaves, bulbs, chemicals
- Administered through truncated cow horn/ hollowed reed

Outline

- Aristolochic acid nephropathy (Chinese herbal nephropathy)
- Pathogenesis of AAN
- AAN is more widespread than previously anticipated…
- Balkan endemic nephropathy is actually AAN!
- The problem of misclassification of herbs
- Could the mysterious CIN in Indian subcontinent be phytotherapy-induced?

Rapidly progressive renal failure in young women



Vanhengherhem, Lancet 1993

Rapidly progressive interstitial fibrosis in young women: association with slimming regimen including Chinese herbs

Slimming regimens	Formula 1 (1975-May 1990)	Formula 2 (May 1990-May 1992)
Injection (ID, once a week)		
Artichoke extract (Chophytol S)	0.2	0.2*
Euphyllin	0.5	0.5
Capsule A (3 times a day, orally)		
Fenfluramine	17-25	17-25
Diethylpropion	17-25	17-25
Meprobamate	0-50	0-50
Capsule B (3 times a day, orally)		
Pancreas powder	100	0
Laminaria powder	50	0
Fucus extract	50	0
Cascara powder	20-150	20-150
Acetazolamide	25-45	25-45
Belladonna extract	0	1-2
Stephania tetrandra	0	100-200
Magnolia officinalis	0	100-200

1561

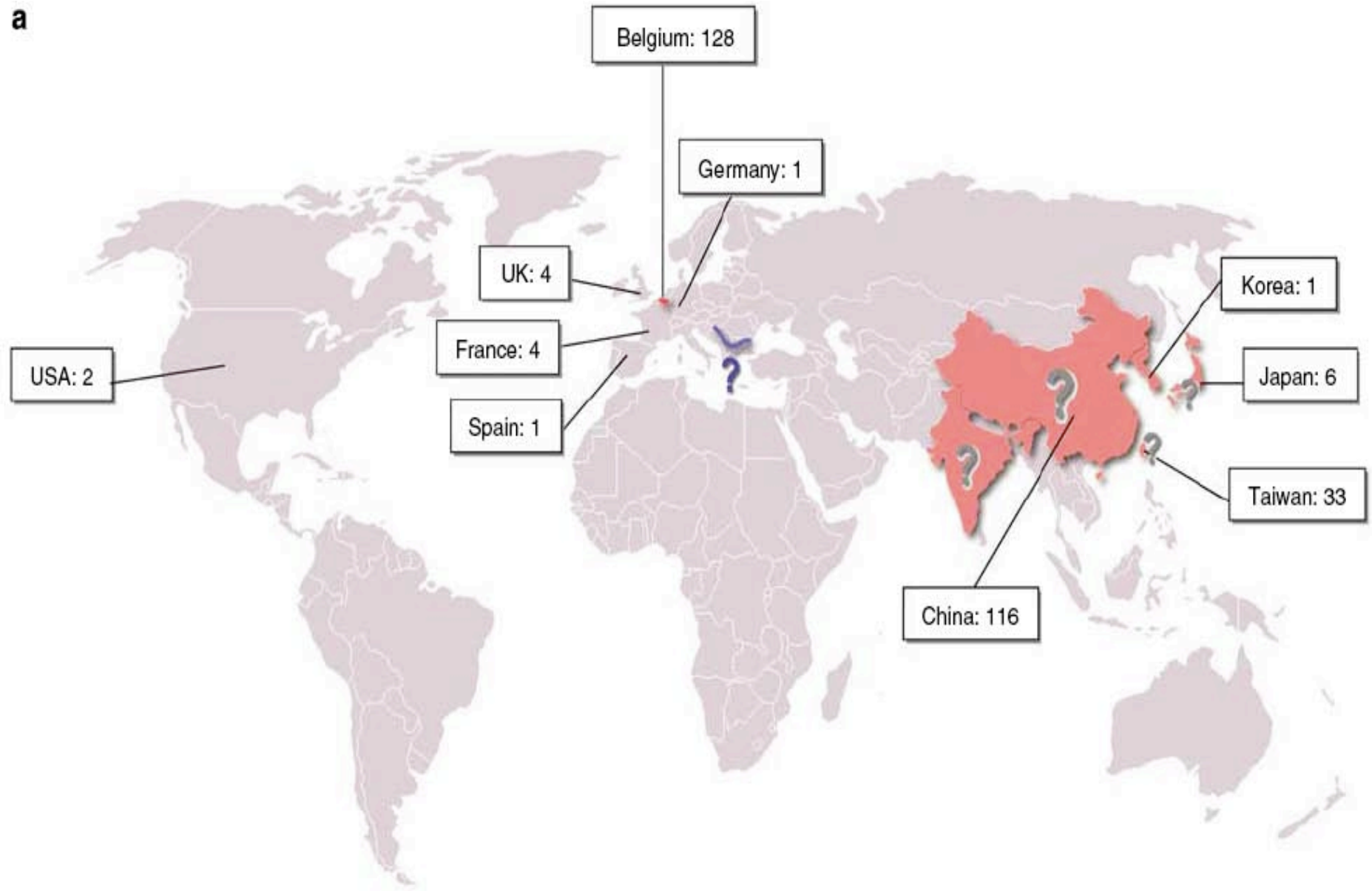
Jean-Louis Vanherweghem et al: Lancet 341: 387-91, 1993

Chinese herbal nephropathy

- Explanation
  - Confusion between Chinese herbs
    - *Stephania tetranda* (Fangji)
    - Aristolochia fangchi
  - No evidence of tetradine (active ingredient of Stephania) in samples taken after 1990
  - Studies established the association between Aristolochic acid and renal lesion
  - Classical finding: presence of AA-DNA adducts

Chinese herbal nephropathy

- Described worldwide since then
- Presentation
  - Rapidly pregressive renal failure
  - Minimal hypertension
  - Non-nephrotic proteinuria
- Pathology : Chronic TIN, minimal infiltration, rare Fanconi's
- Important: high risk of urothelial cancers



Debelle, KI 2008

Herbal Therapy Is Associated With the Risk of CKD in Adults Not Using Analgesics in Taiwan

Jinn-Yuh Guh, MD,[1] Hung-Chun Chen, MD,[1] Jung-Fa Tsai, MD,[1] and Lea-Yea Chuang, PhD[2]

Background: Taiwan has the greatest incidence rate of end-stage renal disease in the world. Several cases of Chinese herb nephropathy were reported in Taiwan. Therefore, we studied the association between herbal therapy and chronic kidney disease (CKD) in Taiwan.

Study Design: Cross-sectional survey.

Setting & Participants: 1,740 adults in the Nutrition and Health Survey in Taiwan (1993 to 1996).

Predictor: Herbal and analgesic therapy.

Outcomes & Measurements: CKD after adjustment for potential confounding variables.

Results: Among medication users, prevalences of herbal therapy and analgesic use were 21.6% and 13.2%, respectively. The prevalence of CKD was 9.9%. Participants with CKD were older and had more analgesic use, diabetes, hypertension, and cardiovascular disease. Analgesic use was associated independently and positively with CKD (odds ratio, 2.2; 95% confidence interval, 1.4 to 3.5; $P = 0.003$) and CKD stage (odds ratio, 2.3; 95% confidence interval, 1.4 to 3.6; $P = 0.003$). Conversely, herbal therapy was associated independently and positively with CKD (odds ratio, 1.39; 95% confidence interval, 1.2 to 1.7; $P = 0.002$) and CKD stage (odds ratio, 1.38; 95% confidence interval, 1.1 to 1.7; $P = 0.004$) only in participants who did not use analgesics.

Limitations: Because this was a cross-sectional study, cause and effect could not be ascertained.

Conclusions: Herbal therapy was associated with CKD in adults in Taiwan who did not use analgesics.

Am J Kidney Dis 49:626-633.

Clinical Nephrology, Vol. 72 – No. 4/2009 (298-302)

clinical nephrology

Original

ISSN 0301-0430

End-stage renal disease in both husband and wife in Taiwan

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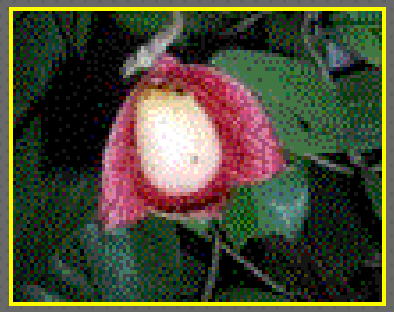
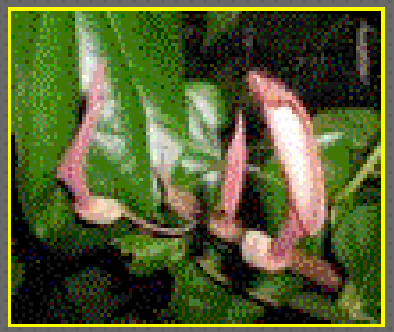
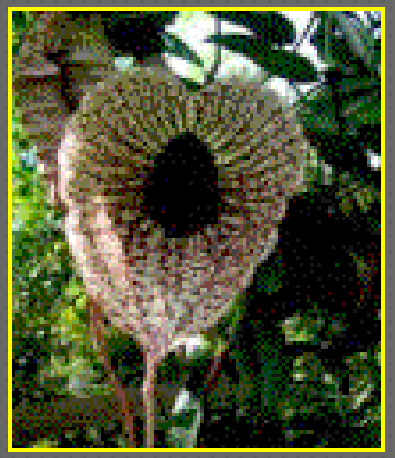
Key words
couples — chronic tubulointerstitial nephritis – end-stage renal disease – Chinese herbs nephropathy – family history – transitional cell carcinoma

Abstract. Aim: The incidence and prevalence of end-stage renal disease (ESRD) are extremely high in Taiwan. It is an interesting fact that both the husband and wife in some families of Taiwan suffer from ESRD. Therefore, we attempted to identify the potential risk factors of such couples. Methods: This is a retrospective observational study. Six couples receiving maintenance dialysis in our

will reach 2.5 million by 2010 [Moeller et al. 2002]. There is an extremely high incidence and prevalence of ESRD in Taiwan, and by the end of 2004, the incidence rate was 376 per million populations (pmp) and the prevalence rate was 1,706 pmp. Both of these statistics ranked the first and second place in the world, respectively [Hwang et al. 2005,

Aristolochia Species





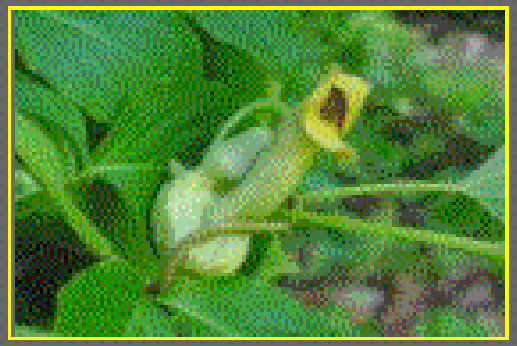


Table 1 | Botanicals known or suspected to contain aristolochic acid and their vernacular names[55–59]

Botanical name	Common or other names
Aristolochia spp.	Aristolochia, Guan Mu tong, Guang Mu tong
Aristolochia acuminata (Syn. *Aristolochia tagala*)	Oval leaf Dutchman's pipe
Aristolochia bracteata	Ukulwe
Aristolochia clematitis	Birthwort
Aristolochia contorta	Ma Dou Ling (fruit), Bei Ma Dou Ling (root), Tian Xian Teng (herb)
Aristolochia cymbifera	Mil homens
Aristolochia debilis (Syn. *Aristolochia longa, A. recurvilabra, A. sinarum*)	Ma Dou Ling (fruit); Tian Xian Teng (herb), Qing Mu Xiang (root), Sei-Mokkou (Japanese), Birthwort, Long birthwort, Slender Dutchman's pipe
Aristolochia fangchi	Guang Fang ji (root), Fang ji, Fang chi, Mokuboi (Japanese), Kou-boui (Japanese), Kwangbanggi (Korean)
Aristolochia heterophylla	Han Fang Ji
Aristolochia indica	Indian birthwort (root), Yin Du Ma Dou Ling
Aristolochia kaempferi (Syn. *Aristolochia chrysops, A. feddei., A. heterophylla, A. mollis, A. setchuenensis, A. shimadai, A. thibetica, Isotrema chrysops, I. heterophylla, I. lasiops*)	Yellowmouth Dutchman's pipe, Zhu Sha Lian
Aristolochia macrophylla (Syn. *Aristolochia sipho*)	Dutchman's-pipe
Aristolochia manschuriensis (Syn. *Hocquartia manshuriensis*, Syn. *Isotrema manchuriensis*)	Manchurian birthwort, Manchurian Dutchman's pipe (stem) Guan Mutong (stem), Kan-Mokutsu (Japanese), Mokuboi (Japanese), Kwangbanggi (Korean)
Aristolochia maxima (Syn. *Howardia hoffmannii*)	Maxima Dutchman's pipe, Da Ma Dou Ling
Aristolochia mollissima	Wooly Dutchman's pipe, Mian Mao Ma Dou Ling
Aristolochia moupinensis	Moupin Dutchman's pipe, Huai Tong
Aristolochia serpentaria (Syn. *Aristolochia serpentaria*)	Virginia snakeroot, Serpentaria, Virginia serpentary
Aristolochia triangularis	Triangular Dutchman's pipe, San Jiao Ma Dou Ling
Aristolochia tuberosa	Tuberous Dutchman's pipe, Kuai Jing Ma Dou Ling
Aristolochia tubiflora	Tubeflower Dutchman's pipe, Guan Hua Ma Dou Ling
Aristolochia versicolar	Versicolorous Dutchman's pipe, Bian Se Ma Dou Ling
Asarum canadense (Syn. *Asarum acuminatum, A. ambiguum, A. canadense, A. furcatum, A. medium, A. parvifolium, A. reflexum, A. rubrocinctum*)	Wild ginger, Indian ginger, Canada snakeroot, False coltsfoot, Colic root Heart snakeroot, Vermont snakeroot, Southern snakeroot, Jia Na Da Xi Xin
Asarum himalai(y)cum	Tanyou-saishin (Japanese)
Asarum splendens	Do-saishin (Japanese)

Clinical Toxicology, 44:371–378, 2006

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650600671712

ARTICLE

Aristolochic Acids Detected in Some Raw Chinese Medicinal Herbs and Manufactured Herbal Products – A Consequence of Inappropriate Nomenclature and Imprecise Labelling?

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Research and Development Division, School of Chinese Medicine, Hong Kong Baptist University, HKSAR

Chun G. Li, Ph.D.
The Chinese Medicine Research Group, Division of Chinese Medicine RMIT University, Australia

Herbal Sample		Level (ppm)		
Botanical name	Common Chinese name	*AA-I*	*AA-II*	*AA-I + AA-II*
Diuretics				
Aristolochia manshuriensis	*Guan Mu Tong*	41	–	41
Clematis armandii	*Chuan Mu Tong*	–	–	–
Aucklandia lappa Decne	*Mu Xiang*	–	–	–
Aristolochia contorta Bge.	*Ma Dou ling*	195	33	228
Poria cocos (Schw.) Wolf	*Fu Ling*	–	–	–
Pyrrosia lingua (Thunb.) Farw	*Shi Wei*	–	–	–
Dioscorea hypoglauca Palif.	*Bei Xie*	–	–	–
Coix lachryma jobi L.	*Yi Yi Ren*	–	–	–
Plantago asiatica L.	*Che Qian Zi*	–	–	–
Polyporus umbellatus (Pers.) Fr.	*Zhu Ling*	–	–	–
Alisma plantago-aquatica L. var. *orientale* Samuels	*Xe Xie*	–	–	–
Artemisia capillaries Thunb.	*Yin Chen Hao*	–	–	–
Tetrapanax papyriferus (Hook) K. Koch	*Tong Cao*	–	–	–
Anti-rheumatics				
Aristolochia fangchi Wu	*Guang Fang Ji*	943	59	1002
Stephania tetrandra S. Moore	*Han Fang Ji*	–	–	–
Asarum sieboldii (either: *A.. splendens* or *A.. himalaicum*)	*Xi Xin*	trace	28	28
Acanthopanax gracilistylus	*Wu Jia Pi*	–	–	–
Viscum coloratum (Kom.) Nakai	*Sang Ji Sheng*	–	–	–
Chaenomeles lagenaria (Loisel.) Koidz	*Mu Gua*	–	–	–
Clematis chinessis Osbeck	*Wei Ling Xian*	–	–	–
Gentiana macrophylla Pall	*Qin Jiao*	–	–	–
Angelica pubescens Maxim	*Du Huo*	–	–	–
Lysimachia christinae Hance	*Jin Qian Cao*	–	–	–
Purgatives				
Prunus japonica Thunb.	*Yu Li Ren*	–	–	–
Rheum palmatum	*Da Hunag*	–	–	–
Cassia angustifolia Vahl	*Fan Xie Ye*	–	–	–
Aloe vera L. var. chinesis (Haw.) Berger	*Lu Hui*	–	–	–

Manufactured product		Level (ppm)		
Chinese proprietary name	Pharmaceutical Co. (China)	*AA-I*	*AA-II*	*AA-I* + *AA-II*
(1) Chuan Xiong Cha Tiao Wan	Lanzhou Fu Ci	8	8	16
(2) Dao Chi Pian	Tian Jin	40	210	250
(3) Xin Yi Wan	Lanzhou Minshan	–	–	–
(4) Xiao Qing Long Tang	Lanzhou Minshan	–	–	–
(5) Ba Zheng San	Lanzhou Fu Ci	–	–	–
(6) Xiao Feng San	Lanzhou Fu Ci	–	–	–
(7) Long Dan Xie Gan Tang	Lanzhou Da Bao	–	–	–

Food Chem Toxicol. 2009 Oct;47(10):2661-5. Epub 2009 Aug 3.

Sub-acute toxicity evaluation of an aqueous extract of Labisia pumila, a Malaysian herb.

Singh GD, Ganjoo M, Youssouf MS, Koul A, Sharma R, Singh S, Sangwan PL, Koul S, Ahamad DB, Johri RK.

Division of Pharmacology, Indian Institute of Integrative Medicine, Jammu 180001, India.

Abstract

Labisia pumila (Myrsinaceae), is a popular herb among the women in Malaysia known locally as "Kacip Fatimah". Recently many nutraceutical products containing the powdered or extracted parts of the plant have become available for women's health care. However no evaluation of the effect of the repeated dosing of any herbal product of this plant had been undertaken prior to a 28-day sub-acute study presented in this report. The results showed that a dose of 50mg/kg of an aqueous extract of L. pumila corresponded to no-adverse-effect-level (NOAEL), whereas higher doses were associated with some toxicity concerns.

PMID: 19654032 [PubMed - indexed for MEDLINE]

Transactions of the Royal Society of Tropical Medicine and Hygiene (2007) 101, 1013–1017

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journal homepage: www.elsevierhealth.com/journals/trst

Chronic renal failure in North Central Province of Sri Lanka: an environmentally induced disease

Kamani P. Wanigasuriya[a,*], Roshini J. Peiris-John[b], Rajitha Wickremasinghe[c], Ariyasena Hittarage[d]

Chronic Interstitial Nephritis

	Chinese Herb	Balkan
Time Course	Months	decades
Inheritance	None	Familial
Gender	Female 10:1	1 : 1
Cortex	Universal involvement of columns of Bertin	Infrequent involvement of Columns of Bertin
Infiltrate	Relatively acellular	Chronic inflammatory
Uroepithelial Malignancies	2 – 6 years	Decades

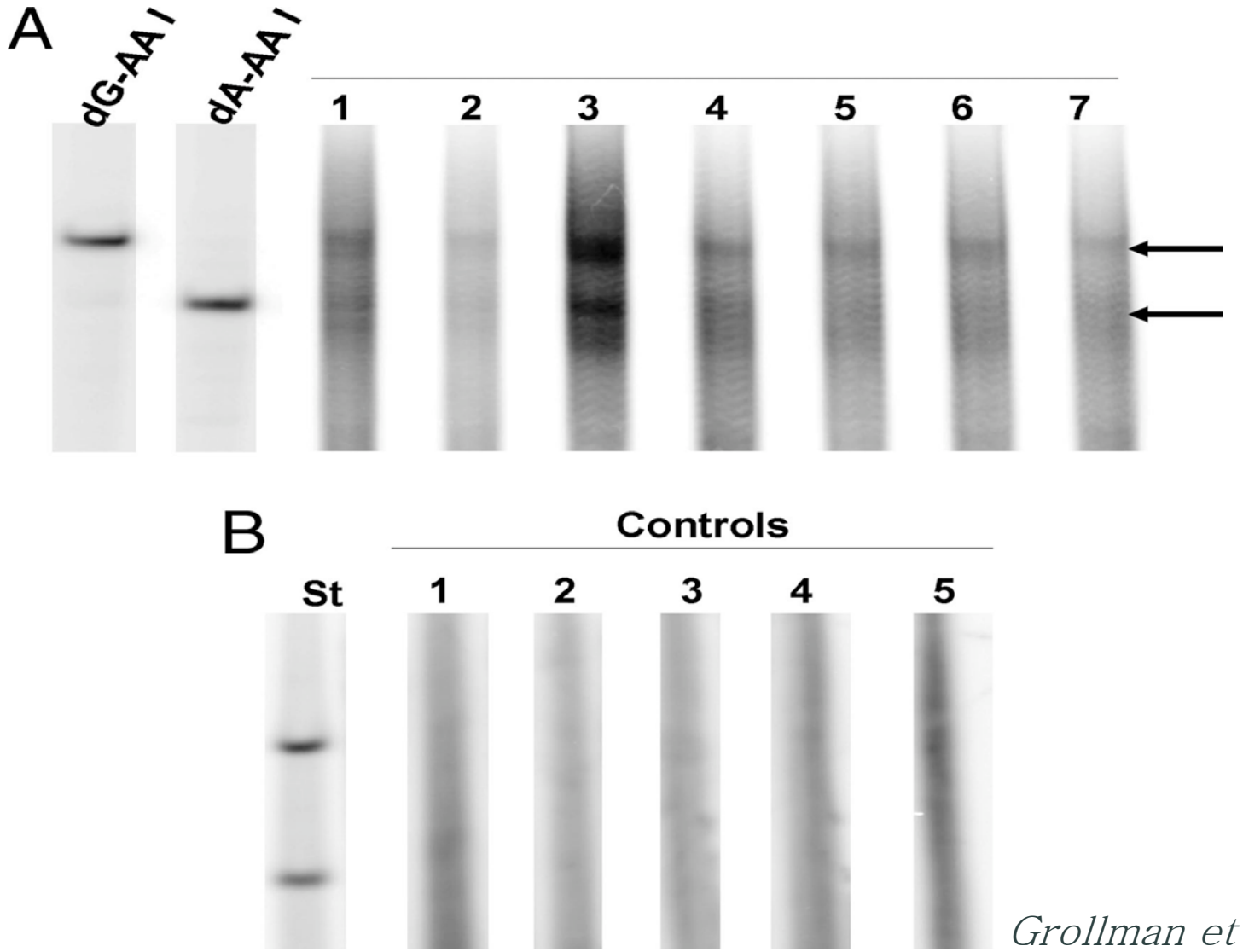
Endemic foci of BEN

Aristolochia clematitis (birthwort)

www.biolib.de

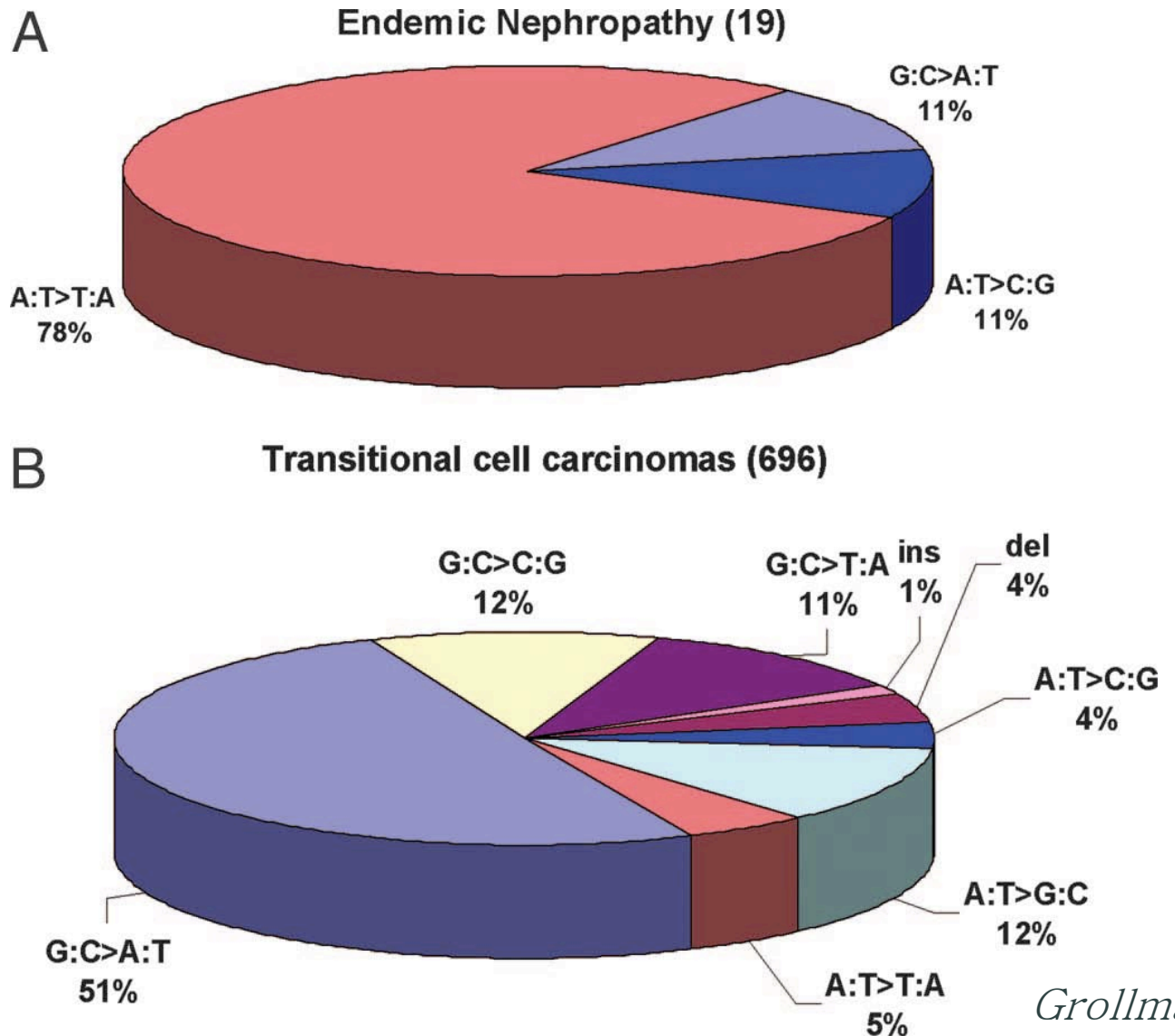
Deballe et al, KI 2008

AA-DNA adducts in renal tissue of BEN patients

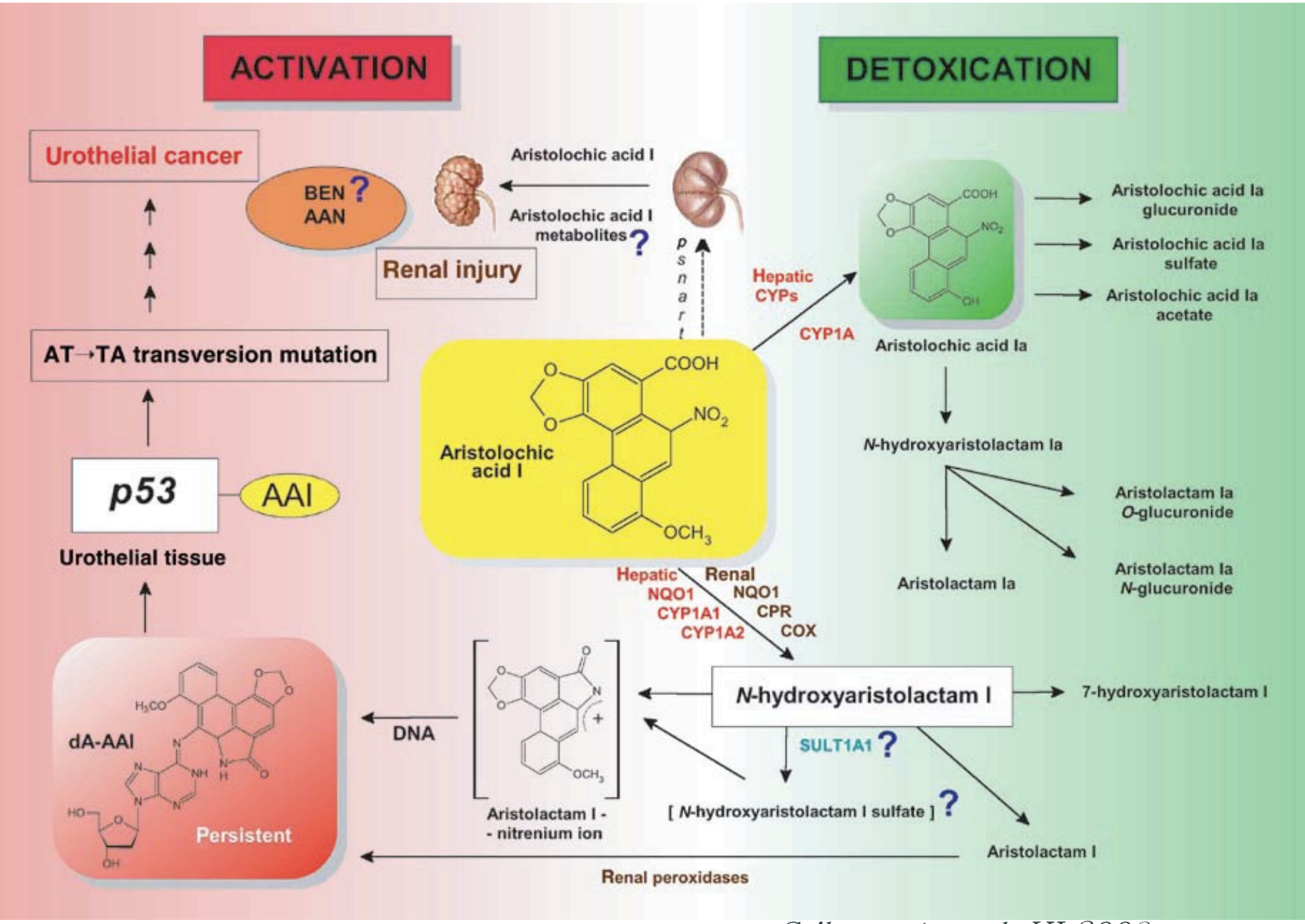


Grollman et al, PNAS 2

p53 mutation spectra in BEN-associated and sporadic TCC

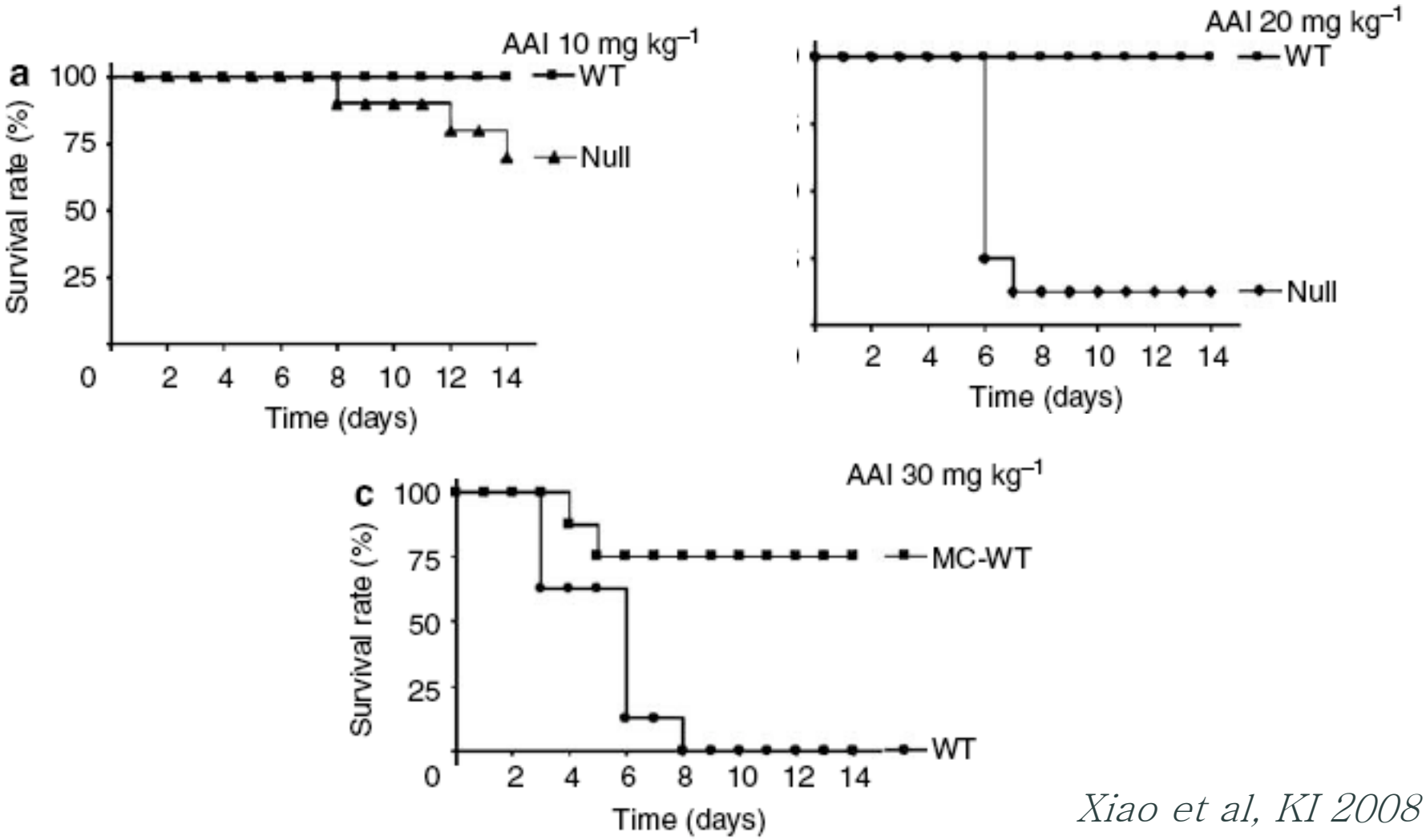


Grollman et al, PNAS 2



Stiborová et al, KI 2008

Cytochrome P450 system and AA toxicity

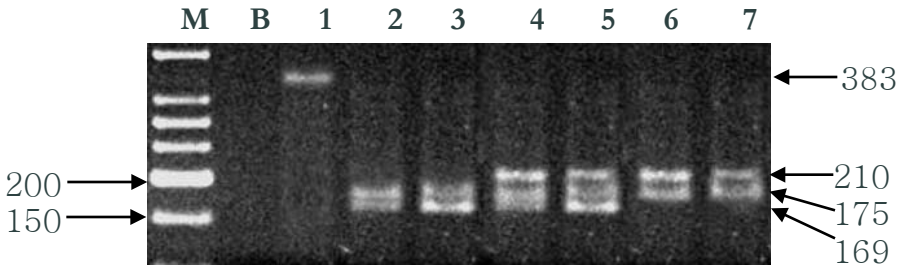


Xiao et al, KI 2008

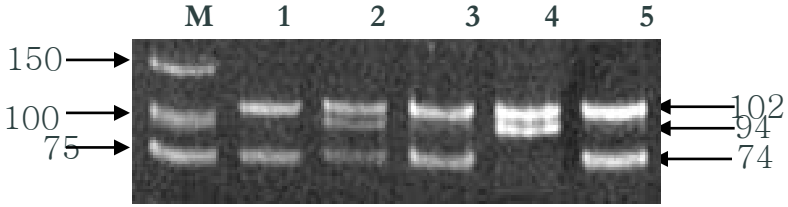
Variations in CY3A family

- CYP3A4 and CYP3A5 are the main CYP3A isoenzymes
- Interindividual expression and function variability linked mostly to genetic factors
- More than 50 SNPs in both genes
- *CYP3A4*: *1B (-392 A>G)
- *CYP3A5*: *3 (6986 A>G)

http://www.cypalleles.ki.se/



Lane M: Low Molecular Weight Marker;
Lane B: Blank; Lane 1: PCR products (383bp);
Lane 2,3: AA Homozygotes (175 & 169);
Lane 4,5: AG Heterozygotes(210,175 & 169bp);
Lane 6,7: GG Homozygotes(210,175bp).



Lane M: Low Molecular Weight Marker (NEB)
Lane 1,3,5: AA Homozygotes (102,74 bp)
Lane 2: AG Heterozygotes (102,94,74bp)
Lane 4: GG Homozygotes (102,94 bp)

CYP3A5, CYP3A4 and ABCB1 SNPs in ESRD and control population

	ESRD (n=355)	**Control (n=300)**
CYP3A5A6986G*		
AA	10 (2.8)	16 (5.3)
AG	104 (29.3)	106 (35.3)
GG	241 (67.9)	178 (59.4)
CYP3A4A-290G**		
AA	336 (94.6)	294 (98)
AG	19 (5.4)	6 (2)
GG	0	0
ABCB1C1236T***		
CC	39 (11)	34 (11.3)
CT	92 (25.6)	122 (40.7)
TT	224 (63.1)	144 (48)
ABCB1G2677T		
GG	171 (48.2)	150 (50)
GT	158 (44.5)	115 (38.3)
TT	26 (7.3)	35 (11.7)
ABCB1C3435T		
CC	39 (11)	51 (17)
CT	198 (55.8)	143 (47.7)
TT	118 (33.2)	106 (35.3)

Figures in parentheses are percentages. * GGvAA/AG, p=0.028; **GGvAG, p=0.038; ***TTv CC/CT, p<0.0001

Semin Nephrol. 2008 Jul;28(4):416-28.

Natural medicines causing acute kidney injury.

Jha V, Rathi M.

Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. vjha@pginephro.org

Abstract

The use of alternative remedies derived from plants and animals is increasing worldwide. Their source and composition varies depending on the prevalent local practices. They are not tested for efficacy and safety; their ingredients are unknown and the dosage and route of administration are not standardized. Potentially toxic chemicals are added to them to increase their potency and mistaken identity has led to the use of toxic plants instead of the originally intended herb. Kidneys play a vital role in the metabolism and excretion of these substances and acute kidney injury is a common and important manifestation of their toxicity. The most usual renal lesions include acute tubular necrosis, cortical necrosis, and interstitial nephritis. Patients often present late to hospitals with multi-organ involvement. The diagnosis may be missed if the history is not sought specifically. These factors culminate in high mortality rates. Study of this entity is difficult because of the remoteness of the areas, unfamiliarity with local cultures, and mystery and secrecy surrounding the natural medicines used. Physicians need to be aware of this condition to make a timely diagnosis and provide appropriate management. Public awareness and regulation of the use of these medicines are required to eradicate this entity from the community.

PMID: 18620964 [PubMed - indexed for MEDLINE]

Conclusions

- Use of herbal products may not always be harmless
- Mislabeling and substitution shown as the cause of AAN
- AA also shown as the environmental cause of BEN
- Such lesions are likely to be commoner and more widespread than previously believed
- More epidemiologic and laboratory research needed to establish cause-and-effect
- Regulations required to ensure safety of herbal products