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The King's Centre for Integrative Chinese Medicine

伦敦国王学院整合中医药学中心

KING'S College LONDON

# Chinese herbal medicine:
# A Herbal journey with a nephrologist.

## 一位肾病学家的中药探索之旅

Dr Qihe Xu's PPT for his lecture at the School of Chinese Pharmacy, Beijing University of Chinese Medicine, 30th March 2023.

徐启河博士在北京中医药大学中药学院学术讲座PPT（2023年3月30日 · 中国北京）

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# Chinese herbal medicine:

## A herbal journey with a nephrologist

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**King's College London**
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# Discover King’s



# Discover King's

- **Aspiring to "Become a LEGEND"**, King's men and women have netted 14 Nobel prizes, including 5 since 2010.
- **King's is ranked 35th in the world** (THE 2023), **with health-related subjects all ranked top-20 worldwide** (QS 2023).
  - Nursing No. 2;
  - Dentistry No. 5;
  - *Life Sciences & Medicine No. 17;*
  - *Pharmacy & Pharmacology No. 19*; and
  - Psychiatry & Psychology No. 20.


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University of London
Distinguish yourself

**As a nephrologist for 30 years**, …

- I choose to “distinguish myself” by developing an integrative Chinese medicine approach to biomedical research & education.
- This includes research & teaching on CHM.

  - **2006-2023**: Nephrol., KCL, UK
  - **2005-2006**: Nephrol., NIDDK, NIH, USA
  - **1999-2005**: Nephrol., UCL, UK
  - **1992-1999**: Nephrol., PLA General Hospital, China
  - **1989-1992**: Nephrol., Peking University 1st Hospital, China

# Personal Statement

My talks aim to illustrate the dual potential of herbal medicines in:

- **Renal medicine**; and
- **Global healthcare**.

**I do NOT recommend any products!**

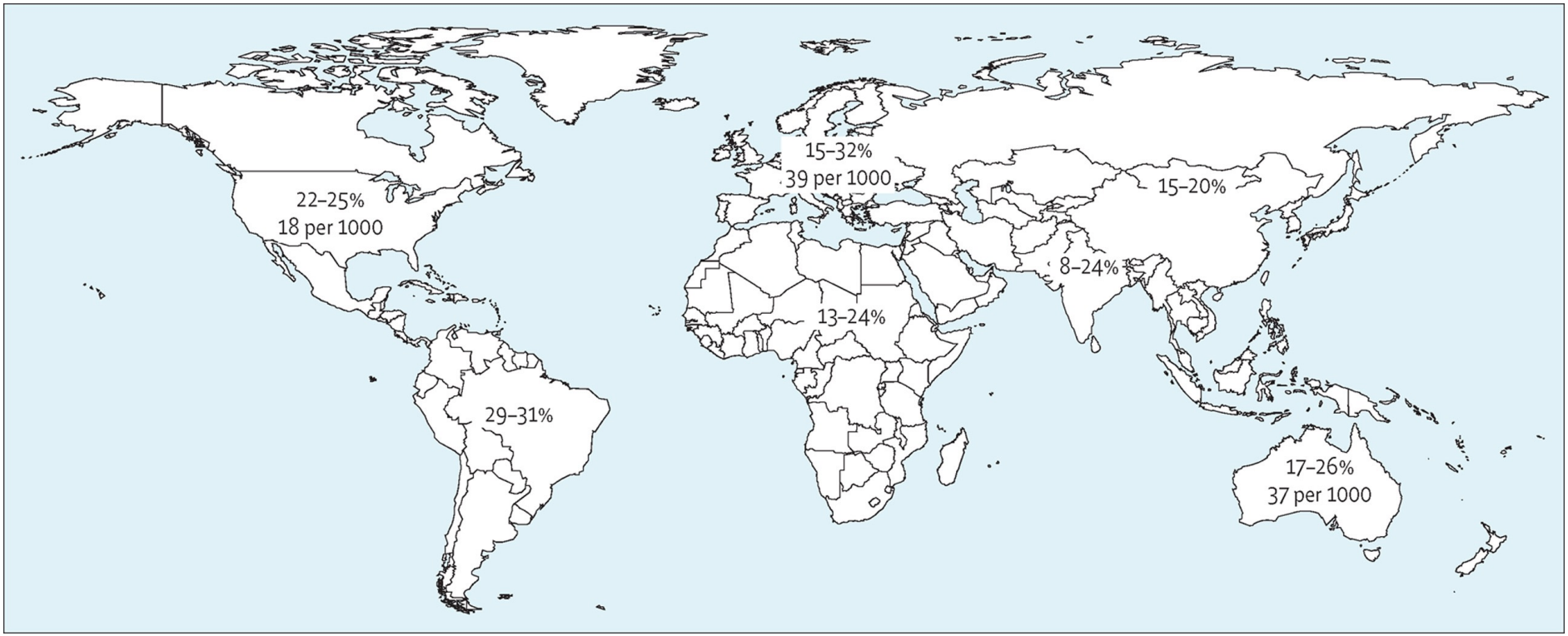
# Two main challenges in nephrology

- Acute Kidney Injury/Disease (AKI/AKD)
- Chronic Kidney Disease (CKD)

# **Worldwide, ~20% hospitalised patients suffer from AKI.**

This, plus community-acquired AKI, often leads to mortality.

AKI epidemiology per hospital admission (%) and
corresponding incidence by region (per 1000 person)



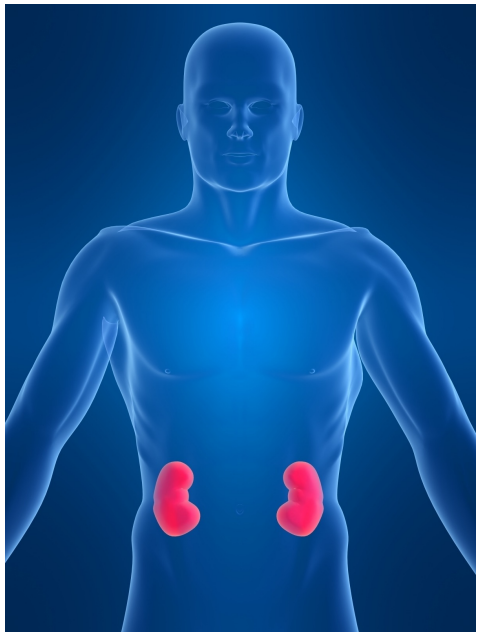

***Lancet***. 2019;394:1949-1964.

# CKD – An even bigger threat of the AKI/CKD double whammy

- CKD affects ~10% of the world's population—more than diabetes and cancer combined.
- CKD is one of the seven major diseases, death rates of which are increasing worldwide.
- CKD is tipped to become a top-5 cause of mortality worldwide by 2040.

*Lancet*. 2020;395:179
*Lancet*. 2015;385:117-71
*Lancet* 2018;392:2052-2090

# AKD/CKD are interconnected syndromes



Insults

**Normal kidneys**

**AKI (Up to 7 days)**

**AKD (8-90 days)**

- **Renal Replacement Therapies**
- **Lifespan loss**

**CKD (>90 days)**

**End-stage renal disease (ESRD)**

# AKI comes with high mortality:
# England as an example

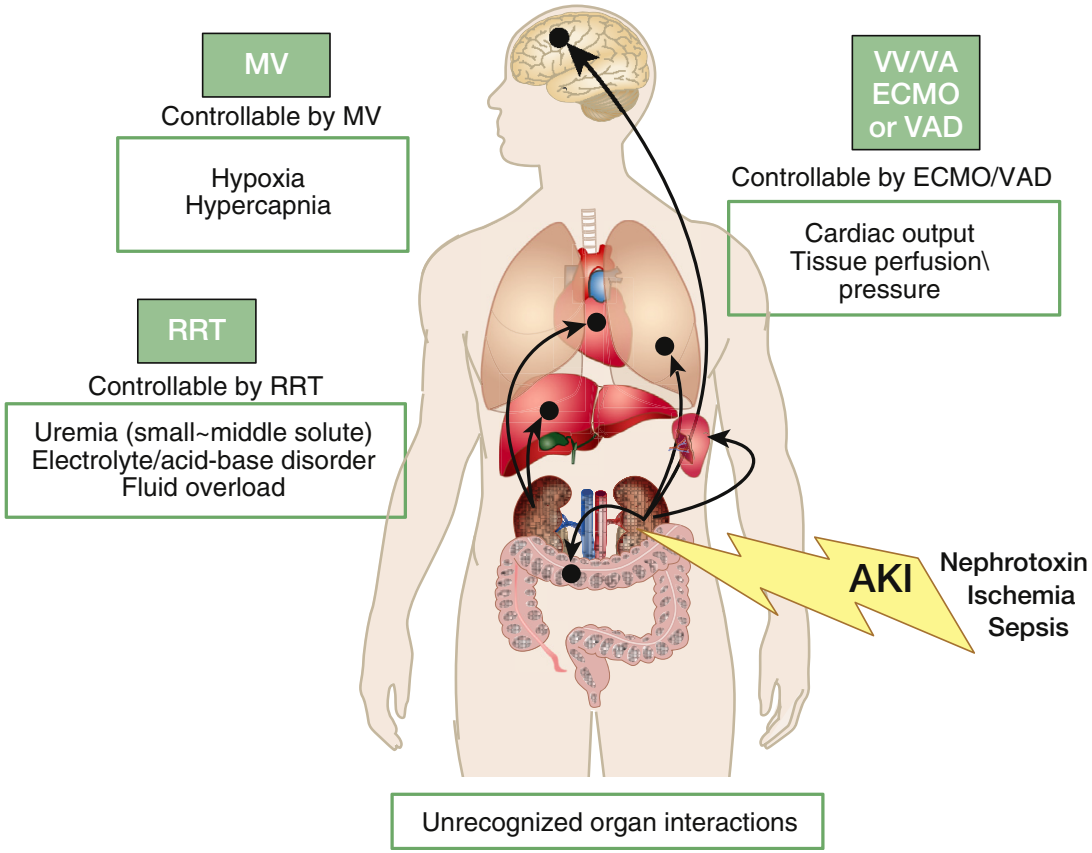
**Table 1. Adjusted (males aged 65–74 years) 30 day mortality for patients with an AKI episode by clinical setting in 2017**

| | All AKI episodes | Setting of AKI episode | | |
|---|---|---|---|---|
| | | CA | CAH | HA |
| Number | 441,699 | 127,767 | 171,266 | 142,666 |
| % | | 28.9 | 38.8 | 32.3 |
| % died by 30 days from AKI start | 18.0 | 8.3 | 20.6 | 23.6 |
| ADJUSTED MORTALITY (%) BY PEAK AKI STAGE | | | | |
| 1 | 12.2 | 6.2 | 13.5 | 15.5 |
| 2 | 26.0 | 20.5 | 24.5 | 31.1 |
| 3 | 28.3 | 21.8 | 26.4 | 36.6 |

CA – community acquired; CAH – community acquired, subsequently hospitalised; HA – hospital acquired

Andrew Lewington and Becky Bonfield, **Global Perspectives in Acute Kidney Injury: England,** Kidney360, Publish Ahead of Print, 2022, 10.34067/KID.0000052022

# AKI is more than a kidney disease!




Doi K, et al. **Impact of AKI on distant organ function: recent findings and potential therapeutic targets.** *Kidney Int* 2016;89:555.

**Table 1 | Mechanisms of distant organ effects in AKI**

| Organ | Reference |
|---|---|
| Lung | |
| Immune cell infiltration such as neutrophil, T cell, and macrophage | Kramer *et al.*,[33] Awad *et al.*,[35] Ishii *et al.*,[36] Lie *et al.*,[41] Altmann *et al.*[42] |
| Systemic IL-6 elevation and pulmonary CXCL1 expression | Klein *et al.*,[38] Ahuja *et al.*,[39] Andres-Hernando *et al.*[40] |
| TLR4 activation by increased plasma HMGB1 | Doi *et al.*[50] |
| Heart | |
| Cellular apoptosis by cardiac TNF-α expression | Kelly[65] |
| Mitochondrial fragmentation and apoptosis by dynamin-related protein 1 upregulation | Sumida *et al.*[69] |
| Macrophage infiltration by osteopontin | Tokuyama *et al.*[68] |
| Hypertrophy and fibrosis with increased cardiac angiotensin 1 converting enzyme 2 activity | Burchill *et al.*[67] |
| Spleen | |
| Supporting protective effect of TLR9 inhibitor chloroquine | Yasuda *et al.*[81] |
| Secretion of lethal mediator HMGB1 | Leelahavanichkul *et al.*[82] |
| Transient reservoir of mobilized transient endothelial progenitor cells | Patschan *et al.*[86] |
| Cholinergic anti-inflammatory pathway activation by exposure of the kidney to ultrasound waves | Gigliotti *et al.*[88] |
| Secretion of protective splenic IL-10 for lung injury | Andres-Hernando *et al.*[40] |
| Brain | |
| Increased chemokine expression of keratinocyte-derived chemoattractant and granulocyte-colony stimulating factor in cortex and hippocampus | Liu *et al.*[93] |
| TLR4 upregulation in hippocampus and striatum | Salama *et al.*[95] |
| Liver | |
| Leukocyte infiltration, increased oxidative stress, and hepatocyte apoptosis | Miyazawa *et al.*,[126] Golab *et al.*[127] |
| Altered cytochrome P450 3A enzyme activity | Lane *et al.*[132] |
| Gut | |
| Production of protective short-chain fatty acid for renal injury by microbiota | Jang *et al.*,[135] Andrade-Oliveira *et al.*[139] |
| Paneth cell activation (IL-17A production) | Park *et al.*[147] |

AKI, acute kidney injury; CXCL1, chemokine (C-X-C motif) ligand 1; HMGB1, high-mobility group box protein B1; IL, interleukin; TLR4, Toll-like receptor 4; TLR9, Toll-like receptor 9; TNF-α, tumor necrosis factor-α.

# Legrand M, Rossignol P. N Engl J Med 2020;382:2238-47.

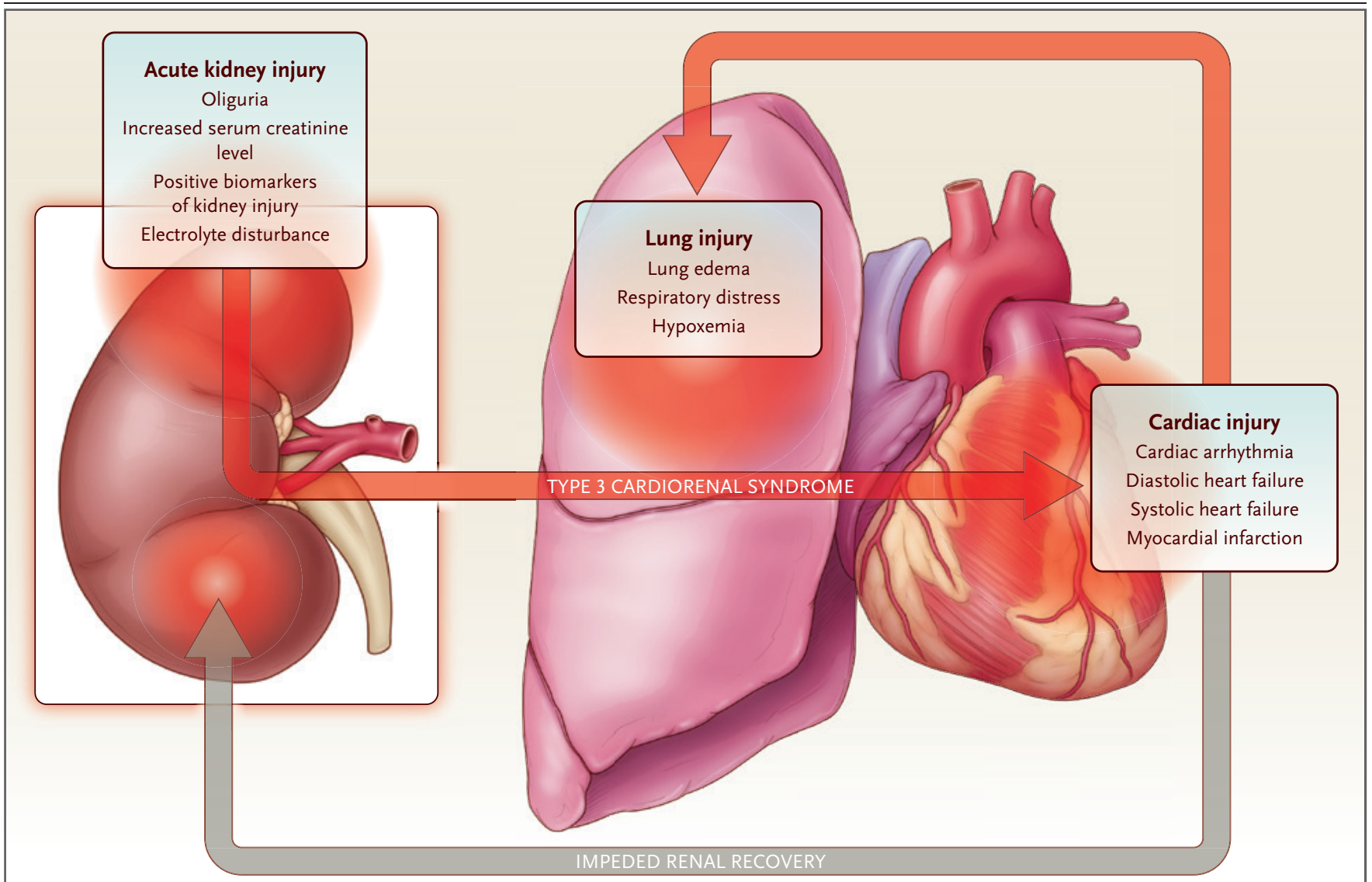



**Figure 1. Cardiac and Pulmonary Consequences of Acute Kidney Injury.**

Acute kidney injury has been shown to promote cardiac injury and dysfunction, defined as type 3 cardiorenal syndrome. Heart failure, in turn, can impede renal recovery. Lung injury and hypoxemia after acute kidney injury can arise both from increased capillary permeability and from increased hydrostatic capillary pressure due to heart failure.

# AKI causes heart injury and increases mortality

Legrand M, Rossignol P. **NEJM** 2020;382:2238-47.

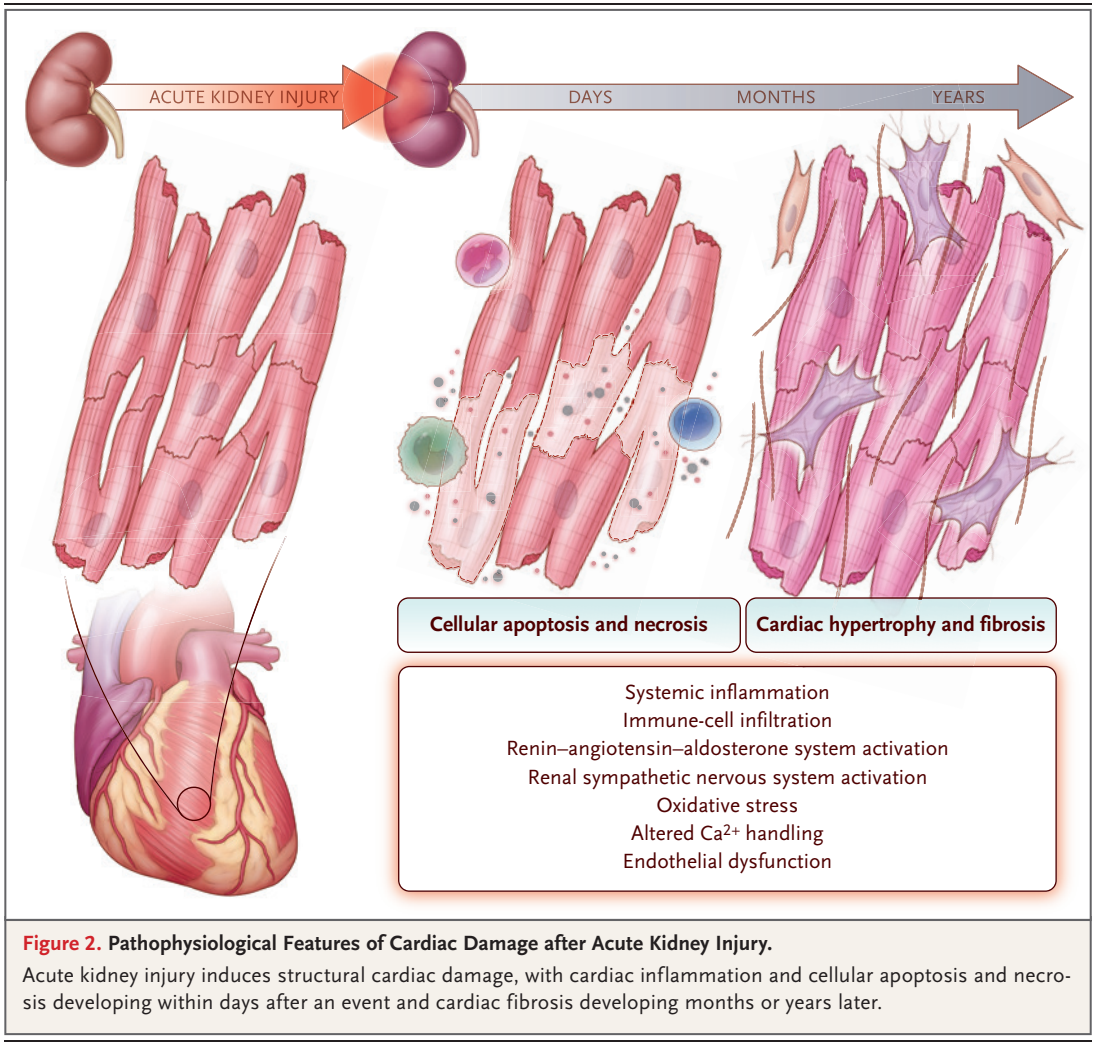



**Figure 2. Pathophysiological Features of Cardiac Damage after Acute Kidney Injury.**
Acute kidney injury induces structural cardiac damage, with cardiac inflammation and cellular apoptosis and necrosis developing within days after an event and cardiac fibrosis developing months or years later.

- **Cardiac inflammation**
- **Cardiac fibrosis**
- **Neurohormonal activation**
- **Electrolyte disturbances**

**AKI is associated with**

- 86% increase in death from cardiovascular cause in 1.4 years
- 58% increase in chronic heart failure in 2.9 years of follow-up;
- 40% increase in acute myocardial infarction in 2.3 years of follow-up
- 15% increase in the risk of stroke over a period of 2.7 years

(Odutayo A, et al. AKI and long-term risk for cardiovascular events and mortality. J Am Soc Nephrol 2017;28:377-87)

- No drug is widely accepted for prevention and treatment of AKI.
- Can herbal medicines meet the unmet needs?

DOI: 10.15806/j.issn.2311-8571.2015.0019 World J Tradit Chin Med 2015; 1(3): 47–66

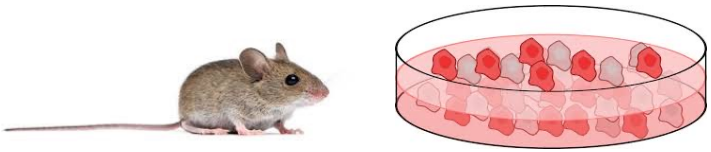
TCM Clinical Research

# Herbal Medicines for Acute Kidney Injury: Evidence, Gaps and Frontiers

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# Summary to preclinical findings



1. 16 formulae and a few herbal extracts were reported to prevent AKI in animal models, including those induced by cisplatin, ischemia/reperfusion (I/R) and sepsis;

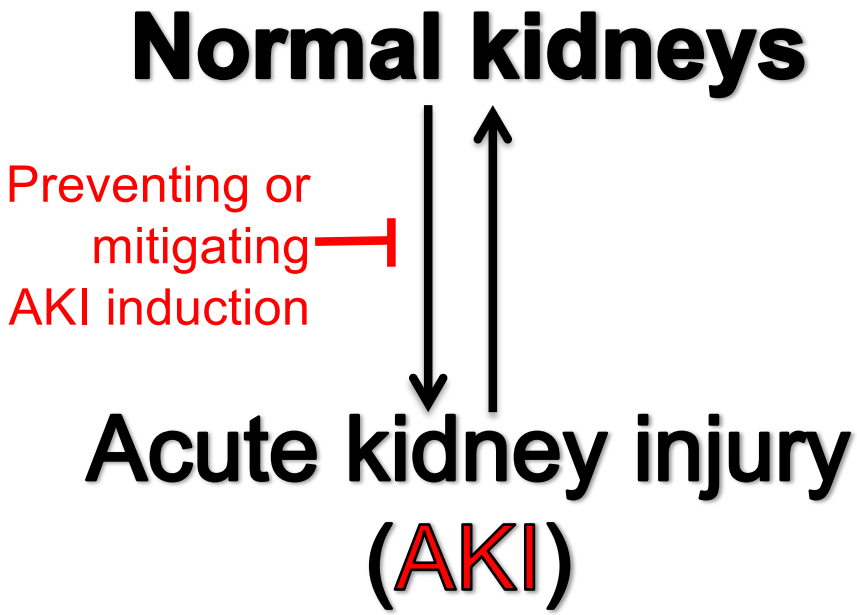


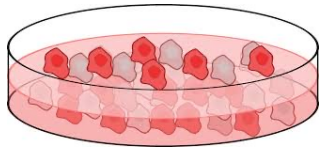

**Table 1. Formulae for preventing AKI in *in vivo* and *in vitro* models.**

- Adenine and ethambutol hydrochloride-induced AKI
  - Ermiao San
- Adenine and oteracil potassium-induced AKI
  - Fufang Xi Xian Cao Capsule
- Cisplatin-induced AKI
  - Recipe for nourishing kidney and activating blood
  - Zhibai Dihuang Wan
  - Gujingdan
  - Shenkangning
  - VI-28
- Glycerol-induced AKI
  - WH30+
  - Shenshuai Mixture
  - Shensheng fang
- Ischaemia-reperfusion-induced AKI
  - Dang Gui Bu Xue Tang
  - Wen-Pi-Tang
  - Wen-Pi-Tang-Hab-Wu-Ling-San
  - Shenhua Tablet
- Over-exercise-induced AKI
  - Yishen Huanji Decoction
- Sepsis-induced AKI
  - Xuebijing

**WJTCM 2015:1:47-66**

# Summary to preclinical findings





2. 4 formulae accelerated recovery and/or prevented CKD in AKI animal models induced by AA, gentamicin and I/R.

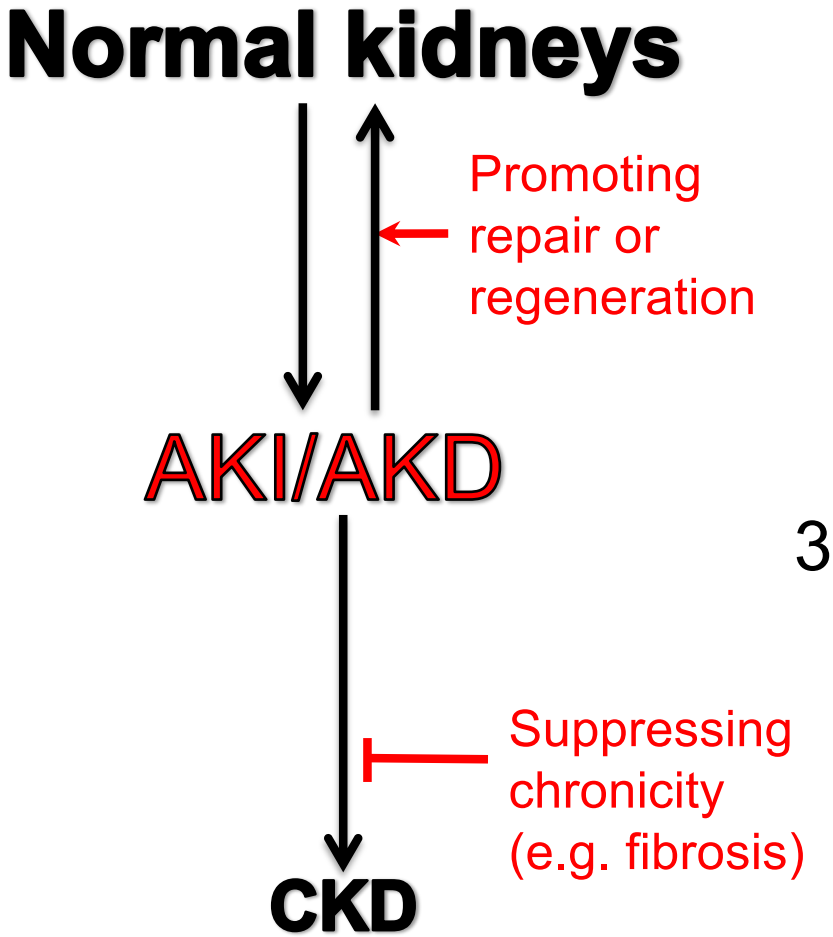



**Table 2. Formulae for treating established AKI *in vivo* and *in vitro*.**

- Aristolochic acid-induced AKI/CKD
  - Wen Yang Huo Xue Fang
- Gentamicin-induced AKI
  - Huanghuai Wendan Recipe
  - Shenshuaikang enema
- Ischaemia-reperfusion-induced AKI:
  - Wen-Pi-Tang-Hab-Wu-Ling-San

3. Top-3 most used herbs have well-established antifibrotic activities

**Table 7.** Fourteen herbs most commonly prescribed in herbal remedies for AKI (more than 5 citations in the reports summarised in Tables 1-6).

| Herb | Number of citations in Tables 1-6 |
|---|---|
| Dà huáng (Rhei Radix et Rhizoma) | 16 |
| Dān shēn (Salviae Miltiorrhizae Radix) | 16 |
| Huáng qí (Astragali Radix) | 14 |

**WJTCM 2015:1:47-66**




# Summary to findings of clinical studies

4. 7 intrarectal herbal medicines were reported to increase extrarenal clearance of uraemic toxins.

5. 13 additional clinical trials reported herbal interventions in AKI of different aetiologies.

**Table 3. Herbal medicines for AKI: Five randomised controlled trials indexed in Pubmed**

| Herbal medicines, route of administration |
|---|
| • A decoction of 11 herbs, p.o. |
| • Chongcao Shenkang Capsules, a commercial product comprising three herbs, p.o. or by gavage |
| • Corbrin Capsules, a fermented dōng chóng xià cǎo (Cordyceps) power, p.o. |
| • Danhong Injection, a commercial product comprising extracts of two herbs, i.v. |
| • Qishen Huoxue Granule, a commercial product comprising extracts of 6 herbs, by gavage. |

**Table 4. Herbal medicines for AKI: 14 randomised controlled trials NOT indexed in Pubmed**

| Herbal medicines, route of administration |
|---|
| • Six decoctions comprisng three to seven ingredients, rectal administration |
| • A fourteen-ingredient decoction, p.o. or by gavage |
| • Bailing Granule, mainly comprising fermented dōng chóng xià cǎo (Cordyceps), p.o. or by gavage |
| • Bailing Granule, mainly comprising fermented dōng chóng xià cǎo (Cordyceps), p.o. |
| • Jinshuibao Capsule, mainly comprising fermented dōng chóng xià cǎo (Cordyceps), p.o. or by gavage |
| • Jiushentang, p.o. |
| • Jiushen decoction, p.o. |
| • Shennong 33", i.v. |
| • Sheshangliangxue mixture, p.o. |

**WJTCM 2015:1:47-66**

# TCM for In-Hospital AKI:

## A Systematic Review and Meta-Analysis

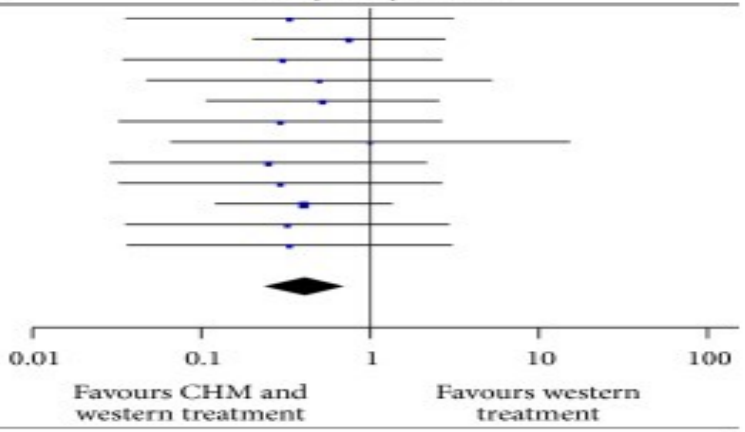
- Chen T et al. *eCAM* 2016: 7592705
- 15 RCTs published by Jun 2015, involving 966 patients.

# In-hospital mortality.

| Study or subgroup | CHM and western treatment Events | Total | Western treatment Events | Total | Weight | Risk ratio M-H, fixed, 95% CI |
|---|---|---|---|---|---|---|
| Deng and Wang 2000 | 1 | 80 | 3 | 80 | 7.3% | 0.33 [0.04, 3.14] |
| Jiang 2012 | 3 | 15 | 4 | 15 | 9.7% | 0.75 [0.20, 2.79] |
| Pan et al. 2009 | 1 | 22 | 3 | 20 | 7.6% | 0.30 [0.03, 2.68] |
| Ru 2013 | 1 | 38 | 2 | 38 | 4.9% | 0.50 [0.05, 5.28] |
| Sun et al. 2001 | 2 | 21 | 4 | 22 | 9.5% | 0.52 [0.11, 2.56] |
| Sun et al. 2007 | 1 | 34 | 3 | 30 | 7.7% | 0.29 [0.03, 2.68] |
| Wang 2010 | 1 | 30 | 1 | 30 | 2.4% | 1.00 [0.07, 15.26] |
| Wen and Liu 2003 | 1 | 62 | 4 | 62 | 9.7% | 0.25 [0.03, 2.17] |
| Yang 2007 | 1 | 34 | 3 | 30 | 7.7% | 0.29 [0.03, 2.68] |
| Yu et al. 2010 | 3 | 25 | 8 | 27 | 18.7% | 0.41 [0.12, 1.36] |
| Zhang and Mao 2003 | 1 | 33 | 3 | 32 | 7.4% | 0.32 [0.04, 2.95] |
| Zhu and Tang 2014 | 1 | 41 | 3 | 41 | 7.3% | 0.33 [0.04, 3.07] |
| **Total (95% CI)** | | **435** | | **427** | **100.0%** | **0.41 [0.24, 0.71]** |
| Total events | 17 | | 41 | | | |

Heterogeneity: $\chi^2 = 1.89$, df = 11 ($P = 1.00$); $I^2 = 0\%$

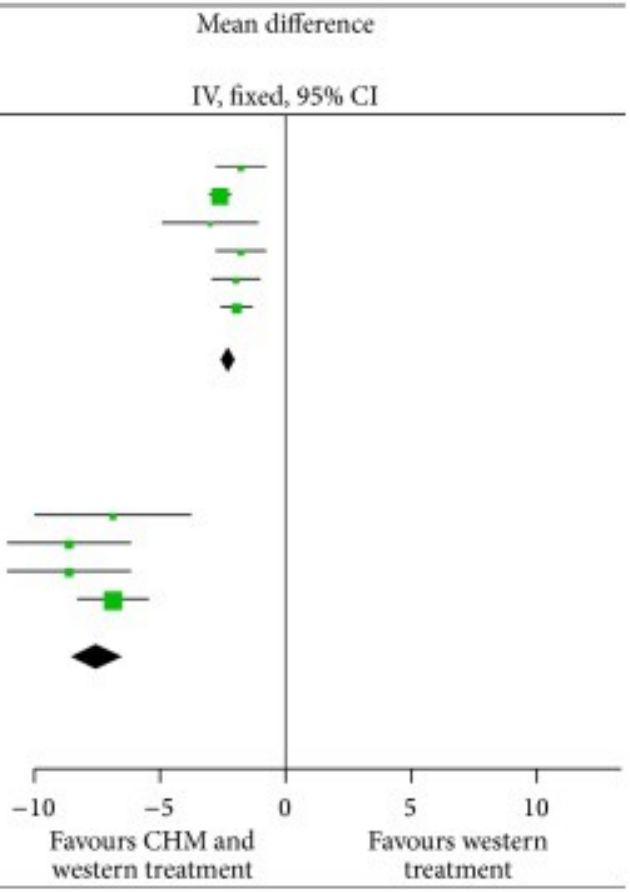
Test for overall effect: $Z = 3.24$ ($P = 0.001$)



# Time to recovery of kidney function

Chen T et al. *eCAM* 2016: 7592705

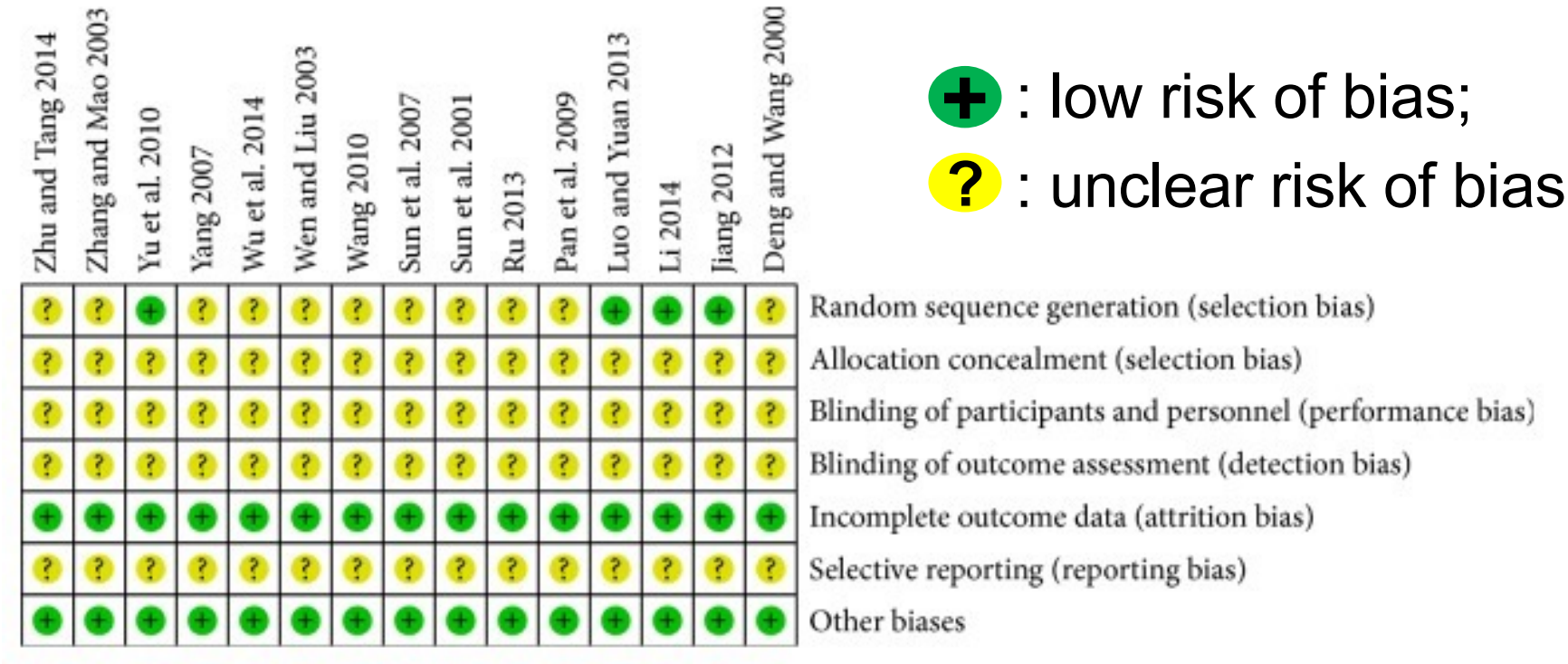
| Study or subgroup | CHM and western treatment Mean | SD | Total | Western treatment Mean | SD | Total | Weight | Mean difference IV, fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| *1.3.1 Time to oliguria* | | | | | | | | |
| Sun et al. 2007 | 2.25 | 1.08 | 31 | 4.03 | 2.47 | 27 | 9.1% | −1.78 [−2.79, −0.77] |
| Wen and Liu 2003 | 2.61 | 1.12 | 61 | 5.22 | 1.31 | 58 | 47.6% | −2.61 [−3.05, −2.17] |
| Wu et al. 2014 | 3.8 | 2.14 | 26 | 6.8 | 4.15 | 22 | 2.5% | −3.00 [−4.92, −1.08] |
| Yang 2007 | 2.25 | 1.08 | 31 | 4.03 | 2.47 | 27 | 9.1% | −1.78 [−2.79, −0.77] |
| Zhang and Mao 2003 | 2.04 | 1.23 | 33 | 4.02 | 2.52 | 32 | 9.8% | −1.98 [−2.95, −1.01] |
| Zhu and Tang 2014 | 3.41 | 1.82 | 41 | 5.36 | 1.07 | 41 | 22.0% | −1.95 [−2.60, −1.30] |
| **Subtotal (95% CI)** | | | **223** | | | **207** | **100.0%** | **−2.26 [−2.57, −1.96]** |
| Heterogeneity: $\chi^2 = 5.97$, df = 5 ($P = 0.31$); $I^2 = 16\%$ | | | | | | | | |
| Test for overall effect: $Z = 14.64$ ($P < 0.00001$) | | | | | | | | |
| *1.3.2 Time to Scr and BUN level recovery* | | | | | | | | |
| Pan et al. 2009 | 11.71 | 4.26 | 22 | 20.74 | 5.86 | 20 | 11.1% | −9.03 [−12.15, −5.91] |
| Sun et al. 2007 | 14.85 | 2.53 | 31 | 25.62 | 6.08 | 27 | 17.9% | −10.77 [−13.23, −8.31] |
| Yang 2007 | 14.85 | 2.53 | 31 | 25.62 | 6.08 | 27 | 17.9% | −10.77 [−13.23, −8.31] |
| Zhang and Mao 2003 | 15.1 | 3.23 | 33 | 24.12 | 2.62 | 32 | 53.1% | −9.02 [−10.45, −7.59] |
| **Subtotal (95% CI)** | | | **117** | | | **106** | **100.0%** | **−9.65 [−10.69, −8.61]** |
| Heterogeneity: $\chi^2 = 2.49$, df = 3 ($P = 0.48$); $I^2 = 0\%$ | | | | | | | | |
| Test for overall effect: $Z = 18.17$ ($P < 0.00001$) | | | | | | | | |






# Uncertain risk of bias!!!

Chen T et al. *eCAM* 2016: 7592705




+ : low risk of bias;

? : unclear risk of bias.

# More than 200 new original publications since the *WJTCM* 2015 publication

(Razna Ahmed, Mashal Huda, Qihe Xu)

1. Nephrotoxic AKI
2. Septic AKI
3. Ischaemia-reperfusion-induced AKI

# Illustration of preclinical findings (1)

Among all types of nephrotoxic AKI, herbal prevention of cisplatin-induced kidney injury is the most studied, with 28 *in-vivo* reports.

## In mouse models (n=21):



- Oh SM et al. 2017. 10 herbs in vitro and 2 in mouse models
- Meng XM et al. 2018. Wogonin
- Chen X et al. 2019: Hesperetin
- Tan RZ et al. 2019. Quercetin
- Li Y et al. 2020. Jian-Pi-Yi-Shen formula
- Rui-Zhi T et al. 2021. Isoliquiritigenin.
- Yang Q et al. 2021. Naringenin, an herbal Smad3 inhibitor
- Wang G et al. 2021. Wedelolactone
- Zhai J et al. 2021. Ginsenoside Rg3
- Lei XY et al. 2021. Artesunate
- Chen C et al. 2021. Hydroxytyrosol
- Kim DU et al. 2021. Loganin
- Qi J et al. 2021. Berberine
- Zhou L et al. 2022. polydatin
- Shi L et al. 2022. A two-herb formula
- Kim DU et al. 2022. Ojeoksan
- Li H et al. 2023. Neferine
- Jin X et al. 2023. Shenshuaifu Granule
- Shao YF et al. 2023. Kaempferide
- Liu J et al. 2023. San-Huang decoction
- Qi J et al. 2023. Yi-Shen-Xie-Zhuo formula



## In rat models (n=7):

- Liu Q et al. 2017. Zhen-Wu-Tang
- Shin HK et al. 2017. *Dendrobium nobile*
- Wu Z. et al. 2020. Puerarin
- Ashry M et al. 2021. *Saussurea costus*
- Afsar T et al. 2021. *Acacia hydaspica*
- Safhi FA et al. 2022. *Clitoria ternatea.*
- Liu Z et al. 2022. Zhibai Dihaung Granule

# Summary of preclinical findings (2)

## Ischaemia-reperfusion AKI is the next hot spot (n=19).

## In mouse models (n=10):



- Jiang C, et al. 2016. Tanshinone IIA
- Meng QH, et al. 2016. Polydatin
- Choi DR et al. 2018. An extract of *Rhus verniciflua* rich in gallic acid
- Wu L et al. 2019. Hyperoside
- Han BH et al. 2021. Geumgwe-Sinkihwan
- Luan ZL et al 2021. A naturally occurring FXR agonist, alisol B 23-acetate
- Ye Q et al. Xiaoyu Xiezhuo Drink
- Tan RZ et al. 2021. Oridonin
- Liao Y et al. et al. 2021. Nodakenin
- Zhao W. et al. 2022. total glucosides of paeony
- Shao YF et al. 2023. Kaempferide

## In rat models (n=8):



- Zhang Z, et al. 2018. Salvianolic acid A
- Ahmadvand H, et al. 2019. Gallic acid
- Li QP, et al. 2019. Shenhua Tablet
- Akinrinde AS. et al. 2020. methanol extract of Moringa oleifera leaves
- Chen F. et al. 2020. Total Glucosides of Paeony
- Tai H et al. 2021. Tanshinone IIA + Cyclosporine A (ameliorates lung injury in IRI-AKI )
- Tai H et al. 2021. Tanshinone IIA + Cyclosporine A (ameliorates heart injury in IRI-AKI )
- Han L et al. 2022. Leonurine attenuates IRI-AKI in rats (2022)

## In haemorragic shock-AKI pigs Yuan W et al. 2021. Shen-fu injection



# Summary of preclinical findings (3)

## LPS/sepsis-induced AKI is another hot spot, with 18 reports

### In mouse models (n=16)



- Su Z, et al. 2018. Fangjifuling
- Zhang F, et al. 2018. Lidanpaidu prescription
- Gu L et al. 2019. Polydatin
- Islam MS et al. 2019. Extract of *Illicium henryi*
- Liu X et al. 2019. Dihydroartemisinin
- Tan J et al. 2019. Quercetin
- Xia S et al. 2019. Honokiol
- Shu G et al. 2020. Fucoidan
- Wang S. et al. 2020. *Achyranthes bidentata*
- Cui Y et al. 2021. Oleuropein
- Li J et al. 2021. Ginkgolide A
- Sun J et al. 2021. Astragalus Polysaccharide
- Zheng Y et al. 2021. Rhizoma Coptidis extracts
- Shi Q et al. 2021. Echinacea polysaccharide
- Zhang B et al. 2022. Shionone
- Zhang S et al. 2022. Tanshinone IIA

### In rat models (n=2):



- Liu J et al. 2021. in two different journals. **Xuebijing injection**

# Summary of clinical findings (1)




## Herbal prevention of contrast-induced AKI was most studied

**1.** Hami M, et al. *Iran J Kidney Dis.* **2019**;13:304-309.

- **A small RCT (**n=30/group**) found no protective effect of curcumin** (single dosing regimen) in patients with moderate-to-severe CKD.

**2.** Wang J et al. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2020;45:1193-1198.

- A retrospective study showed that Danhong treatment was associated with a lower incidence of contrast-induced AKI than a standard care control group (2.4% vs 5.7%, $p<0.05$).

**3.** Zhang DW, et al. *J Ethnopharmacol.* 2020;248:112354.

- In an RCT, Fufang Chuanxiong and Xinyue capsule adjunct therapy (open-label, no placebo control) after PCI for 6 months in CKD patients reduced relative risks of meeting primary & secondary cardiovascular endpoints, and improved eGFR at 12-month follow-up.

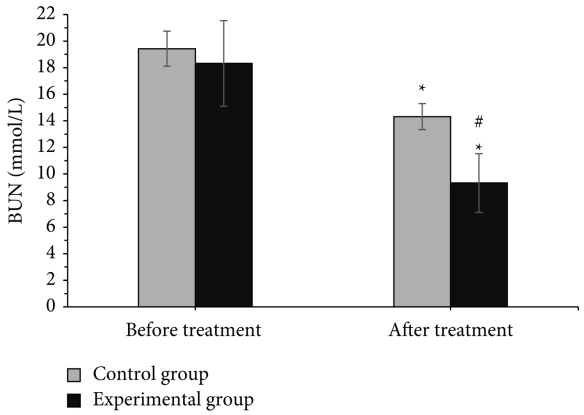
# Summary of clinical findings (2)



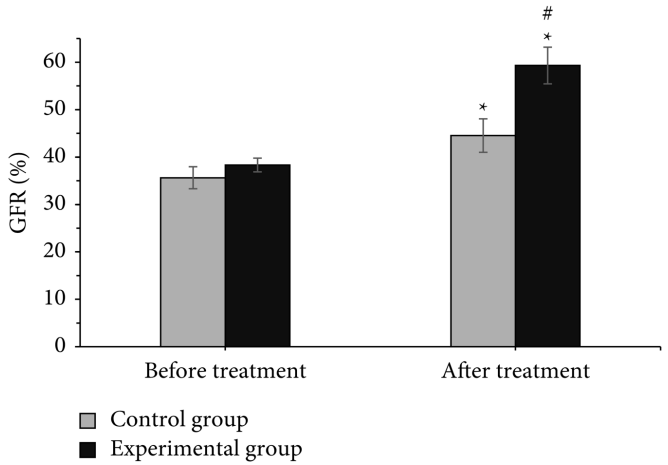

## Herbal prevention of septic AKI

- An AI-based retrospective analysis of 640 patients suggests that **Xuebijing** injection is effective.

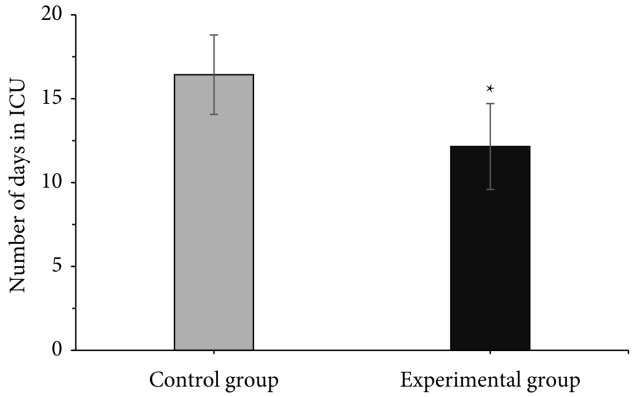
**Reduced BUN**



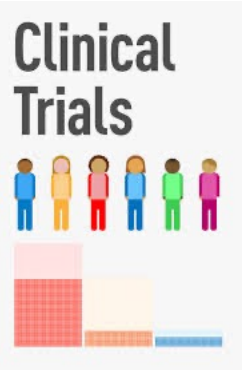

**Improved GFR**




**Reduced ICU stay**




Xia Y et al. *J Healthc Eng.* 2022;2022:8414135.

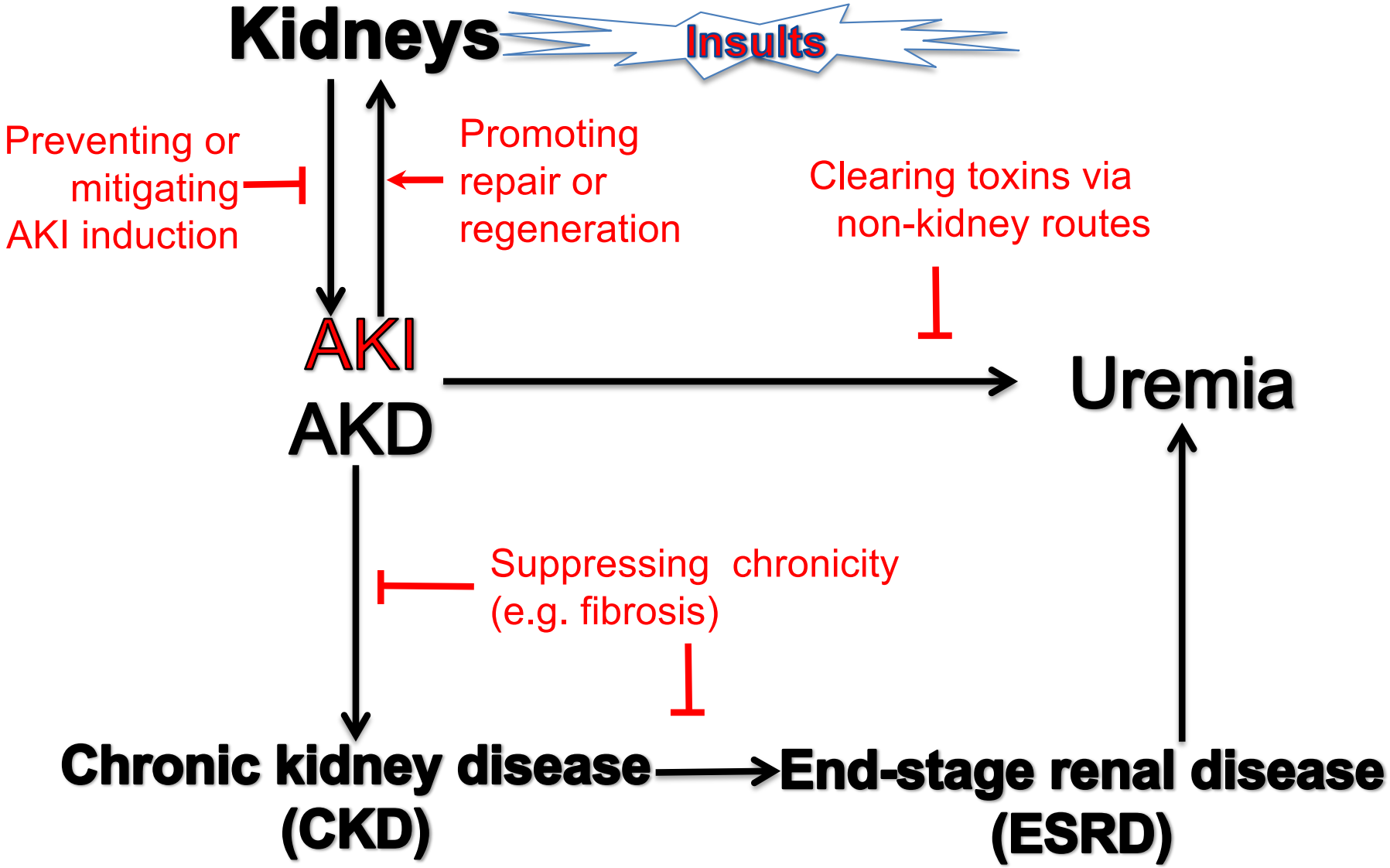



No new clinical studies on herbal intervention in AKI induced by:

- Cisplatin; and
- Renal ischaemia-reperfusion injury.

# Overall conclusion:

- Preclinical studies showed the efficacy of numerous herbals that might work through varying mechanisms; but
- Inadequate clinical evidence prevents making any clinical recommendations.



# Herbals for CKD?

- **As reviewed in KI and AJKD a decade ago, herbal use in CKD is common in China.**
  - Zhong Y, et al. Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. *Kidney Int.* 2013;84:1108-1118.
  - Zhong Y, et al. Recent advances in traditional Chinese medicine for kidney disease. *Am J Kidney Dis*. 2015;66:513-522.
- **A study of ~25k CKD patients in Taiwan showed that herbal use was associated with a better prognosis.**
  - Lin M, et al. *Kidney Int.* 2015;88:1365–1373.

# Three recent RCTs

Zheng Y, et al. ***Chin Med J;* 2017**;130(20):2402-2409.

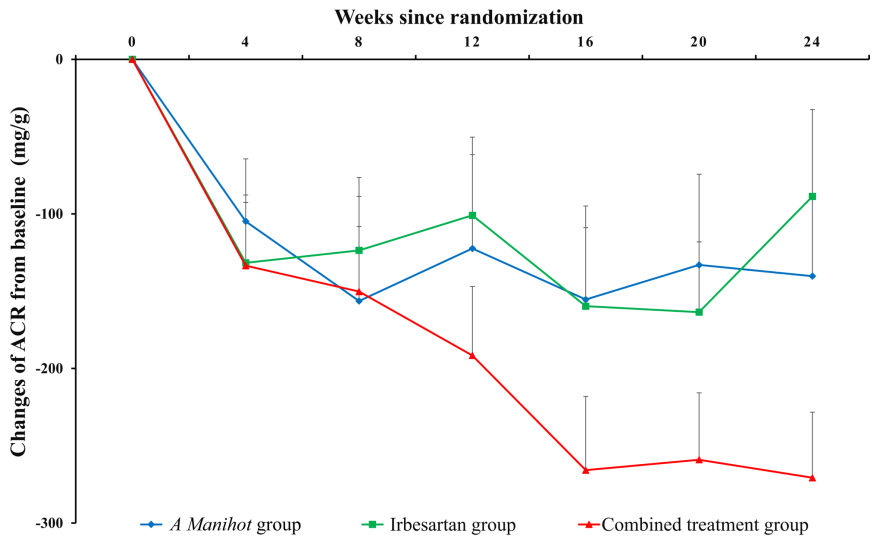
- A double-blind placebo-controlled multicentre RCT of 300 patients concluded that **Niaoduqing granule** treatment of CKD (stage 3b-4) patients for 24 weeks was efficacious in delaying CKD progression.

Li P et al. ***Phytomedicine* 2020**;76:153231.

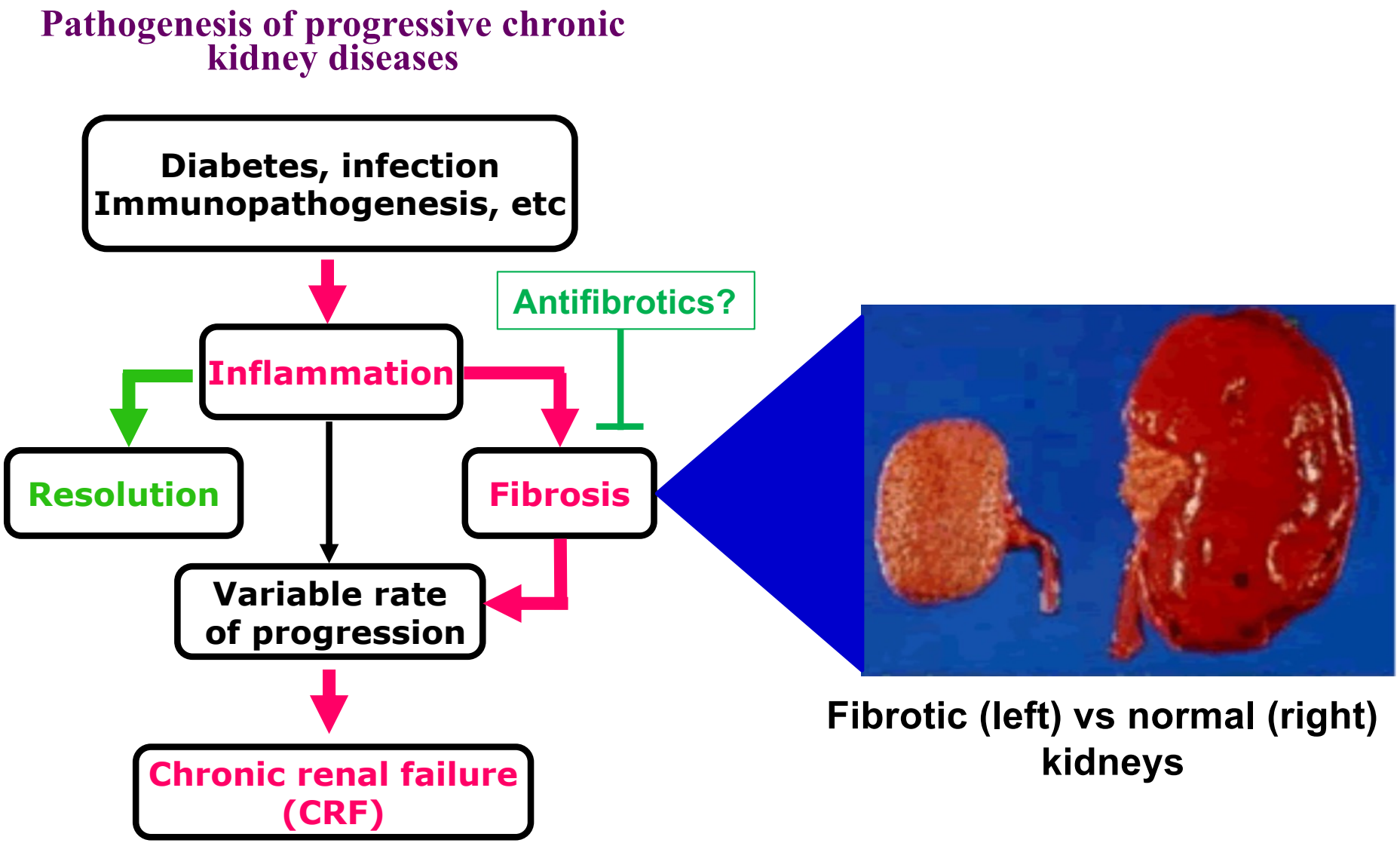
- A multicentre RCT of 1,470 IgAN patients found that ***Abelmoschus manihot* (AM, 黄葵) and losartan** were similarly effective in reducing proteinuria and did not differ in their effects on eGFR, Scr and the incidence of RRT.

Zhao J, et al. ***Diabetes Care*** 2022;45:e113

- A multicenter double-blind RCT of 413 patients with T2D & DN showed that **AM (黄葵) & Irbesartan combined therapy** w**as** more effective than irbesartan monotherapy in reducing **albumin-to-creatinine ratio** (P<0.001).



# CKD, kidney fibrosis and the lack of antifibrotics

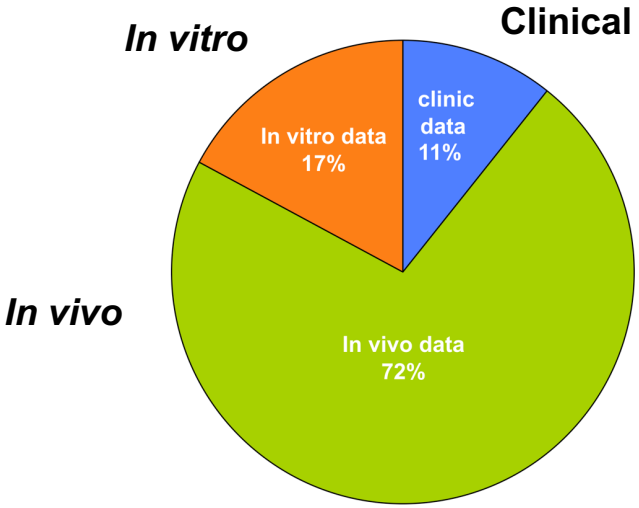


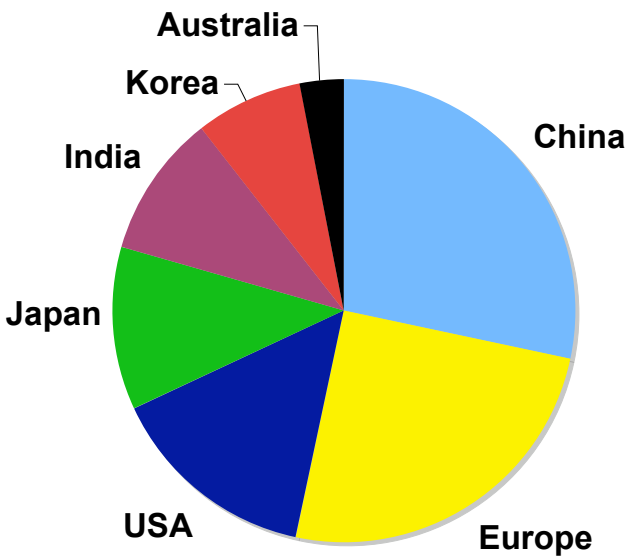

Fibrotic (left) vs normal (right) kidneys

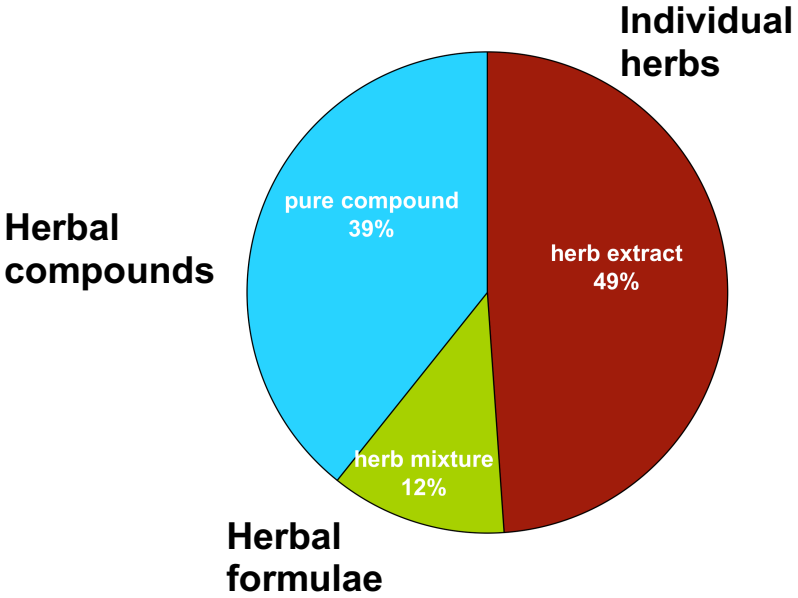
Ruiz-Ortega M, et al. *Am J Kidney Dis.* 2022. PMID: 34999158

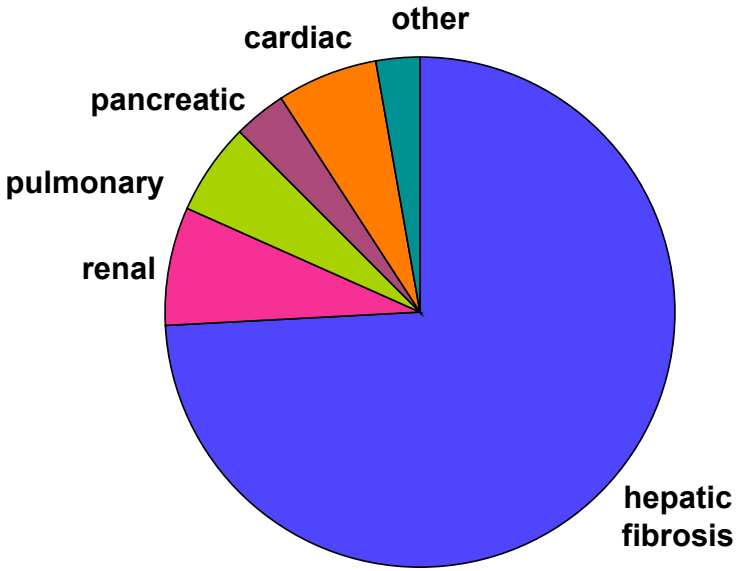
# “Anti-fibrotic”herbal compounds, herbs and herbal formulae?

???




Xu Q, et al. In: Niu J, ed. Fundamentals of Fibrosis and Its TCM Prevention & Treatment. Beijing, 2008

# Xu Q, et al. *Science* 2014; 346 (6216 Suppl), S19-S20

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## The hunt for antifibrotic and profibrotic botanicals

**Authors:**
Qihe Xu[1*],
Yibin Feng[2],
Pierre Duez[3],
Bruce M. Hendry[1],
Peter J. Hylands[4]

The U.S. government estimates that 45% of deaths in the United States can be attributed to fibrotic diseases, which are characterized by tissue scarring and often lead to chronic organ failure (*1*). Over the past several decades, researchers have investigated the underlying mechanisms involved in fibrosis and successfully pinpointed a number of possible drug targets, such as molecular mediators and effector cells.

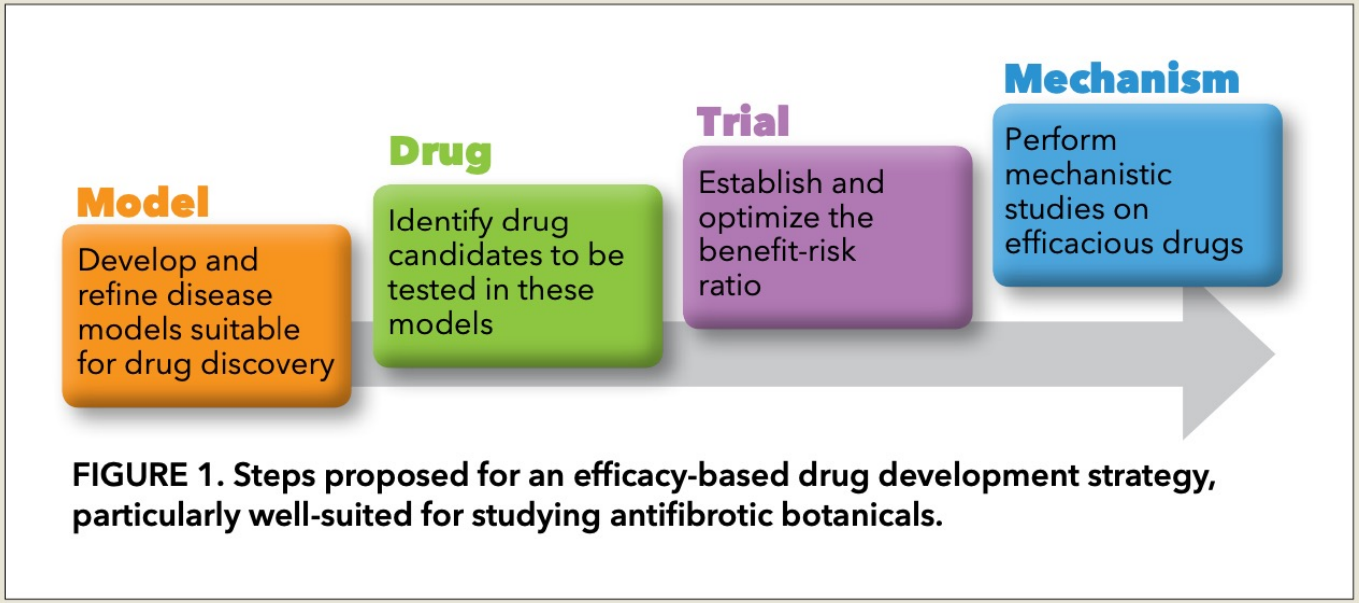
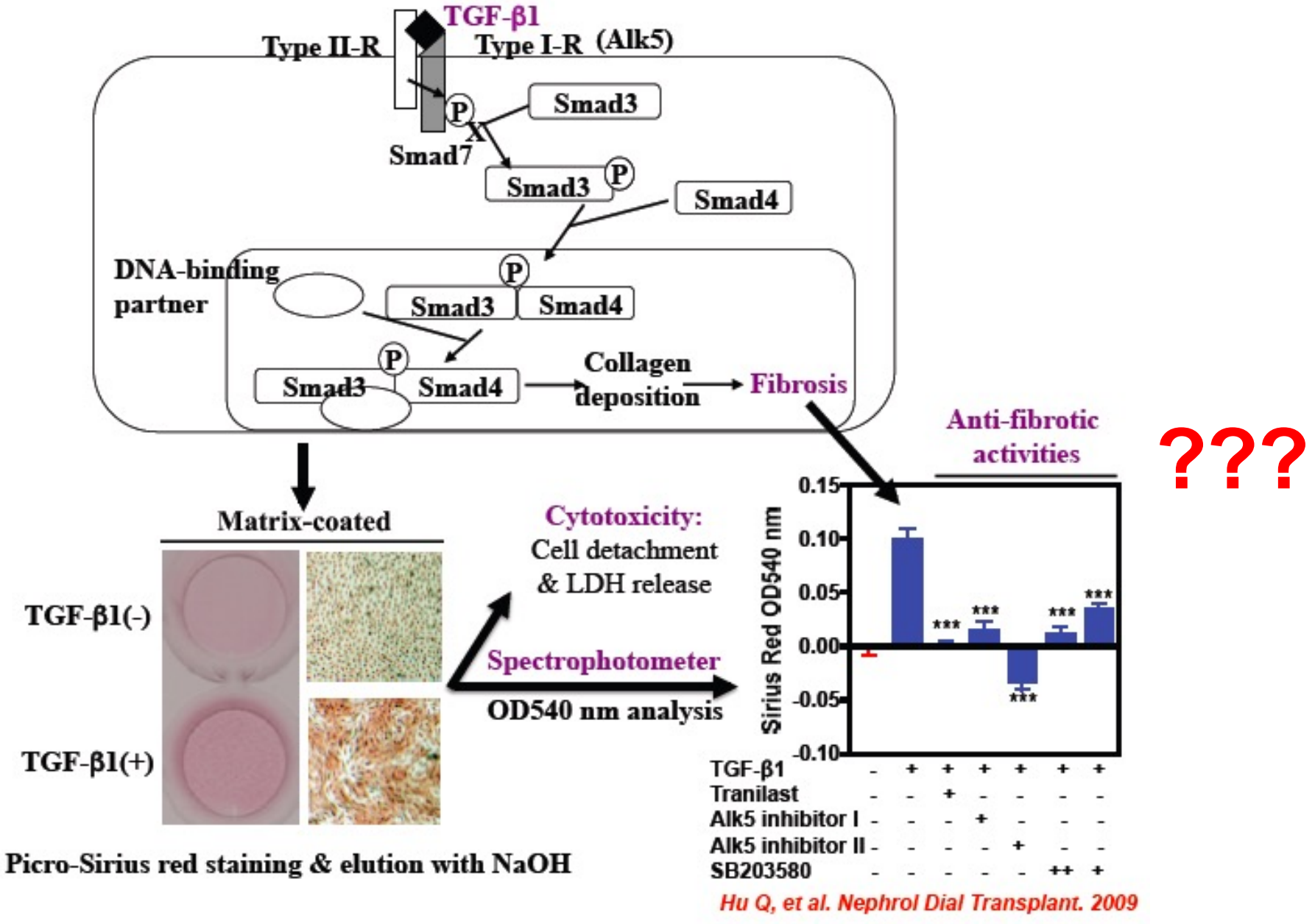



**FIGURE 1. Steps proposed for an efficacy-based drug development strategy, particularly well-suited for studying antifibrotic botanicals.**

# *In vitro* model of fibrosis suitable for HTP quantification of anti-fibrotic activities




*Hu Q, et al. Nephrol Dial Transplant. 2009*

# 16/27 herbal formulae had *in vitro* anti-fibrotic activities

Yinchenhao (No. 1)
Mahuang (No. 2)
Guiyuan (No. 3)
Yigankang (No. 4)

Guzhangpiao (No. 6)
Fuzhenghuayu (No. 7)
Yiqihuoxue (No. 8)

Xiaochaihu (No. 10)
Qingganhuoxue (No. 11)

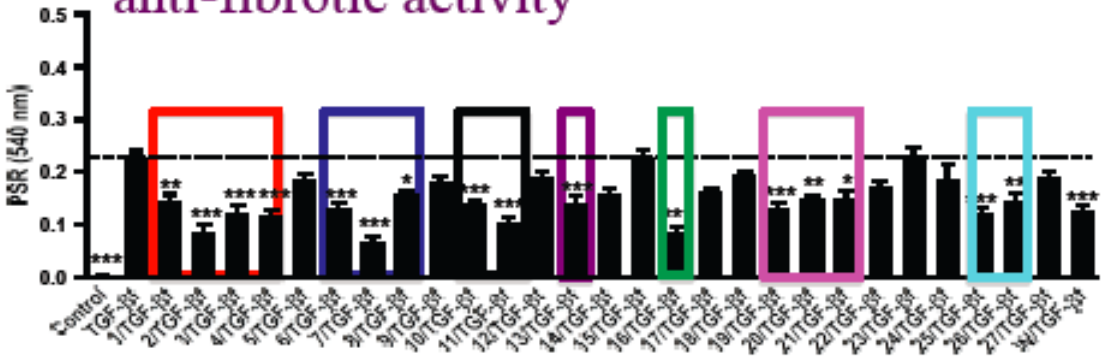
Buzhongyiqi (No. 13)

Bushenrougan (No. 16)

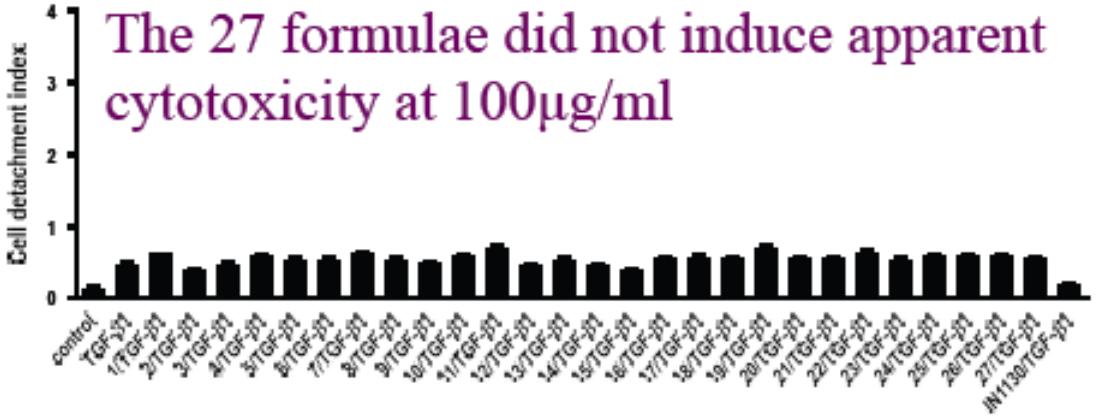
Kangxianbaogan (No. 19)
Huji granule (No. 20)
Cailing (No. 21)

Baweidihuang (No. 25)
Xuelong granule (No. 26)

16/27 formulae showed *in vitro* anti-fibrotic activity

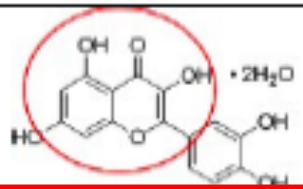
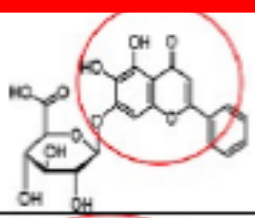
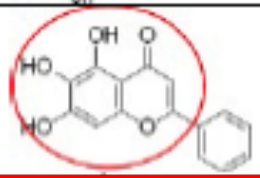
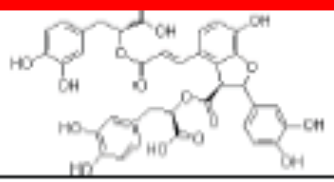
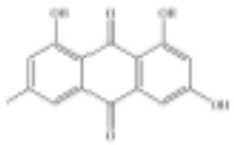



The 27 formulae did not induce apparent cytotoxicity at 100μg/ml




*Hu Q, et al. Nephrol Dial Transplant. 2009*

# 5 herbal compounds and related herbs showed anti-fibrotic activity

| | Compound | Molecular structure | ED50 (mM) | Plant resource | ED50 of plant (methanol extract) mg/ml |
|---|---|---|---|---|---|
| Flavonoids | Quercetin |  | 22.26 | Many fruits and vegetables | N/A |
| | Baicalin |  | 45.92 | *Scutellaria baicalensis* Georgi (黄芩) SRM | 51.78 |
| | Baicalein |  | 24.65 | | |
| Non-flavonoids | Salvianolic acid B |  | 4.99 | *Salvia miltiorrhiza* Bge. (丹参) | 31.84 |
| | Emodin |  | 13.58 | *Rheum palmantum* L. (大黄) | 66.84 |

*Hu Q, et al. Nephrol Dial Transplant. 2009*

*Zhou S, et al. Phytomedicine. 2022;100:154049*

# Additional extracts of 8 herbs were anti-fibrotic and 3 were pro-fibrotic

| Group | Pinyin name (Chinese name) | Anti-fibrotic or pro-fibrotic doses (μg/ml) | Changes at optimum doses compared to TGF-β1 group | Cytotoxic doses (μg/ml) |
|---|---|---|---|---|
| Anti-fibrotic | Baibeiyegen (白背叶根) | 20-40 | -81.4% (40 μg/ml)<br>-63.3% (20 μg/ml) | ≥80 |
| | Liedang (列当) | 80-160 | -61.2% (160 μg/ml)<br>-59.3% (80 μg/ml) | 200 |
| | Gusuibu (骨碎补) | 160-200 | -36.8% (200 μg/ml)<br>-30.0% (160 μg/ml) | -- |
| | Jixueteng (鸡血藤) | 10-40 | -75.0% (20 μg/ml)<br>-63.0% (10 μg/ml) | ≥80 |
| | Lingzhi (灵芝) | 10-80 | -34.9% (80 μg/ml)<br>-47.4% (40 μg/ml) | ≥160 |
| | Meiguiqie (玫瑰茄) | 160-200 | -28.0% (200 μg/ml)<br>-21.0% (160 μg/ml) | -- |
| | Moyao (没药) | 10-40 | -57.2% (40 μg/ml)<br>-67.9% (20 μg/ml) | ≥80 |
| | Shiliuhua (石榴花) | 10-40 | -78.0% (40 μg/ml)<br>-61.2% (20 μg/ml) | ≥80 |
| Pro-fibrotic | Chuanwutou (川乌头) * | ≥20 | +90.2% (40 μg/ml)<br>+68.5% (20 μg/ml) | -- |
| | Dangshen (党参) | 200 | +32.4% (200 μg/ml) | -- |
| | Yimucao (益母草) | 160-200 | +65.7% (200 μg/ml)<br>+53.9% (160 μg/ml) | -- |

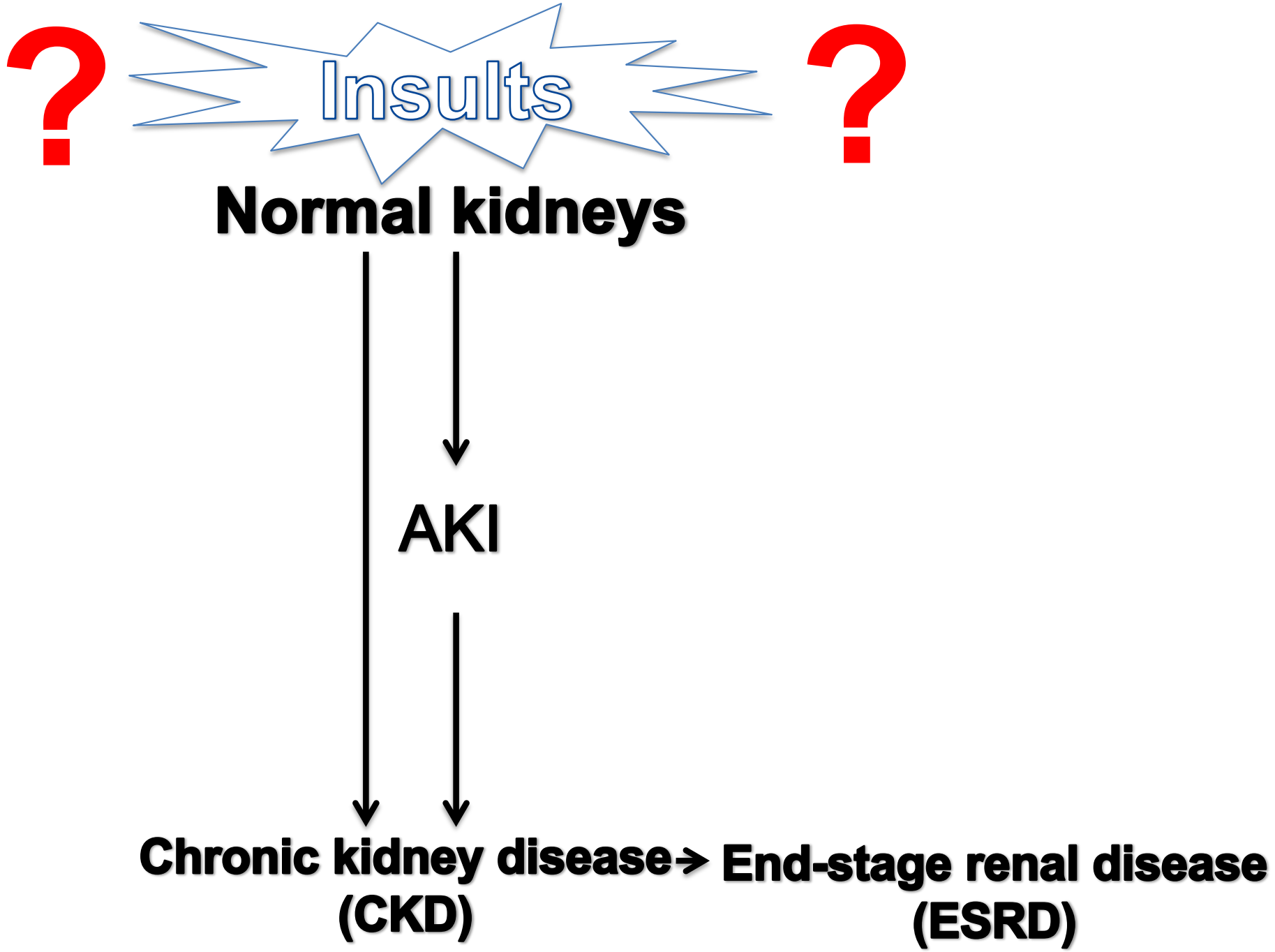
*Not reproducible

*Wong WF, et al.* In: Kuang X ed. Recent Advances in Theories and Practice of Chinese Medicine, Intech, 2012, pp337-352.

# HM for CKD?

- HM is a promising source for novel therapies against CKD and fibrotic diseases;
- Emerging RCT reports are encouraging, and further R&D is warranted.

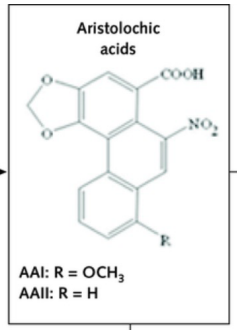
# Botanicals-induced Kidney Injury (BIKI)

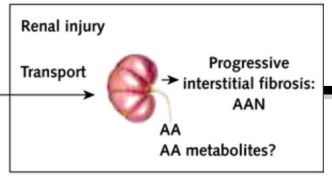


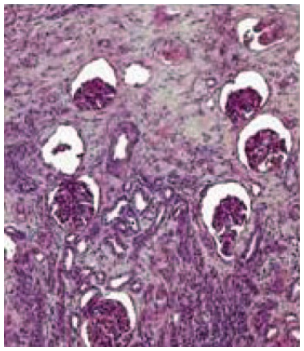
# The lessons from aristolochic acid nephropathy

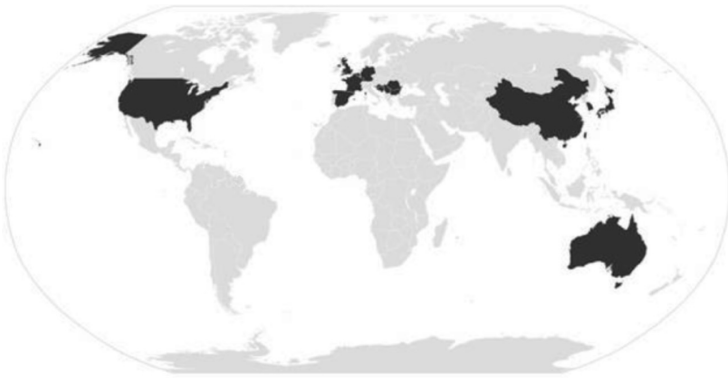


Products containing aristolochic acids



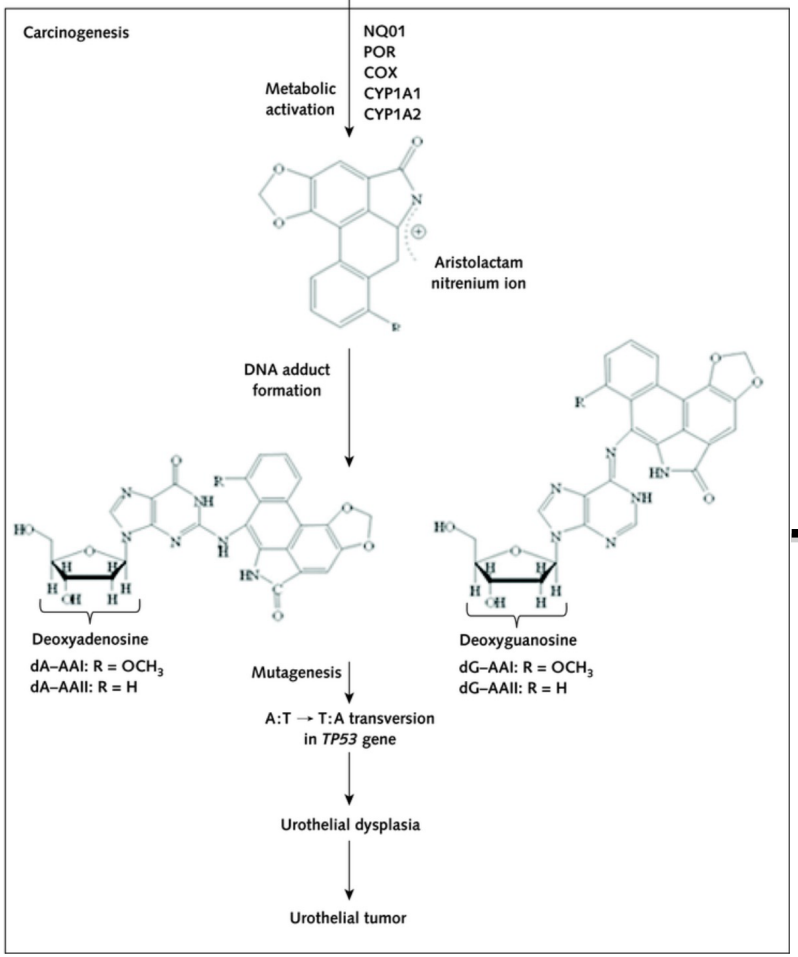



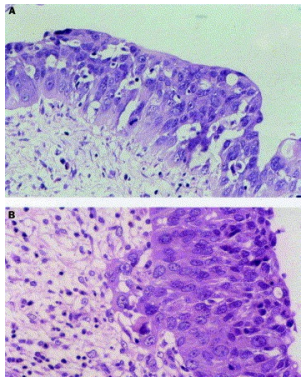



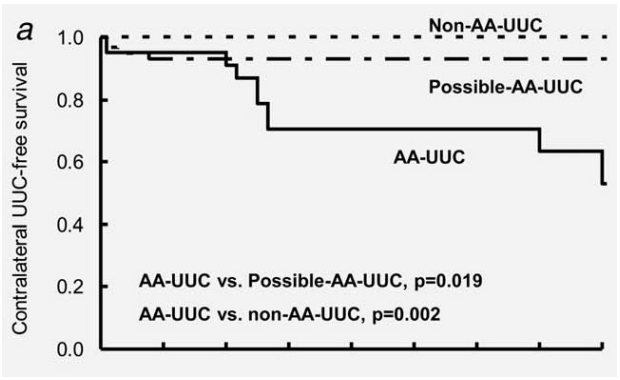


**Aristolochic acid nephropathy (AAN)**

*Gökmen MR, …, Lord GM. Ann Intern Med. 2013;158:469-477*






**Aristolochic acid upper tract urothelial carcinoma (AA-UUC)**

*Lord GM. et al. Lancet 2001; 358: 1515–1516*

*Chen CH, et al. Int J Cancer. 2013 Jan 7. [Epub ahead of print]*

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Review Article

# Taming the Fire of Nephrotoxic Botanicals

**Francesca Holden[a,b], Vanisha Amin[a,b], Dominic Kuek[a,b], Jeffrey B. Kopp[c], Bruce M. Hendry[a], Qihe Xu[a]**

[a]Department of Renal Medicine, Centre for Integrative Chinese Medicine, School of Immunology and Microbial Sciences, Faculty of Life Sciences and Medicine, King's College London, Western Education Centre, [b]GKT School of Medical Education, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom, [c]Kidney Disease Section, NIDDK, National Institutes of Health, Bethesda, MD, USA

## Abstract

Criteria for diagnosing nephropathy and urothelial neoplasms induced by botanicals containing aristolochic acids (AAs) are well established. Highlights of recent research on AAs include mechanisms of AA intrarenal transport and metabolism and vigorous debate on whether AAs may also cause liver cancers. Many other botanicals may also cause renal injury, but a generalized framework for diagnosing botanical-induced kidney injury (BIKI) is lacking. Based on what we have learnt about the wide spectrum of phenotypes of BIKI attributed to AAs and a recently published standardized phenotypic framework of drug-induced kidney disease, we propose that BIKI may be categorized into six phenotypes (acute kidney injury, tubular dysfunction, glomerular disorders, nephrolithiasis, chronic kidney disease, and neoplasms) and four mechanistic types (A, predictable; B, idiosyncratic; C, chronic; and D, delayed). We call for international cooperation assembling a task force to develop, refine, and regularly appraise an online BIKI database, documenting botanical use, phenotypes, mechanisms, and levels of evidence. Once established, such a database may be linked with electronic patient records and pharmacovigilance channels to generate alerts, guide clinical decision-making, direct future research, and support evidence-based regulation of herbal medicines and education of healthcare professionals and the public. Finally, to prevent BIKI, we propose that a proactive approach integrating the triad of botanicals, users, and stakeholders will be needed.

Holden F et al. *WJTCM* 2019;5: 151-163.

http://www.wjtcm.net/article.asp?issn=2311-8571;year=2019;volume=5;issue=3;spage=151;epage=163;aulast=Holden

# Expert opinions appraised

- Wojcikowski K, et al. Medicinal herbal extracts — renal friend or foe? Part one: the toxicities of medicinal herbs. *Nephrology.* **2004**;9:313-318
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- Luyckx VA, Naicker S. Acute kidney injury associated with the use of traditional medicines. *Nat Clin Pract Nephrol.* **2008**;4:664-71
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- Baudoux T, Nortier JL. Nephrotoxicity of Herbal Products. In Toxicology of Herbal Products. Springer **2017**;pp. 307-344.
- Kiliś-Pstrusińska K, et al. Nephrotoxicity of Herbal Products in Europe—A Review of an Underestimated Problem. *Int J Mol Sci.* **2021**;22(8):4132.

# Limitations of expert opinions

1. Phenotypes are not standardised;
2. Confidence levels often obscure;
3. Causal relations and mechanisms often unestablished;
4. Strategies for detection & prevention inconsistent.

# Towards standardising BIKI phenotypes & developing an integrated BIKI database.

policy forum

http://www.kidney-international.org

© 2015 International Society of Nephrology

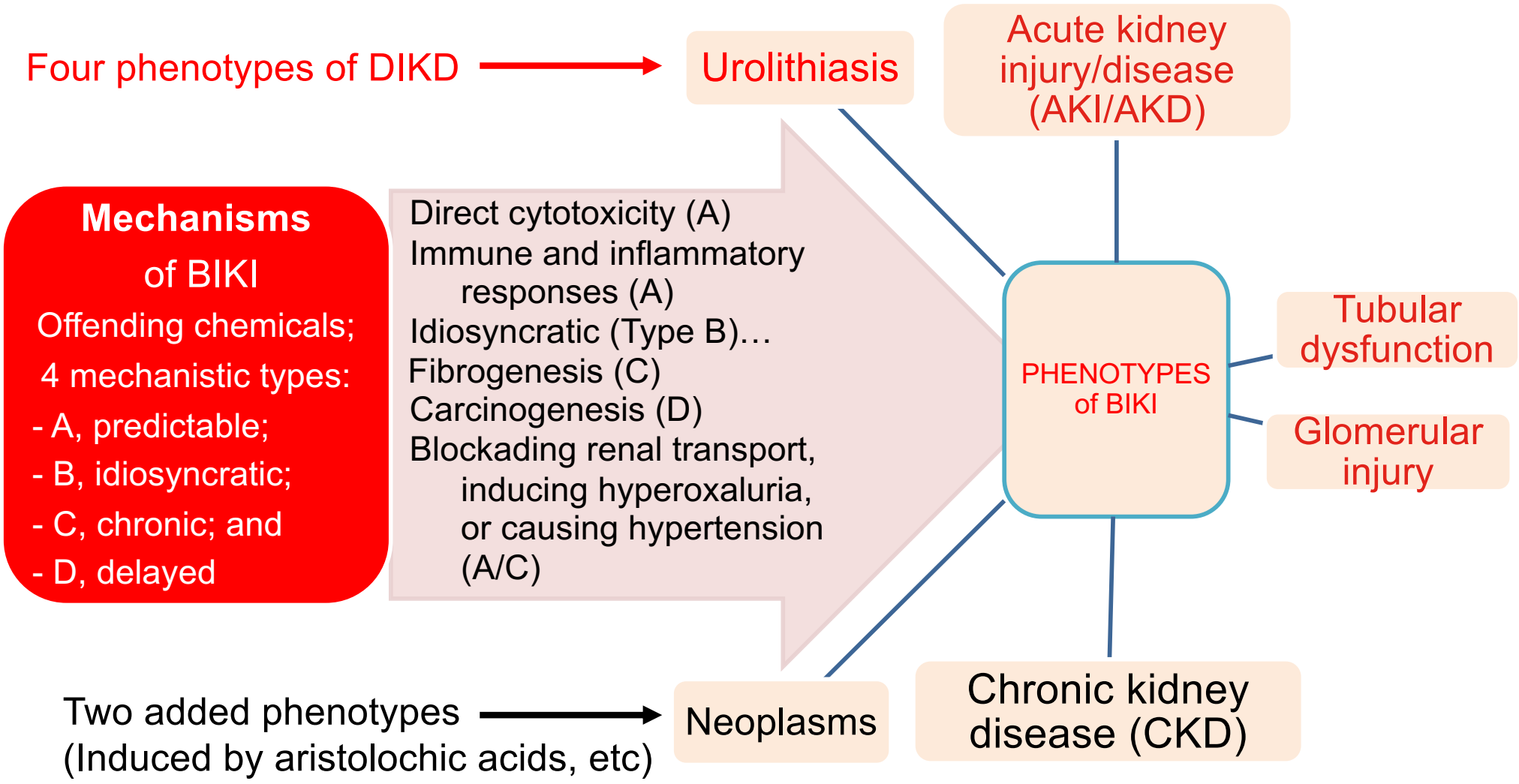
## Phenotype standardization for drug-induced kidney disease

Ravindra L. Mehta[1,10], Linda Awdishu[2,10], Andrew Davenport[3], Patrick T. Murray[4], Etienne Macedo[5], Jorge Cerda[6], Raj Chakaravarthi[7], Arthur L. Holden[8] and Stuart L. Goldstein[9]

- As Part of the phenotype standardization project initiated by the **International Serious Adverse Events Consortium**, drug-induced kidney disease (DIKD) have been standardised into **4 phenotypes.**
- **Clinical criteria to support the phenotype definition have been described.**

Mehta RL et al. Kidney Int 2015;88:226–234.

# Botanicals and usage




# Evidence & confounding factors

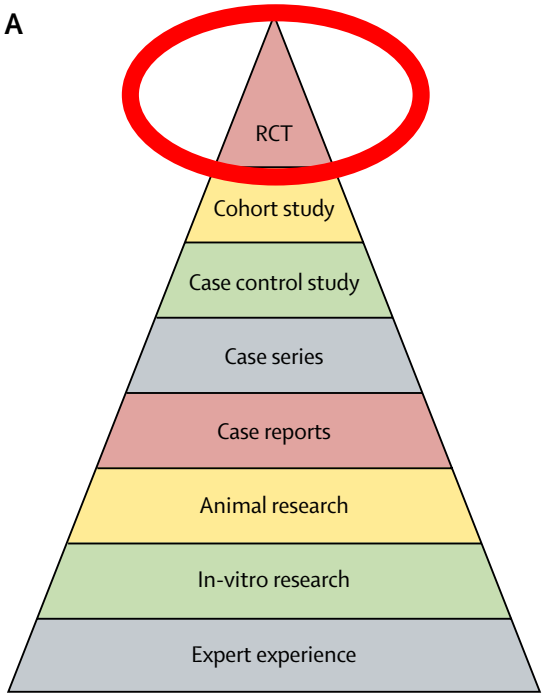
# The evidence challenge

## Progress in evidence-based medicine: a quarter century on

*Benjamin Djulbegovic, Gordon H Guyatt*

**In response to limitations in the understanding and use of published evidence, evidence-based medicine (EBM)** *Lancet* 2017; 390: 415–23

A




B

| Quality of evidence | Study design | Lower quality if* | Higher quality if† |
|---|---|---|---|
| High | Randomised trial | Study limitations<br>- 1 serious<br>- 2 very serious<br><br>Inconsistency<br>- 1 serious<br>- 2 very serious<br><br>Indirectness<br>- 1 serious<br>- 2 very serious<br><br>Imprecision<br>- 1 serious<br>- 2 very serious<br><br>Publication bias<br>- 1 likely<br>- 2 very likely | Large effect<br>+ 1 large<br>+ 2 very large<br><br>Dose response<br>+ 1 evidence of a gradient<br><br>All plausible confounders<br>+ Would reduce a demonstrated effect or<br>+ Would suggest a spurious effect when results show no effect |
| Moderate | | | |
| Low | Observational study | | |
| Very low | | | |

***Figure 1:*** **Hierarchy of evidence: traditional EBM versus GRADE**
Comparison of traditional EBM hierarchy of evidence (1991–2004)[26] with GRADE classification of the quality of evidence (confidence, certainty; 2004 to present).[27] (A) Traditional EBM hierarchy of evidence. (B) GRADE classification of the quality of evidence. EBM=evidence-based medicine. GRADE=Grading of Recommendations Assessment, Development, and Evaluation. RCT=randomised controlled trial. *Quality of study moves down one or two grades. †Quality of study moves up one or two grades.

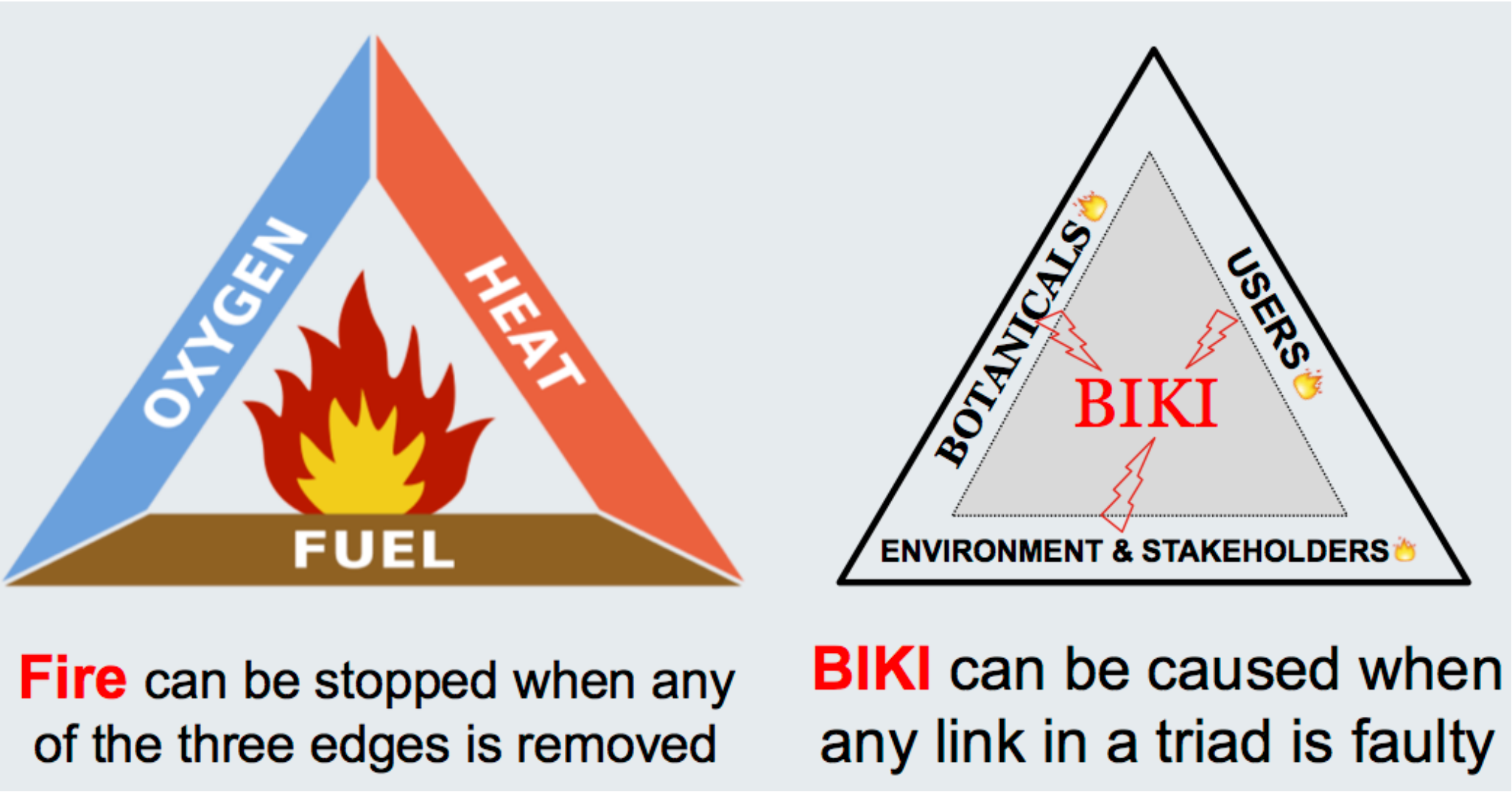
**Djulbegovic B, Guyatt GH, *et al*. *Lancet*. 2017;390:415-23.**

# To integrate *in-silico*, *in-vitro*, *in-vivo*, clinical and pharmacovigilance evidence

| Strategy | Information yielded |
|---|---|
| Analytical chemistry | • Chemical profiles, identification of components of interest or concern |
| In vitro, in silico methods and nonmammalian animal models, eventually combined with 'omics-based methods | • Identification of main pharmacological and toxicological issues<br>• Comparison of toxicity profiles<br>• Deciphering toxic activities at a molecular level |
| Mammalian models, eventually combined with 'omics-based methods | • Acute and repeated dose toxicities (animal models only)<br>• Pharmacokinetic data, metabolism<br>• Identification of pharmacological and toxicological issues<br>• Identification of exposure or toxicity biomarkers<br>• Genotoxicity, carcinogenicity; reproductive and developmental toxicity |
| Clinical studies, eventually combined with 'omics-based, personalized methods | |
| Pharmacoepidemiology and pharmacovigilance | • Evaluation of safety in clinical use<br>• Identification of clinically relevant adverse effects |

Williamson EM, *et al*. Evaluating the safety of herbal medicines: Integrated toxicological approaches. *Science* 2015;347(6219 Suppl), S21-3.

# Taming the fire of nephrotoxic botanicals demands an integrative strategy




**BIKI**: Botanical–induced Kidney Injury

Holden F et al. *WJTCM* 2019;5: 151-163.

# Please spread the words!!!

## King's College London news 21/03/19

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21 March 2019

### Researchers call for international collaboration to prevent kidney injury caused by botanicals

**Hannah Forrest, Communications & Engagement Officer**

Call for a generalised framework to monitor and measure kidney damage caused by botanicals.



https://www.kcl.ac.uk/news/news-article?id=3b151982-ff7d-4bb5-a457-e2031d45fe8b

## Kidney Research UK news 16/06/19

Kidney Research UK
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### Researchers call for international collaboration to prevent kidney injury caused by plant-based drugs or food

Maria Thompson | 17 June 2019

Researchers at King's College London are calling for scientists and doctors across the world to work together to prevent kidney injury caused by botanicals - which are drugs or food made from plants.

Published in the World Journal of Traditional Chinese Medicine and with Kidney Research UK funding, the team has developed a framework for a new database to promote safe use of botanicals across the world.

**Beneficial to health, but not without risk**

Botanicals are used widely in traditional medicine and have demonstrated benefits in a variety of conditions, including where conventional medicine has failed.

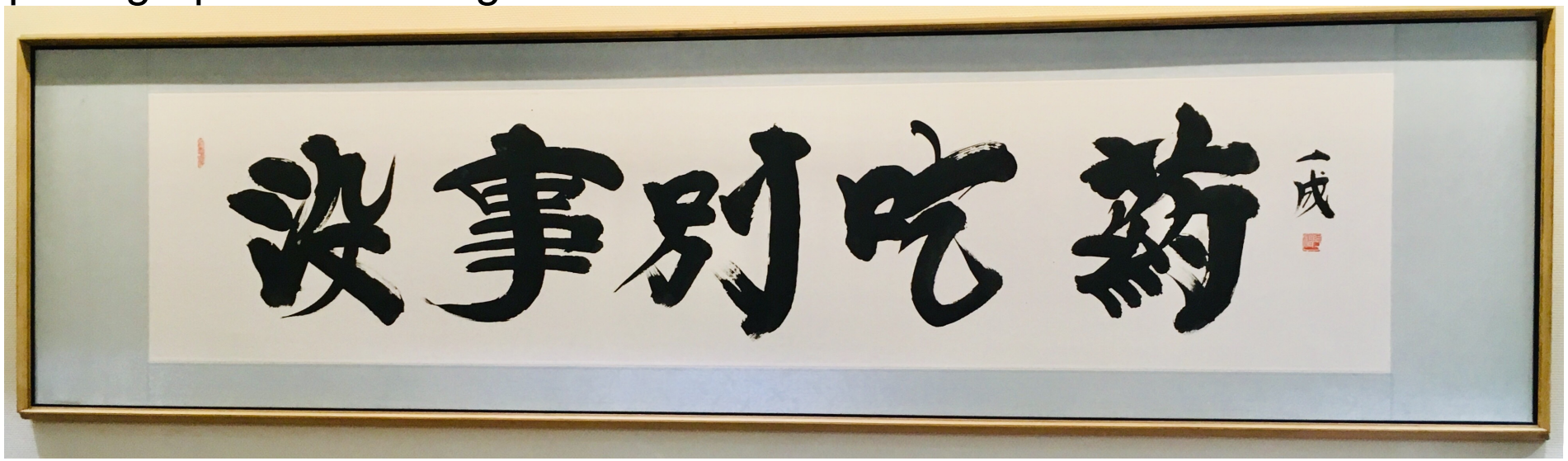
https://www.kidneyresearchuk.org/news/researchers-call-for-international-collaboration-to-prevent-kidney-injury-caused-by-plant-based-drugs-or-food?

# Finally, a piece of advice to everyone




**Drugs, herbal or not,**
**are more or less toxic.**

**“Don’t take them unless indicated!”** -- Chinese calligraphy, photographed at Chengdu First Pharmaceutical Museum 06/07/2019.



A 5-min break before the next talk…

# The importance of herbal medicine in a globalised world:

Chinese herbal medicine as an example