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Modeling Organ-Specific Aristolochic Acid Toxicity Using an Integrated Liver-Kidney Organotypic System

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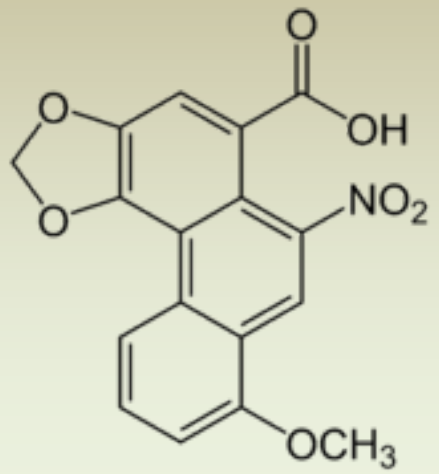
Problem: Aristolochic Acid Nephropathy *(AAN)*

Aristolochia clematitis



Aristolochic Acid (AA-I)

- Chinese-herb nephropathy (CHN) / Balkan endemic nephropathy (BEN)
- Chronic kidney disease (CKD) and upper urinary tract urothelial carcinoma (UUC)

IARC classifications :

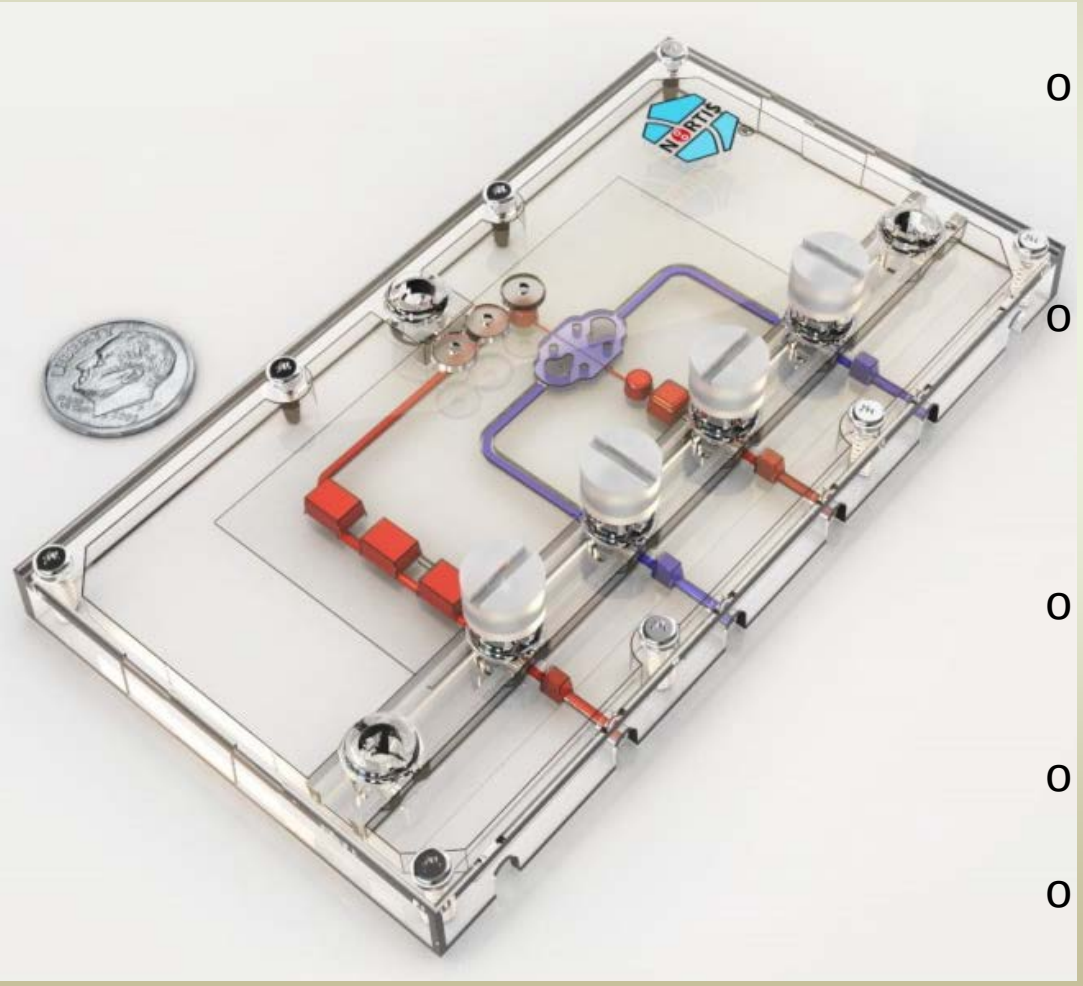
Herbal remedies containing plant species of the genus *Aristolochia* are carcinogenic to humans (Group 1).

Naturally occurring mixtures of AA are probably carcinogenic to humans (Group 2).

- Can we model AAN using an *ex vivo* organotypic system?

  - *Direct <u>and</u> functional coupling of liver→kidney to recapitulate 1st pass metabolism/bioactivation*

Platform: Nortis Microphysiological System (MPS)



Technical details:

- Gas-permeable PDMS silicone, polycarbonate base, collagen type I ECM, with a microscope coverslip
- Incorporation of “bubble traps” (port 1) at media entry point, as well as option for “ablumenal” flow (ports 2/4)
- Diameter of “tubule” is ~120 µM with an internal volume of ~70 nL
- Typical flow rate of 0.5-1.0 µL/min
- A 6 mm tubule contains ~5000 PTECs

www.kidney-international.org

basic research

Development of a microphysiological model of human kidney proximal tubule function

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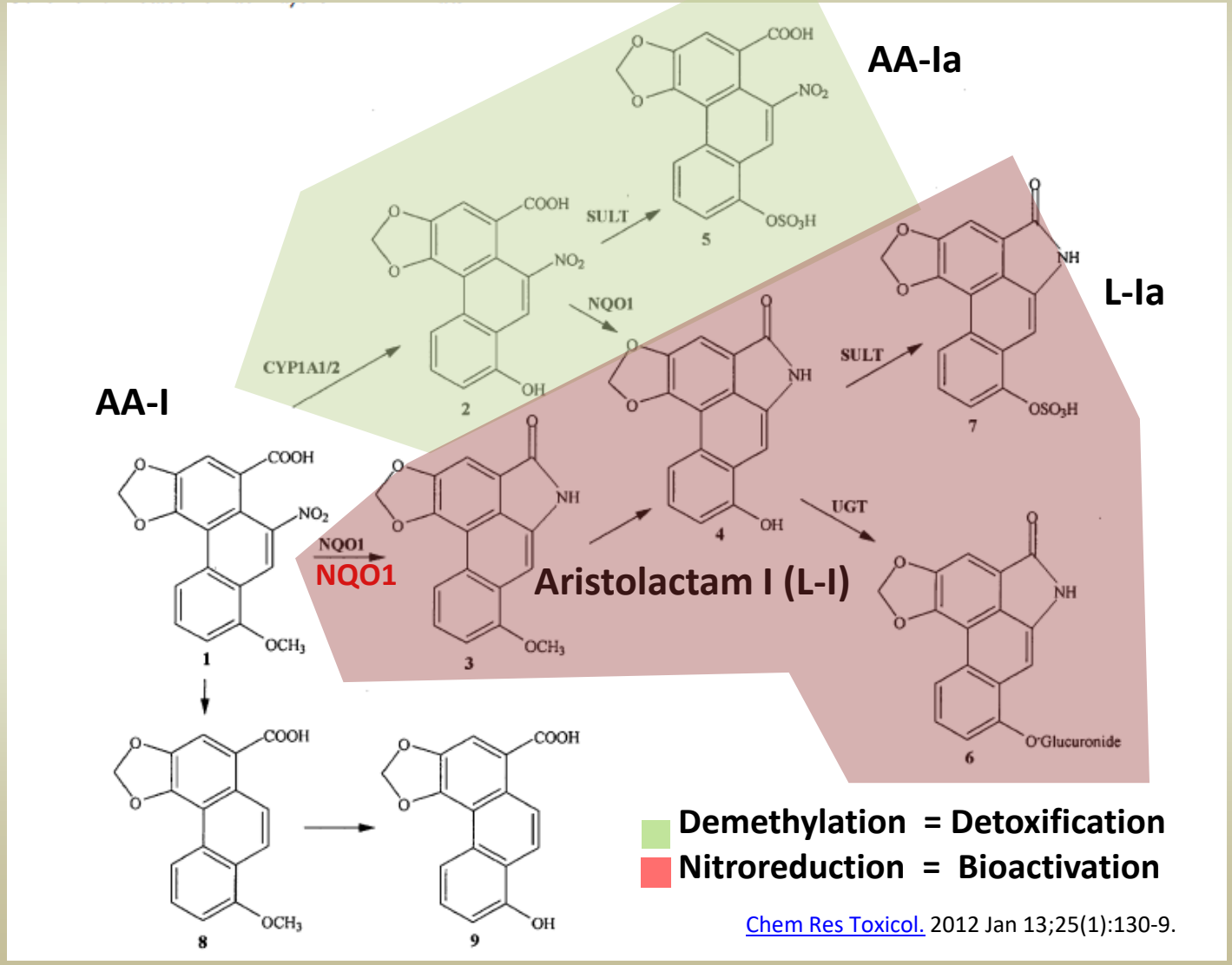
What is the role of the liver in AA-I first-pass metabolism?



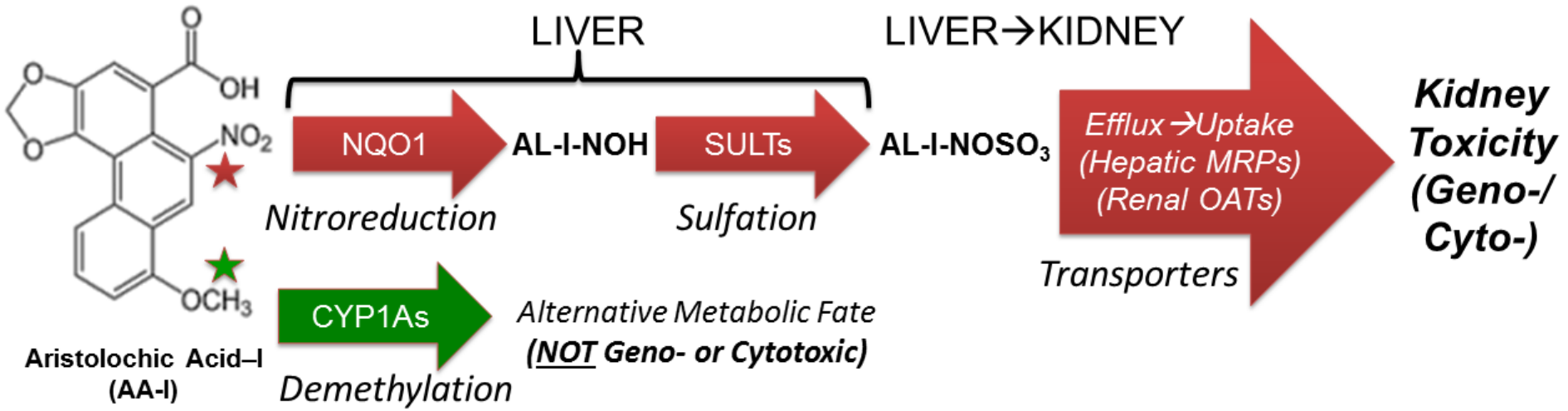
Chem Res Toxicol. 2012 Jan 13;25(1):130-9.

Study Design

AA-nephrotoxicity via hepatic bioactivation

DNA adduct formation from bioactivated AA-I

The role of the liver in bioactivation of AA-I



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