

ARISTOLOCHIA: THE MALIGNANT LIE AND THE BENIGN TRUTH

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This article was commissioned in response to a recent piece in the Lancet (Daniel Kell, Justin Stebbing. 'Aristolochia: the malignant truth' (under 'Quackery' rubric), in www.thelancet.com/oncology Vol 14 January 2013) which revisits the aristolochia story. The trigger for this revisit was a completely unrelated case of acute liver failure in a patient poisoned by arsenic oxide, contained in a remedy that she had been taking (the nature of the remedy is not specified). Arsenic, the authors note, is a 'well known poison that has been linked to the death of several historical figures, including George III. Although we cannot discount the potential medicinal properties of many natural and alternative therapies...this case serves to highlight the potential dangers associated with the use of unlicensed or undervalued products or their use without strict medical supervision. What better example of this than the traditional Chinese medicine aristolochia?' Editor

A black cat, in a dark room, is hard to find. Especially when it is not there... (Kung Fu Tzu)

The story of Aristolochia and its toxicity has cast a twenty year long shadow over Traditional Chinese Herbal Medicine (TCHM) and Complementary and Alternative Medicine alike. Although new cases have not occurred in the past decade, the same evidence and incidence is being recycled year after year in scientific papers, invariably referring to these cases to highlight the dangers of (herbal) quack-medicine. Under the heading 'Quackery' and the title 'Aristolochia: the malignant truth', *The Lancet* deemed it necessary to freshen up our memory once more in its January issue

For different reasons, all highlighted further on, writing about Aristolochia is an extremely delicate matter, technically as well as ethically. Therefore, let it be clear in advance that nobody in his right mind disputes the ban on Aristolochia species. However, the *Lancet* article is one more sad example of how this case is abused for other agendas: highlighting the dangers of unlicensed medicines, the alleged absence of testing and quality control and the inevitable connection to quackery. It is simply revolting how the authors connect a case of arsenic poisoning and, bloody hell... the death of King George III, to the case of Aristolochia. The saying goes that for a man with only a hammer, everything begins to look like a nail... It is remarkable that the virulent attacks on traditional herbal medicine are systematically reduced to the problem of Aristolochia, in an

unprecedented stream of scientific echolalia, without providing new information or even mentioning the existence of alternative and more nuanced hypotheses.

The Belgian case: not a quack or herbalist to be seen

First of all one should be aware that the Aristolochia stigma on TCHM, goes back to the major 'clear-cut' case in Belgium, a drama that took place exclusively in the medical prescription- and pharmaceutical dispensing circuit. No quack nor even a herbalist on the horizon! It beggars belief that the sceptic establishment points its guns so disproportionately to herbal medicine at a time juncture when all aspects of safety-efficacy evaluation for regular medicine are under scrutiny. In Belgium, 2000 deaths per year are officially attributed to licensed medicine (overdosages not included). A list of over 1600 licensed products considered ineffective is circulating in EU. On a regular basis phase '1-3 clinically tested medicinals' are withdrawn from the market because of severe side-effects and deaths. Can the authors present a similar negative curriculum for botanical food supplements and medicinals? Moreover, recent research points out that in one third of scientific papers, results and data are 'massaged' under the urge to publish, and more and more cases of scientific fraud are being revealed. Likewise, the selective combination of truths, half-truths, concealment and conjecture that characterizes the Aristolochia hypothesis leads one to suspect that plenty of anomalous information was diligently transformed into accomplished fact. To such an extent that one would sigh: 'Where's Edzard Ernst when you really need him?'... because this case cries out for a meta-analysis.

The poverty of the EU model

Meanwhile in the 'usual suspects' discourse that we are so familiar with, clearly reference is made to Aristolochia to legitimize the stringent safety and quality guidance as required under the THMPD. However, this EU directive involves a registration model that wrings traditional phytotherapy into an unworkable straitjacket since it fails dramatically to reconcile statutory regulation with efficient Quality Safety-control. The EU model seems to solve all problems that have never existed, and leaves the few real problems unsolved. It is symptomatic for the poor understanding of

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traditional processing by the regulatory authorities, and shows how little lessons have been drawn from the Aristolochia tragedy: traditional ingredients should not be used frivolously outside their traditional context and preparation form, which are quite specific.

Aristolochia: vital to distinguish intrinsic toxicity and the wider context of its use

Since all potential safety issues associated with herbal remedies seem to epitomize in the case of Aristolochia, it may be worthwhile to distinguish the real, intrinsic toxicity from the circumstantially caused damage. Coming back to the Belgian case, some facts that were poorly highlighted in the scientific papers.

- The Aristolochia case involved an adulteration of species due to poor identity control by the responsible supervising pharmacists! Aristolochia fang ji was used in stead of Stephania tetrandra (Han fang ji)
- Both the original herb and the adulterant are only remotely indicated for the intended diuretic action and both herbs were traditionally prescribed as ingredients of a classical formula or a multi-herbal tailored prescription, not as single ingredient.
- The herbs were prescribed by medical doctors devoid of any experience with TCHM. All recommendations regarding dosage, processing, length of administration and traditional contra-indications were systematically ignored.
- The herbal ingredients were added to a cocktail, consisting of dexfenfluramines, diethylpropion, diamox, meprobramate, a.o. All of these licensed medicinals were withdrawn from the market in the years to follow because of severe side effects. Two of those turned out to cause cardiac valvulopathies and peritoneal and pulmonary fibrosis similar to the pattern encountered in the majority of the victims.
- It is commonly accepted that the common denominator in all cases of interstitial fibrosis as established in the victims, was Aristolochia. This is basically correct, but of little use, since thousands of women visiting this slimming clinic, were administered Aristolochia but did not develop such pathology. Far more interesting is the fact that all victims but one, issued from one surgery where, in a 4 month stretch, high dosages of serotonin enhancers were injected. Not a single victim issued from the 4 surgeries where the same criminal cocktail was administered for 2 years. The epidemiological data of this unsavoury case were never published in full. The combination of high dosages of administered serotonin with the dexfenfluramine which prevents the re-uptake of serotonin by blocking the 5-HT receptors turned the poor women into ticking time-bombs calling for more tranquillizers (meprobramate) and high amounts of diuretics. Several expert-nephrologists pointed to serotonin as the principal causative agent of the rapidly progressing interstitial fibrosis, but their voices went unheard in the subsequent hysterical aristophobia. [1]
- It is very well possible that Aristolochic Acid is partly responsible for this fibrotic syndrome, but only in a secondary phase of the evolving pathology since the kidney lesions rather point to serotonin. Unlike what the papers say, the toxicity of the Aristolochia plant is well known from pharmacopoeae all over the world and comparable to colchicine. Pathology is acute and reversible, unlike the chronic, degenerative and irreversible renal failure syndrome encountered in the victims. In Hippocratic medicine Aristolochia is considered a powerful amphoteric drug (ie a drug with opposite characteristics). In this context amphoteric means that it has the ability to act as an acid and as base. As such it may have played a part in the pathology, given the fact that, while trying to restore the acid-base balance on the level of the extra-cellular matrix (in obese people already tending to grave acidosis!), it may have contributed to turn the extra-cellular matrix more alkaline, thus further polarising a pre-existing disbalance and accelerating the fibrotic process. Again, under such extreme conditions the role of Aristolochia is to be considered secondary, but it was the wrong ingredient at the wrong place and the wrong time. As such, it proved the ideal scapegoat for the scientific community to reduce the incredible complexity of this pathology to Aristolochia uniquely, but also the ideal escape route for irresponsible doctors and negligent pharmacists only driven by unscrupulous pursuit of profit.
- The bottom line is that the epidemiological data hardly implicate Aristolochia in the kidney pathology. At a very conservative estimate at least 15000 people were exposed to Aristolochia between 1989 and 1993. Herbalists prescribed tailored combinations with Aristolochia for the treatment of fistula with amazing results. All in 'tempore non suspecto'... It is remarkable that only a relatively small number of people, concentrated in one place, developed the fibrotic syndrome. In 2001 the Belgian Ministry of Health conducted a large-scale inquiry, inviting everyone to whom Aristolochia/Stephania had been administered, for a free kidney screening. Between 5000 and 8000 people reacted. (Yes, there is a traceability system in Belgium.) Not even one new case nor suspicious mortality has been reported.

How about the alleged carcinogenicity of Aristolochia? The carcinogenic properties of AA have only been established in rodents and are due to anaerobic bacterial nitroreduction in the forestomach of rats, a mechanism that cannot be extrapolated to humans. If the mechanism would apply, we talk about exorbitant dosages to which no human being has ever been exposed.

- The urothelial carcinoma affecting some of the Belgian victims in the slipstream of the renal pathology, was immediately attributed to AA. Subsequently, AA-DNA adducts were discovered in their renal biopsies by a research team Heidelberg. [2] The results turned out to be qualitatively and quantitatively impossible but were slavishly swallowed by the scientific community, despite multi-leveled incongruities with previous results. One of the co-operators at the time, Professor A. Pfohl-Leszkowicz, could not reconcile to the outcome of the assay and conducted her own research in which she put forward the hypothesis of ochratoxine as the source of BEN, the Balkan Endemic Nephropathy, also attributed to Aristolochia. The ochratoxine hypothesis gained momentum when she was able to re-examine original biopsy samples from the Belgian victims. She identified the adducts as ochratoxine-adducts, and at the same time highlighted the major flaws and anomalies in the AA-hypothesis.[3][4][5] Despite the absence of sound contra-arguments, her conclusions are mainly hushed up among toxicologists. The reason? The big food concerns stick to the AA-hypothesis since the costs for QS control on their cereals would increase exponentially if the OTA-hypothesis were proved right. Interestingly, in the early nineties, a Belgian expert group, advisory to the Department of Health, came to a similar conclusion, but at that time one could not let the truth interfere with a good story...

It is little known that on the basis of the argumentation above and after hearing experts from both sides two Courts of Law final verdicts (Belgium and France) confirmed the absence of any proven causal link between the pathologies and the herbal ingredients!

The *Lancet* article concludes as follows: « ...when comparing conventional therapies with unlicensed or underevaluated herbal products, the old Irish anecdote : 'better the devil you know than the devil you don't', might be more appropriate... This quote illustrates the condescending arrogance that, by combining selective information and model-based biases, finishes off herbal medicine. And, while talking about the devil you know...What to think about the huge slimming scandal in France where a big pharmaceutical company is standing trial for causing the death of at least 500 people and serious valvulopathic complications in over 30000

patients. The licensed medicine Isomeride (Mediator) was registered as an anti-diabetic but promoted and prescribed exclusively as an appetite depressant. Incidentally, Isomeride is a molecule that comes close to the dexfenfluramine discussed above, in fact it is a chemical disguise for it and it shares its destructive properties. As early as 1992 and as a result of the 'Chinese Herb drama', the Belgian authorities were alerted about its implication in the valvulopathies and the fibrotic syndrome. However, the inconvenient truth was kept in the dark for years while the Belgian researchers were pasting together the Aristolochia hypothesis, the more convenient scapegoat. Had there been an objective assessment and nuanced communication the French drama could have been avoided and the health of tens of thousands of people would not have been jeopardized. No herbs involved this time. 'Unlicensed and underevaluated': did we read correctly ?

Again, this is absolutely not a plea for lifting the ban on Aristolochia. But as long as the truth remains in exile, and the 'open ends' in every hypothesis remain, it would be helpful to stop the vitriolic attacks on herbal medicine, especially in cases where the tradition is abused by criminals who disguise molecules like sibutramine, sildenafil and others as herbal remedies. It has been 20 years chewing on the same story and really, there's no more juice in it.

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