EBM journal club

中藥對於慢性腎病的療效

指導醫師：顏宏融醫師/ R5陳星諭醫師/R4楊晉 瑋醫師

報告醫師：R3楊宗憲醫師

Background definition

National Kidney Foundation defines chronic kidney disease as

- glomerular filtration rate **(GFR) < 60** mL/minute/1.73 m2 *for ≥ 3 months.*

or

- **presence of kidney damage** (proteinuria, glomerulonephritis or structural damage from polycystic kidney disease) *for ≥ 3 months.*

Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR

Cause is based on underlying illness and pathology

- Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia)
- Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy)
- Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity)
- Cystic disease (polycystic kidney disease)

Markers of kidney damage may reflect pathology

- Albuminuria as a marker of kidney damage (increased glomerular permeability, urine albumin-to-creatinine ratio [ACR] >30 mg/g).*
- Urinary sediment abnormalities as markers of kidney damage
- Imaging abnormalities as markers of kidney damage (ultrasound, computed tomography and magnetic resonance imaging with or without contrast, isotope scans, angiography).

Causes of CKD

- chronic illnesses leading to renal damage, such as
  - **diabetes mellitus** (accounting for 33% of adult chronic kidney disease [CKD])
  - **hypertension** (accounting for 21% of adult CKD)
  - heart failure
  - systemic lupus erythematosus
  - HIV nephropathy
  - hepatorenal syndrome
- intrinsic renal disease, such as
  - polycystic kidney disease
  - glomerulonephritis
- long-standing obstruction, such as from
  - nephrolithiasis
  - benign prostatic hypertrophy
- toxic exposures, such as
  - nephrotoxic medications
  - intravenous contrast dye or gadolinium exposure
- renal artery stenosis may be responsible for 11%-14% cases of end stage renal failure

Revised CKD classification based upon GFR and albuminuria

GFR stages	GFR (mL/min/1.73 m^2)	Terms
G1	>90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)

Albuminuria stages	AER (mg/d)	Terms
A1	<30	Normal to high normal (may be subdivided for risk prediction)
A2	30-300	High
A3	>300	Very high (may be subdivided into nephrotic and non-nephrotic f differential diagnosis, management and risk prediction)

Prevalence of CKD in United States

- based on National Health and Nutrition Examination Survey (NHANES) 1999-2004
  - **16.8% of adults ≥ 20 years old**
    - prevalence by stage
      - 5.7% stage 1
      - 5.4% stage 2
      - 5.4% stage 3
      - 0.4% stage 4/5
    - prevalence by age (any stage)
      - 39.4% at age > 60 years
      - 12.6% at age 40-59 years
      - **8.5% at age 20-39 years**

Reference - **MMWR Morb Mortal Wkly Rep 2007 Mar 2;56(8):161**

Prevalence of CKD in China

Estimated prevalence of CKD 10.8% in China

- based on cross-sectional study of 47,204 adults ≥ 18 years old in China
- CKD defined as estimated glomerular filtration rate < 60 mL/minute/1.73 m2 or presence of albuminuria
- overall adjusted prevalence of CKD was 10.8%
  - adjusted prevalence of estimated glomerular filtration rate < 60 mL/minute/1.73 m2 was 1.7%
  - adjusted prevalence of albuminuria was 9.4%

Reference - Lancet 2012 Mar 3;379(9818):815

Prevalence of chronic kidney disease in China: a cross-sectional survey

Background The prevalence of chronic kidney disease is high in developing countries. However, no national survey of chronic kidney disease has been done incorporating both estimated glomerular filtration rate (eGFR) and albuminuria in a developing country with the economic diversity of China. We aimed to measure the prevalence of chronic kidney disease in China with such a survey.

Methods We did a cross-sectional survey of a nationally representative sample of Chinese adults. Chronic kidney disease was defined as eGFR less than 60 mL/min per 1·73 m^2 or the presence of albuminuria. Participants completed a lifestyle and medical history questionnaire and had their blood pressure measured, and blood and urine samples taken. Serum creatinine was measured and used to estimate glomerular filtration rate. Urinary albumin and creatinine were tested to assess albuminuria. The crude and adjusted prevalence of indicators of kidney damage were calculated and factors associated with the presence of chronic kidney disease analysed by logistic regression.

Findings 50 550 people were invited to participate, of whom 47 204 agreed. The adjusted prevalence of eGFR less than 60 mL/min per 1·73 m^2 was 1·7% (95% CI 1·5–1·9) and of albuminuria was 9·4% (8·9–10·0). The overall prevalence of chronic kidney disease was 10·8% (10·2–11·3); therefore the number of patients with chronic kidney disease in China is estimated to be about 119·5 million (112·9–125·0 million). In rural areas, economic development was independently associated with the presence of albuminuria. The prevalence of chronic kidney disease was high in north (16·9% [15·1–18·7]) and southwest (18·3% [16·4–20·4]) regions compared with other regions. Other factors independently associated with kidney damage were age, sex, hypertension, diabetes, history of cardiovascular disease, hyperuricaemia, area of residence, and economic status.

Prevalence of CKD in Taiwan

prevalence of CKD 11.9% in Taiwan

- based on cohort of 462,293 persons > 20 years old who had regular screening 1994-2006
- higher prevalence of CKD associated with lower socioeconomic status
- comparing persons with CKD vs. persons without CKD after median 7.5 years
  - all-cause mortality 10.5% vs. 2.08% ($p < 0.05$)
  - cardiovascular mortality 2.6% vs. 0.35% ($p < 0.05$)

Reference - Lancet 2008 Jun 28;371(9631):2173

Region	Screened population	Screening tools	Prevalence	Identified risk factors
Beijing, China[15]	13 925 adults (response rate 90.6%)	Glomerular filtration rate using calibrated serum creatinine level and formula estimation	13%, defined as glomerular filtration rate <60 mL/min per 1.73 m^2 or markers of kidney damage	Independent predictors of CKD • Older age (odds ratio 1.83) • Nephrotoxic medication (odds ratio 2.19) • Rural area (odds ratio 0.47) • History of cardiovascular disease (odds ratio 2.04) • High-density lipoprotein cholesterol <1.03 mmol/L (odds ratio 3.00) • Hypertension status >10 years (odds ratio 1.85)
Australia[16]	11 247 adults (response rate 55.3%)	Spot urine protein to creatinine ratio Haematuria confirmed by urine microscopy Cockcroft-Gault estimated glomerular filtration rate	16% with one or more indicators of kidney damage	Independent predictors of proteinuria • Age ≥65 (odds ratio 2.5) • Diabetes mellitus (odds ratio 2.5) • Hypertension (odds ratio 3.1)
Singapore[17]	189 117 working adults	Dipstick analysis of urine protein and blood	1.1% with proteinuria ≥1 +	Independent predictors of proteinuria • Age ≥61 (odds ratio 2.7) • Malay race (odds ratio 1.3) • Diabetes mellitus (odds ratio 2.0) • Hypertension (odds ratio 1.8) • Renal disease (odds ratio 3.5) • Body mass index ≥30 kg/m^2 (odds ratio 2.5) • Haematuria (odds ratio 2.9) • Family history of kidney disease (odds ratio 2.0)
Japan[18]	574 024 adults	Japanese equation for estimated glomerular filtration rate Dipstick analysis of urine protein	13% with CKD (stage 1–5)	
Taiwan[19]	462 293 adults	MDRD equation for estimated glomerular filtration rate Dipstick analysis of urine protein	12% with CKD	Predictors of CKD • Regular use of Chinese herbal medicine (odds ratio 1.2)
Hong Kong[20]	1 201 adults	Dipstick analysis of urine protein and blood	3.2% with proteinuria ≥1 +	Predictors of urine abnormalities • Family history of diabetes or hypertension

Reference - Nephrology (Carlton). 2011 Sep;16(7):633-41. doi: 10.1111/j.1440-1797.

Possible risk factors with herbs

Lead exposure:

- increased blood lead level associated with increased serum creatinine
  - based on retrospective cohort study
  - 459 veterans had blood lead concentrations analyzed
  - each 10-fold increase in blood lead levels was associated with serum creatinine increase of 0.08 mg/dL (7 mcmol/L)
  - Reference - JAMA 1996 Apr 17;275(15):1177

- increased body lead burden associated with more rapid progression of chronic renal insufficiency
  - based on study of 110 patients with initial creatinine 1.5-4 mg/dL (132.6-353.6 mcmol/L) followed for 2 years
  - improvement noted with chelation therapy in selected patients
  - Reference - Arch Intern Med 2001 Jan 22;161(2):264

Possible risk factors with herbs

Aristolochic acid (Mu Tong or Fangchi):

- aristolochic acid has been associated with nephropathy leading to end stage renal disease and with urological malignancies (FDA MedWatch 2001 Apr 16)
- consumption of cumulative doses > 60 g of Mu Tong or Fangchi associated with increased risk for end-stage renal disease (ESRD)
  - based on case-control study with 25,843 new cases of ESRD and 184,851 controls in Taiwan (1998~2002健保資料庫)
  - Reference - Am J Kidney Dis 2010 Mar;55(3):507

Possible risk factors with herbs

- 自從馬兜鈴酸腎病事件後，行政院衛生署已於2003年11月公告全面禁用下列含馬兜鈴酸的中藥材：廣防己、青木香、關木通、馬兜鈴、天仙藤等。

The general management of the patient with chronic kidney disease involves the following issues

- Treatment of reversible causes of renal dysfunction
- Preventing or slowing the progression of renal disease
- Treatment of the complications of renal dysfunction
- Identification and adequate preparation of the patient in whom renal replacement therapy will be required

2011 KDIGO clinical practice guideline for management of blood pressure in CKD

- proteinuric CKD (500 to 1000 mg/day or more), the blood pressure < 130/80 mmHg.

- nonproteinuric CKD (less than 500 to 1000 mg/day), the blood pressure < 140/90 mmHg =>and to less than 130 to 135 mmHg systolic if it can be achieved without producing significant side effects.

Interventions to slow loss of kidney function

- **ACEi** or **ARB** have renoprotective effects in proteinuric CKD
- **Strict control of diabetes**
- **Statins** may reduce cardiovascular mortality and nonfatal cardiovascular events in patients with chronic kidney disease (CKD) (level 2 [mid-level] evidence)
- for adults with moderate-to-severe CKD, **reduced protein intake** associated with reduced risk of death or ESRD (level 2 [mid-level] evidence)
- **Bicarbonate supplementation** in patients with severe CKD and metabolic acidosis may slow progression of kidney disease and reduce need for dialysis (level 2 [mid-level] evidence)

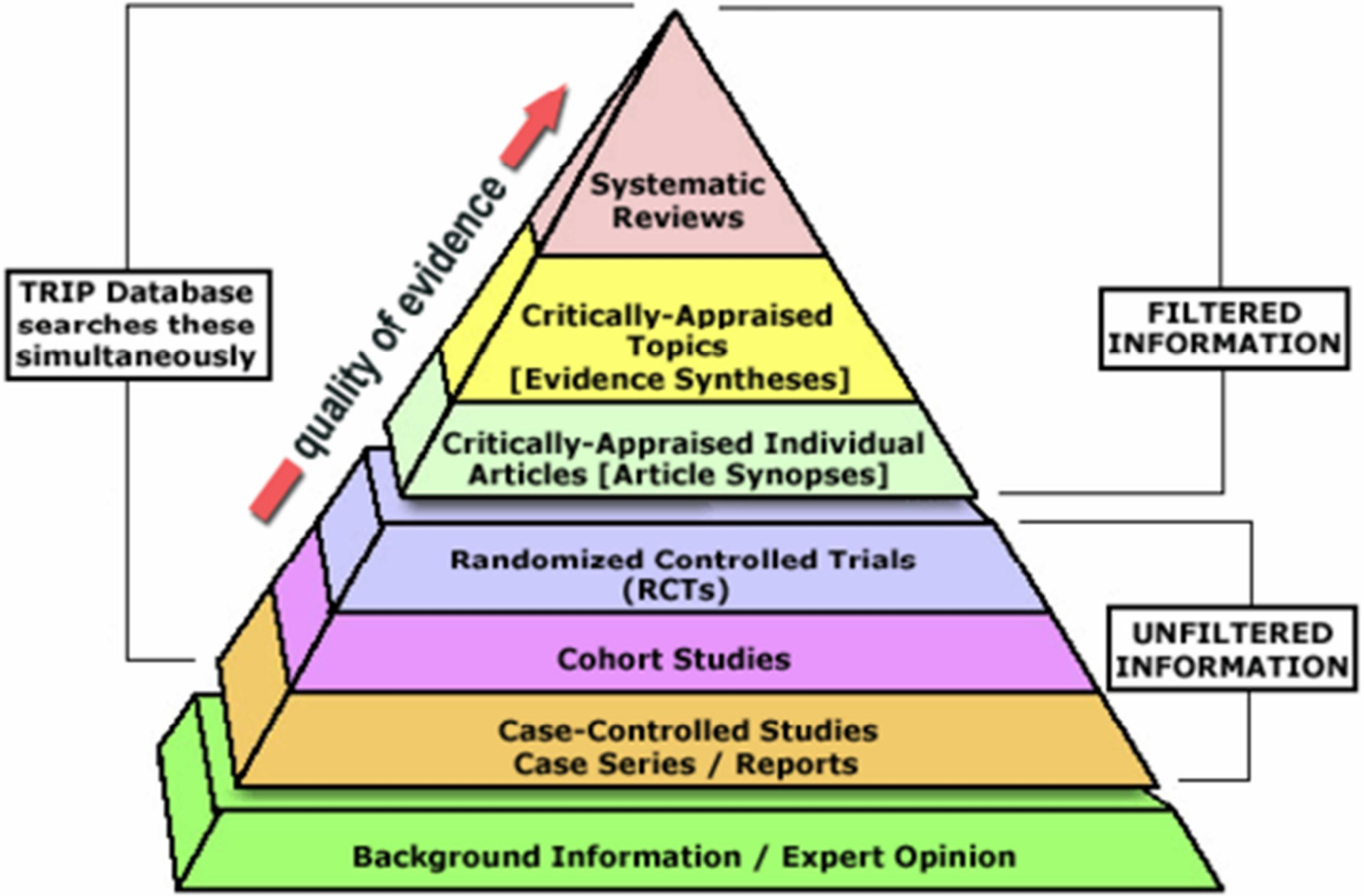
中藥對於慢性腎病的療效?

Step 1- Asking (問)

- Is TCM for chronic kidney disease effective?

PICO

- **Problem:** chronic kidney disease (r/o ESRD) or proteinuria
- **Intervention:** Chinese herbal medicine
- **Comparison:** Placebo or conventional western medicine therapy
- **Outcome:** ameliorate renal function progression or improve proteinuria

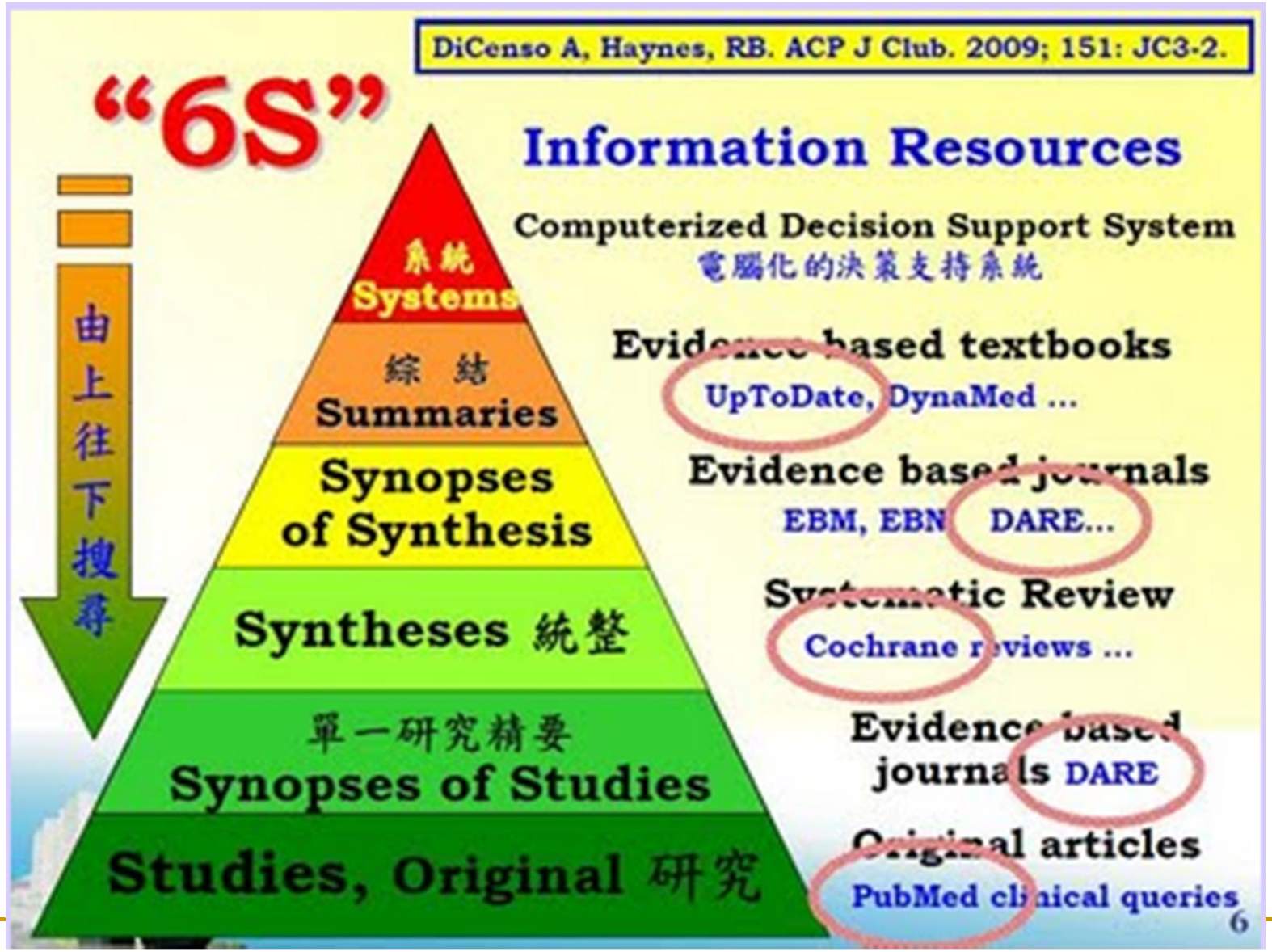


- from: http://www.ebmpyramid.org/help.php

Oxford Center (May 2001)
for Evidence based Medicine Levels of Evidence Evidence

Level	Therapy
1a	系統性回顧 Systematic review（分析數個隨機臨床對照試驗，其結果均類似）
1b	設計良好，結果精確之隨機臨床對照試驗
1c	All or none
2a	系統性回顧（分析數個世代研究，其結果均類似）
2b	世代研究 Cohort study;設計粗糙之隨機臨床對照試驗
2c	"Outcomes" Research; Ecological studies
3a	系統性回顧（分析數個病例-對照研究，其結果均類似）
3b	病例 - 對照研究 Case-control study
4	某家醫院的十年經驗；設計不良之世代研究 及病例 - 對照研究
5	未經考證之專家個人意見，基礎研究，細胞實驗，生理實驗，動物實驗...的結果

Step 2- Assessing(查)



From: http://earthgodandrapiddoc.blogspot.com/2011_08_01_archive.html

Keyword

Problem

- ***Chronic kidney disease*** or ***chronic renal failure*** or ***chronic renal insufficiency***
- ***Proteinuria***

Intervention

- ***Chinese herb*** or ***chinese medicine*** or ***kampo*** or ***herb***

Evidence-based journals

7	⊞ ⓘ	Business Source Complete	Database	EBSCO
8	⊞ ⓘ	Cambridge Books Online(試用至5/14)	Database	Cambridge University Press
9	⊞ ⓘ	DynaMed	Database	EBSCO
10	⊞ ⓘ	EBM Reviews (ALL)	Database	OVID
11	⊞ ⓘ	EBMR--ACP Journal Club	Database	OVID
12	⊞ ⓘ	EBMR--Cochrane Central Register of Controlled Trials	Database	OVID
13	⊞ ⓘ	EBMR--Cochrane Database of Systematic Reviews	Database	OVID
14	⊞ ⓘ	EBMR--Cochrane Methodology Register	Database	OVID

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Search History (5 searches) *(Click to close)*

	# ▲	Searches	Results
☐	1	(chronic kidney disease or chronic renal failure or chronic renal insufficiency).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] ▶	2384
☐	2	proteinuria.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] ▶	1997
☐	3	(chinese herb or chinese medicine or kampo).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] ▶	2263
☐	4	1 and 3 ▶	23
☐	5	2 and 3 ▶	19

[Systematic Review]

AN: 00075320-100000000-00956

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8. ☐ **Chinese herbal medicine Huangqi type formulations for nephrotic syndrome.**

Yuan, Wei. Wang, Juan. Wu, Taixiang.

EBM Reviews - Cochrane Database of Systematic Reviews
Cochrane Renal Group Cochrane Database of Systematic Reviews. 4, 2010.
[Systematic Review]

AN: 00075320-100000000-05021

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9. ☐ **Chinese herbal medicines for treating pre-eclampsia.**

Li, Wenjuan. Tang, Liulin. Wu, Taixiang. Zhang, Jing. Liu, Guan J. Zhou, Lingling.

EBM Reviews - Cochrane Database of Systematic Reviews

- Table of Contents
- Abstract Reference
- Complete Reference

Abstract

Background: At present, there is a lack of safe and effective drugs for nephrotic syndrome (NS). Huangqi type formulations have been used to treat nephrotic syndrome for years in China, however the effects and safety of these formulations have not been systematically reviewed.

Objectives: To assess the benefits and harms of Huangqi and Huangqi type formulations in treating NS in any age group, either as sole agents or in addition to other drug therapies.

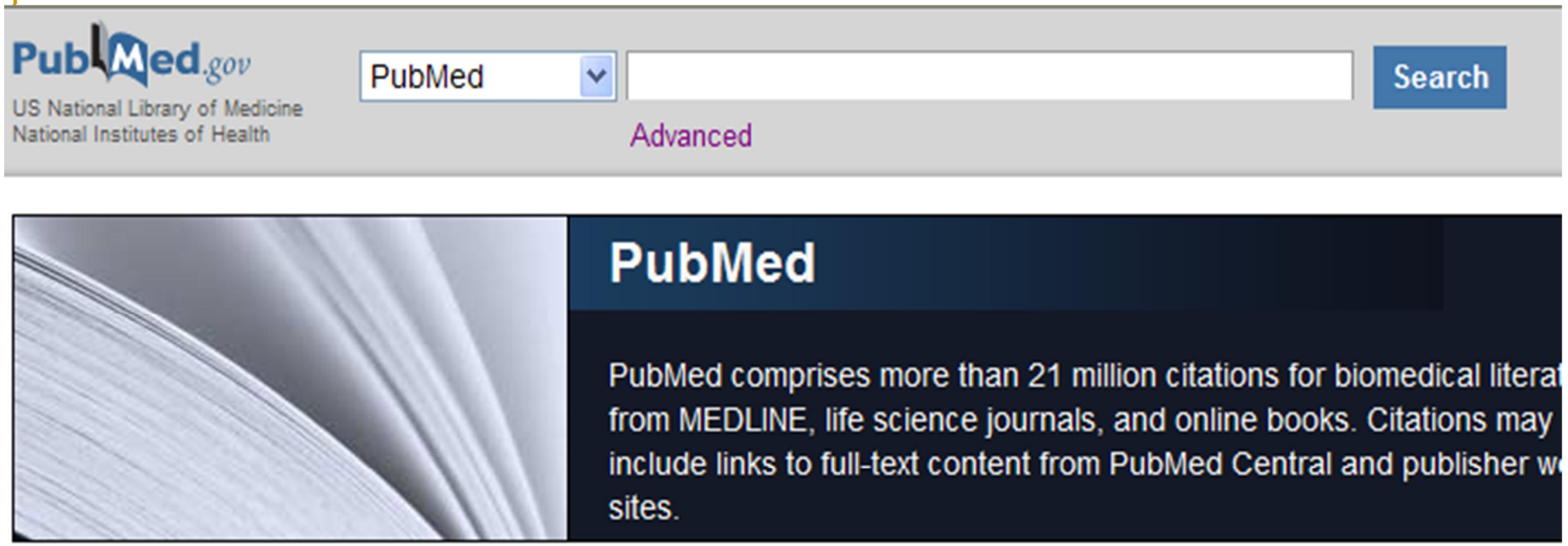
Search strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles. There was no language restriction.

Date of most recent search: June 2006.

Selection criteria: All randomised controlled trials (RCTs) assessing the use of Huangqi or Huangqi type formulations in treating NS in adults and children, either as sole agents or in addition to other drug therapies.

Data collection and analysis: Two authors independently assessed study quality and extracted data. For dichotomous outcomes (remission, side effects and Inefficacy rate), results were expressed as relative risk (RR) and 95% confidence intervals (CI). Continuous outcomes (triglycerides cholesterol, plasma albumin) results were expressed as mean difference (MD) with 95% CI.

28	Nursing Index (Mosby's Index)	Database	Mosby	
29	Oxford Scholarship Online Collection牛津線上學術電子書	Database	Oxford University Press	
30	ProQuest Health and Medical Complete	Database	Proquest	
31	PsycINFO(試用至5/31)	Database	OVID	
32	PubMed	Database	National Library of Medicine, NLM	1948-
33	PubMed (Intranet)	Database	National Library of Medicine, NLM	1948-
34	Reference Manager	Database	Thomson	
35	Regional Business News	Database	EBSCO	
36	Science Direct	Database	Elsevier	1995-
37	Scopus	Database	Elsevier	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PubMed Clinical Queries

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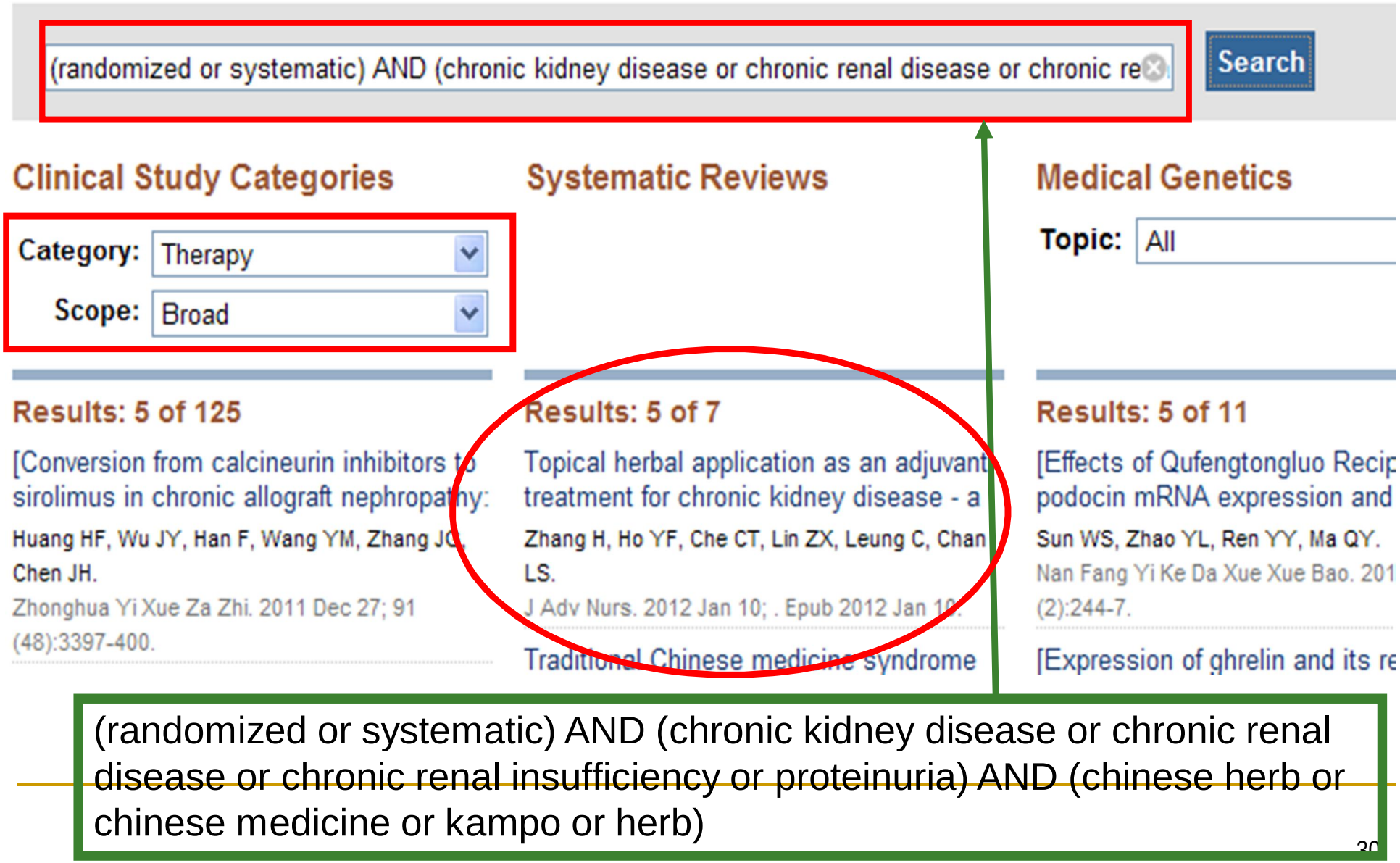
directly.



(randomized or systematic) AND (chronic kidney disease or chronic renal disease or chronic renal insufficiency or proteinuria) AND (chinese herb or chinese medicine or kampo or herb)

Results: 7

1. Topical herbal application as an adjuvant treatment for **chronic** **kidney disease** - a **systematic** review of **randomized** controlled clinical trials.

   Zhang H, Ho YF, Che CT, Lin ZX, Leung C, Chan LS.
   J Adv Nurs. 2012 Jan 10. doi: 10.1111/j.1365-2648.2011.05925.x. [Epub ahead of print]
   PMID: 22229543 [PubMed - as supplied by publisher]
   Related citations

2. Traditional **Chinese medicine** syndrome distribution in **chronic** hepatitis B populations: a **systematic** review.

   Zeng XX, Bian ZX, Wu TX, Fu SF, Ziea E, Woon WT.
   Am J **Chin Med**. 2011;39(6):1061-74. Review.
   PMID: 22083981 [PubMed - indexed for MEDLINE]
   Related citations

3. Education programmes for people with diabetic **kidney disease**.

   Li T, Wu HM, Wang F, Huang CQ, Yang M, Dong BR, Liu GJ.
   Cochrane Database Syst Rev. 2011 Jun 15;(6):CD007374. Review.

Rank	Abbreviated Journal Title *(linked to journal information)*	ISSN	JCR Data						*Eigenfactor*™ Metrics	
			Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	*Eigenfactor*™ Score	*Article Influence*™ Score
1	J ADV NURS	0309-2402	9687	1.540	2.347	0.169	260	8.6	0.01377	0.550

PubMed Clinical Queries

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, u directly.

(randomized or systematic) AND (chronic kidney disease or chronic renal disease or chronic re

Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 125

[Conversion from calcineurin inhibitors to sirolimus in chronic allograft nephropathy

Huang HF, Wu JY, Han F, Wang YM, Zhang JG, Chen JH.

Zhonghua Yi Xue Za Zhi. 2011 Dec 27; 91 (48):3397-400.

Systematic Reviews

Results: 5 of 7

Topical herbal application as an adjuvant treatment for chronic kidney disease - a

Zhang H, Ho YF, Che CT, Lin ZX, Leung C, Chan LS.

J Adv Nurs. 2012 Jan 10; . Epub 2012 Jan 10.

Traditional Chinese medicine syndrome

Medical Genetics

Topic: All

Results: 5 of 11

[Effects of Qufengtongluo Recip podocin mRNA expression and

Sun WS, Zhao YL, Ren YY, Ma QY.

Nan Fang Yi Ke Da Xue Xue Bao. 201 (2):244-7.

[Expression of ghrelin and its re

ahead of print]

PMID: 22229543 [PubMed - as supplied by publisher]

Related citations

6. Optimized project of traditional **Chinese medicine** in treating **chronic kidney disease** stage 3: a multicenter double-blinded **randomized** controlled trial.

Wang YJ, He LQ, Sun W, Lu Y, Wang XQ, Zhang PQ, Wei LB, Cao SL, Yang NZ, Ma HZ, Gao J, Li P, Tao XJ, Yuan FH, Li J, Yao C, Liu X.

J Ethnopharmacol. 2012 Feb 15;139(3):757-64. Epub 2011 Dec 13.

PMID: 22178174 [PubMed - in process]

Related citations

7. Cost implication of team-based structured versus usual care for type 2 diabetic patients with **chronic renal disease**.

Ko GT, Yeung CY, Leung WY, Chan KW, Chung CH, Fung LM, Ip TP, Kum G, Lau KP, Lau IT, Li JK, Siu SC, Tsang MW, Yeung VT, Tong PC, So WY, Chan JC.

Hong Kong Med J. 2011 Dec;17 Suppl 6:9-12. No abstract available.

PMID: 22147352 [PubMed - indexed for MEDLINE] Free Article

Related citations

J Ethnopharmacol. 2012 Feb 15;139(3):757-64. Epub 2011 Dec 13.

Optimized project of traditional Chinese medicine in treating chronic kidney disease stage 3: a multicenter double-blinded randomized controlled trial.

Wang YJ, He LQ, Sun W, Lu Y, Wang XQ, Zhang PQ, Wei LB, Cao SL, Yang NZ, Ma HZ, Gao J, Li P, Tao XJ, Yuan FH, Li J, Yao C, Liu X.

Department of Nephrology, Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang University of Chinese Medicine, Hangzhou, Zhejiang Province, China. Wangyongjunhz@hotmail.com

Abstract

ETHNOPHARMACOLOGICAL RELEVANCE: Stage 3 is the key phase of chronic kidney disease. Traditional Chinese medicine (TCM) has been used for the treatment of chronic kidney disease. But a large sample trial is desirable.

MATERIALS AND METHODS: A total of 578 Chinese patients with primary glomerulonephritis in CKD stage 3 were randomly assigned to three groups: patients received TCM (TCM group), benazepril (Ben group), TCM combined with benazepril (TCM+Ben group). Patients were followed up for 24 weeks. The primary endpoint was the time to the composite of 50% increased of serum creatinine, end stage renal disease or death.

RESULTS: eGFR in the TCM and the TCM+Ben group were improved (week 24 vs. baseline, $P<0.05$) while eGFR in the Ben group was decreased (week 24 vs. baseline, $P>0.05$). 24h urinary protein excretion (UP) and urinary albumin/creatinine (UAlb/Cr) were decreased in the TCM+Ben

Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
		Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
J ETHNOPHARMACOL	0378-8741	15747	2.466	3.216	0.306	527	6.4	0.02334	0.539

TGF-beta1 immunohistochemistry and promoter methylation in

22. **chronic renal failure** rats treated with Uremic Clearance Granules.

Miao XH, Wang CG, Hu BQ, Li A, Chen CB, Song WQ.
Folia Histochem Cytobiol. 2010 Jan;48(2):284-91.
PMID: 20675287 [PubMed - indexed for MEDLINE]
Related citations

23. The clinical research on serum cystatin-C alteration on stage II **chronic kidney disease** with gubenquduyishen decoction treatment.

Dong F, Cheng J, Lin S, Hu Z, Chen G, He L.
J Ethnopharmacol. 2010 Oct 5;131(3):581-4. Epub 2010 Jul 24.
PMID: 20659545 [PubMed - indexed for MEDLINE]
Related citations

24. Anticoagulation during haemodialysis using a citrate-enriched dialysate: a feasibility study.

Cheng YL, Yu AW, Tsang KY, Shah DH, Kjellstrand CM, Wong SM, Lau WY, Hau LM, Ing TS.
Nephrol Dial Transplant. 2011 Feb;26(2):641-6. Epub 2010 Jul 8.
PMID: 20615906 [PubMed - indexed for MEDLINE]

J Ethnopharmacol. 2010 Oct 5;131(3):581-4. Epub 2010 Jul 24.

The clinical research on serum cystatin-C alteration on stage II chronic kidney disease with gubenquduyishen decoction treatment.

Dong F, Cheng J, Lin S, Hu Z, Chen G, He L.

Department of Nephrology, Shuguang Hospital Affiliated with Shanghai University of Traditional Chinese Medicine, Ministry of Education Key Laboratory of Liver and Kidney Disease Syndrome, E-institutes of Shanghai Municipal Education Commission 201203, China.

Abstract

AIM OF THE STUDY: Gubenquduyishen (GBQDYS) decoction, the modified remedy of a classical Chinese prescription named Liuweidihuang decoction, has been clinically employed to treat nephrotic syndrome and chronic nephritis in chronic kidney disease (CKD). The present study was designed to examine whether GBQDYS decoction has a protective effect on renal function associated with the raised level of cystatin-C (Cys-C), serum creatinine (Scr), blood urea nitrogen (BUN) and decreased Glomerular filtration rate (GFR) in stage-II CKD.

MATERIALS AND METHODS: A total of 68 stage-II CKD patients were randomly divided into two groups, the control group and the treatment group who received GBQDYS decoction as an additional therapy supplement.

RESULTS: Following up on a period of 48 months, levels of serum Cys-C, Scr, and BUN were significantly reduced by the treatment of GBQDYS decoction and GFR was elevated in the treated

Abbreviated Journal Title (linked to journal information)	ISSN	JCR Data						Eigenfactor™ Metrics	
		Total Cites	Impact Factor	5-Year Impact Factor	Immediacy Index	Articles	Cited Half-life	Eigenfactor™ Score	Article Influence™ Score
J ETHNOPHARMACOL	0378-8741	15747	2.466	3.216	0.306	527	6.4	0.02334	0.539

Step 3- Appraisal(讀)

Systemic review

- **Chinese herbal medicine Huangqi type formulations for nephrotic syndrome.**

  Yuan, Wei. Wang, Juan. Wu, Taixiang. EBM Reviews - Cochrane Database of Systematic ReviewsCochrane Renal Group Cochrane Database of Systematic Reviews. 4, 2010.

- **Topical herbal application as an adjuvant treatment for chronic kidney disease - a systematic review of randomized controlled clinical trials.**

  Zhang H, Ho YF, Che CT, Lin ZX, Leung C, Chan LS. J Adv Nurs. 2012 Jan 10. doi: 10.1111/j.1365-2648. 2011.05925.x. [Epub ahead of print]

RCT

- **The clinical research on serum cystatin-C alteration on stage II chronic kidney disease with gubenquduyishen decoction treatment.**

  Dong F, Cheng J, Lin S, Hu Z, Chen G, He L.J Ethnopharmacol. 2010 Oct 5;131(3):581-4. Epub 2010 Jul 24.

- **Optimized project of traditional Chinese medicine in treating chronic kidney disease stage 3: a multicenter double-blinded randomized controlled trial.**

  Wang YJ, He LQ, Sun W, Lu Y, Wang XQ, Zhang PQ, Wei LB, Cao SL, Yang NZ, Ma HZ, Gao J, Li P, Tao XJ, Yuan FH, Li J, Yao C, Liu X.J Ethnopharmacol. 2012 Feb 15;139(3):757-64.

VIP 原則證據力分級

- Valid
  - Randomization
  - Blinding
  - Follow-up
- Impact
  - Size of effect
  - Precision of effect
  - Notes
- Pratical
  - Patient
  - Outcome - Benifit vs Harm

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Systemic review appraisal sheet

Are the results of the review valid?

- What question (PICO) did the systematic review address?
- Is it unlikely that important, relevant studies were missed?
- Were the criteria used to select articles for inclusion appropriate?
- Were the included studies sufficiently valid for the type of question asked?
- Were the results similar from study to study?

What were the results?

- How are the results presented?

Chinese herbal medicine Huangqi type formulations for nephrotic syndrome.

Background

At present, there is a lack of safe and effective drugs for nephrotic syndrome (NS). Huangqi type formulations have been used to treat nephrotic syndrome for years in China, however the effects and safety of these formulations have not been systematically reviewed.

Objectives

To assess the benefits and harms of Huangqi and Huangqi type formulations in treating NS in any age group, either as sole agents or in addition to other drug therapies.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles. There was no language restriction.

Date of most recent search: June 2006.

Selection criteria

All randomised controlled trials (RCTs) assessing the use of Huangqi or Huangqi type formulations in treating NS in adults and children, either as sole agents or in addition to other drug therapies.

Data collection and analysis

Two authors independently assessed study quality and extracted data. For dichotomous outcomes (remission, side effects and Inefficacy rate), results were expressed as relative risk (RR) and 95% confidence intervals (CI). Continuous outcomes (triglycerides cholesterol, plasma albumin) results were expressed as mean difference (MD) with 95% CI.

Main results

Three studies were identified (n = 128), all comparing Huangqi type formulations with placebo. Huangqi injection had a positive effect on plasma albumin (MD 6.90, 95% CI 3.60 to 10.20) and cholesterol (MD 2.13, 95% CI -2.97 to -1.29). Huangqi and red Chinese date reduced some adverse reactions (Cushing's syndrome: RR 0.55, 95% CI 0.32 to 0.94; hormone reduced syndrome: RR 0.58, 95% CI 0.39 to 0.85, respiratory tract infection: RR 0.27, 95% CI 0.08 to 0.88), but no benefit on reducing relapse. Huangqi and Danggui had a positive effect on cholesterol (MD -0.85, 95% CI -1.70 to 0.00).

What question (PICO) did the systematic review address?

Title: Chinese herbal medicine Huangqi type formulations for nephrotic syndrome

Is it unlikely that important, relevant studies were missed?

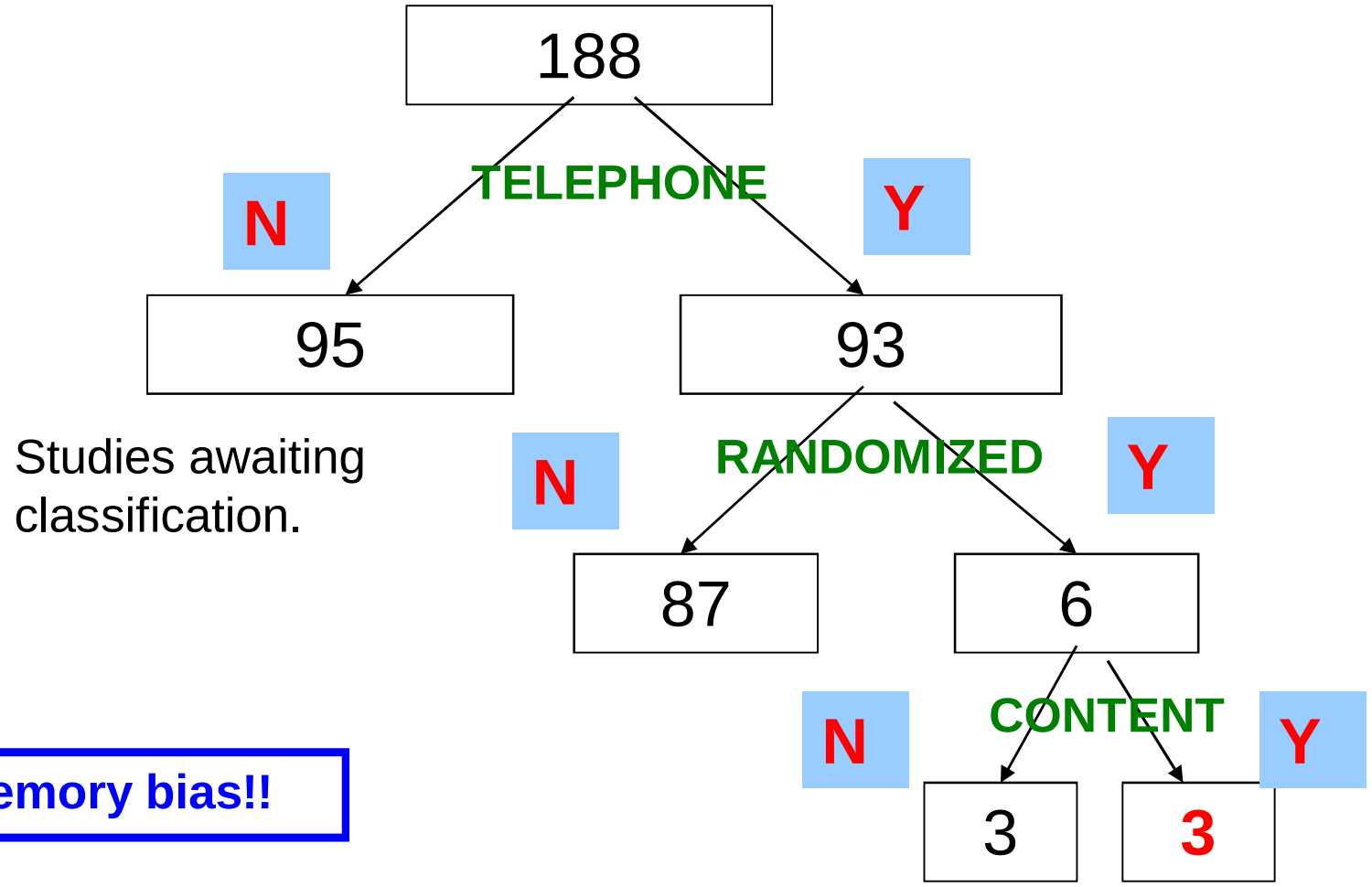
Search strategy

- We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles. *There was no language restriction*.

- Date of most recent search: June 2006.

- We were unable to determine if studies with negative findings remain unpublished.

Is it unlikely that important, relevant studies were missed?



Memory bias!!

Were the criteria used to select articles for inclusion appropriate?

- Method: All randomised controlled trials (RCTs) assessing the use of Huangqi and Huangqi type formulations in treating NS in adults and children, either as sole agents or in addition to other drug therapies. The first period of randomised crossover studies were also included.

- **Types of participants:** Adults and children with primary NS. In the absence of an explicit definition of NS, the diagnosis of NS in adults was based on the excretion of large amount of protein in the urine/d (> 3.5 g/24 h urine) and low serum protein (< 30 g/L), and in children with proteinuria > 3+ on dipstick, urinary protein-creatinine ratio > 0.2 g/mmol, > 40 mg/m²/h or > 50 mg/kg/d. People with secondary NS were excluded.

- **Types of interventions:**
  - Huangqi or Huangqi type formulations versus other drugs, formulations or placebo.
  - Huangqi or Huangqi type formulations in addition to other drugs versus other drugs.

Were the included studies sufficiently valid for the type of question asked?

Chang 2002a

Methods	Randomisation mentioned, but not described in detail. We interviewed the author by telephone, a random number table was used for generating the allocation sequence and the study was single-blinded.
Participants	Number: 30 primary nephrotic syndrome patients.

Hu 2002

Methods	Randomisation mentioned, but not described in detail. We interviewed the author by telephone, they used simple randomisation (minimised imbalance index distribution) and blinding was not used.
Participants	Number: 38 primary nephrotic syndrome patients.

Yuan 2004

Methods	Randomisation was mentioned, but not described in detail. We interviewed the author by telephone, computer generated random numbers sequence was used and single blinding was used.
Participants	Number: 60 frequently relapsing nephrotic syndrome patients of mesangial proliferative glomerulonephritis type.

Were the results similar from study to study?

- **Huangqi injection** had a positive effect on plasma albumin (MD 6.90, 95% Cl 3.60 to 10.20) and cholesterol (MD 2.13, 95% Cl -2.97 to -1.29).

- **Huangqi and red Chinese date** reduced some adverse reactions (Cushing's syndrome: RR 0.55, 95% Cl 0.32 to 0.94; hormone reduced syndrome: RR 0.58, 95% Cl 0.39 to 0.85, respiratory tract infection: RR 0.27, 95% Cl 0.08 to 0.88), but no benefit on reducing relapse.

- **Huangqi and Danggui** had a positive effect on cholesterol (MD -0.85, 95% Cl -1.70 to 0.00).

How are the results presented?

Analysis 1.1. Comparison 1 Huangqi type formulations versus placebo, Outcome 1 Plasma albumin.

Review: Chinese herbal medicine Huangqi type formulations for nephrotic syndrome

Comparison: 1 Huangqi type formulations versus placebo

Outcome: 1 Plasma albumin

Study or subgroup	Huangqi formulation N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Hu 2002	18	38.2 (5.24)	20	31.3 (5.12)		6.90 [3.60, 10.20]

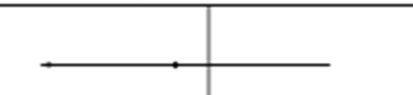
Analysis 1.2. Comparison 1 Huangqi type formulations versus placebo, Outcome 2 Triglycerides.

Review: Chinese herbal medicine Huangqi type formulations for nephrotic syndrome

Comparison: 1 Huangqi type formulations versus placebo

Outcome: 2 Triglycerides

Study or subgroup	Huangqi formulation N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Huangqi injection versus placebo						
Hu 2002	18	1.84 (0.67)	20	1.94 (0.81)		-0.10 [-0.57, 0.37]
2 Huangqi with Danggui (astragalus with angelica) mixture versus placebo						
Chang 2002a	15	1.62 (0.43)	15	1.73 (0.61)		-0.11 [-0.49, 0.27]



Chinese herbal medicine Huangqi type formulations for nephrotic syndrome.

Are the results of the review valid?

Y
- What question (PICO) did the systematic review address?

N
- Is it unlikely that important, relevant studies were missed?

Y
- Were the criteria used to select articles for inclusion appropriate?

N
- Were the included studies sufficiently valid for the type of question asked?

N
- Were the results similar from study to study?

What were the results?

- How are the results presented?

No heterogeneity was calculated

Topical herbal application as an adjuvant treatment for chronic kidney disease - a systematic review of randomized controlled clinical trials

Background. Besides dialysis or renal transplantation, patients with chronic kidney disease, especially those with insufficient renal function, are in a great need of effective conservative treatment methods. Topical application of herbal medicine, a common treatment modality in China, has been found in some clinical studies to benefit the patients with chronic kidney disease.

Data sources. The English databases including CENTRAL (February 2010), Medline (1950 to February 2010), EMBASE (1980 to February 2010), and AMED (1985 to January 2010), and several Chinese databases covering the period of 1949 to February 2010 were searched for randomized controlled trials that compared external use of herbal medicine with no treatment, placebo, or conventional treatment for chronic kidney disease and its complications.

Review methods. We undertook a systematic review and meta-analysis following Cochrane processes.

Results. Twenty-three trials with a total of 1057 patients were included. Their results suggest that herbal paste and bathing or fuming treatment might have a beneficial effect in terms of delaying the progress of renal disease, improving kidney function, and ameliorating some kidney complications in patients with chronic kidney disease. However, the low quality and poor reporting practices of the studies covered led to no definitive conclusion.

Conclusion. Further larger and more rigorously designed clinical trials with proper outcome measures are needed to confirm the findings.

What question (PICO) did the systematic review address?

Title: Topical herbal application as an adjuvant treatment for chronic kidney disease - a systematic review of randomized controlled clinical trials

Is it unlikely that important, relevant studies were missed?

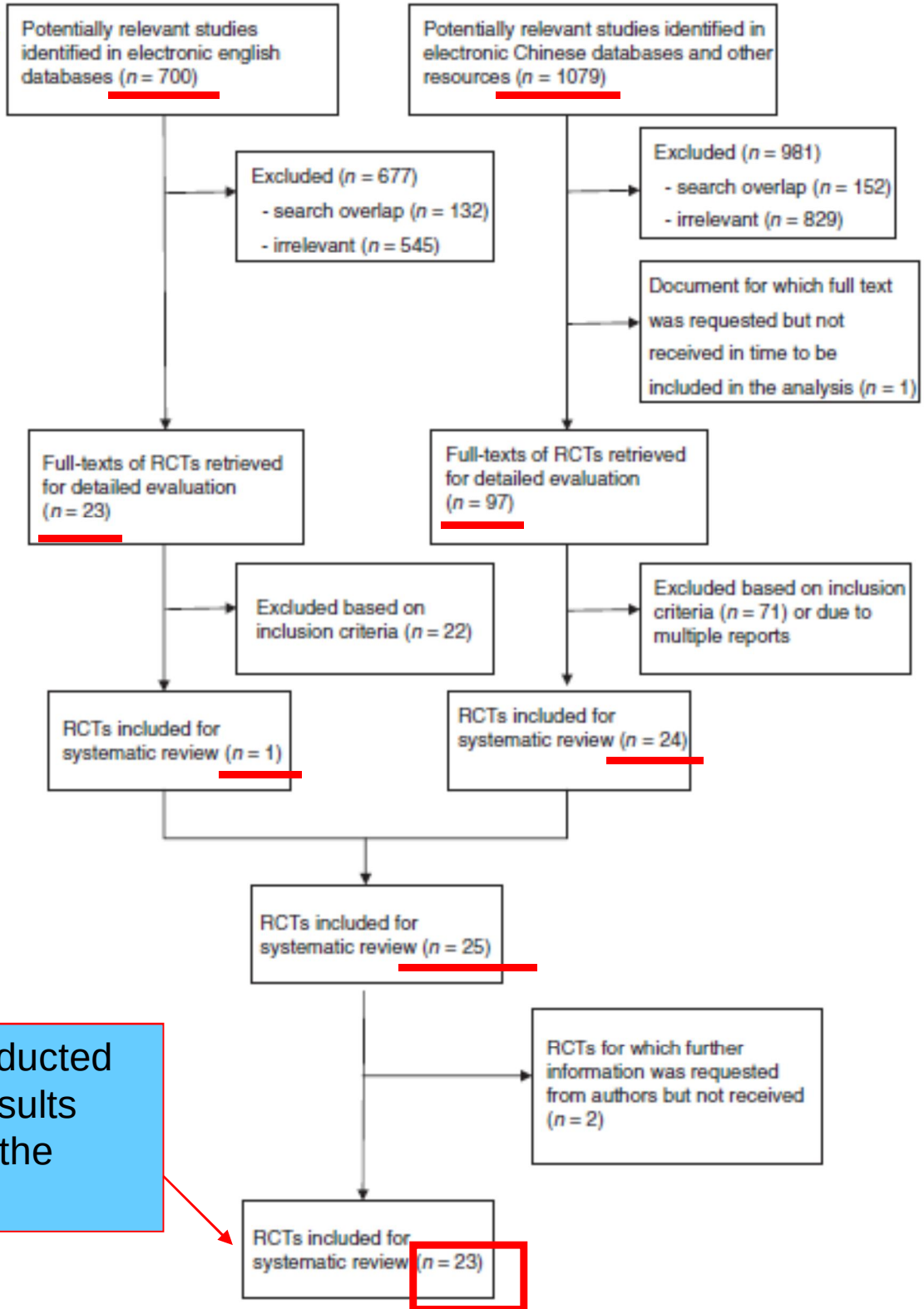
- The English databases: adapted subject headings and text words were developed around '**herbal medicine**', '**chronic kidney disease**', and '**randomized controlled trial**'. In these text words, they were combined with 'or', and then the three kinds of searching terms were combined with 'and'.

- The Chinese databases: The text words for chronic kidney disease in Chinese were as follows: **shen gong neng bu quan 肾功能不全** (literally, incomplete renal function), **shen gong neng shuai jie 肾功能衰减** (renal function failure), **shen shuai** (kidney failure), **niao du zheng 尿毒症** (uraemia), and **dan zhi xue zheng 氮血症** (azotemia); and the text words for external use were **wai zhi 外治** (literally, external treatment), **wai yong 外用** (external application), **fu 敷** (topical application), **tie 貼** (adhesion to skin), **tu 塗** (applying to skin), **xi 洗**(washing), **yu 浴** (bathing), **pao 泡** (soaking), and **xun 薰** (fuming).

Is it unlikely that important, relevant studies were missed?

- We also searched Current Controlled Trials (http://www.controlled-trials.com) and OpenSIGLE (System for Information on Grey Literature in Europe) for *ongoing and unpublished reports*.

- Additional searches were also performed on the *reference lists* of the included studies and significant review articles to *identify any potential missing trials.*



All 23 trials were conducted in China, and their results were all published in the Chinese language.

Were the criteria used to select articles for inclusion appropriate?

Inclusion

(1) those who are undergoing maintenance dialysis treatment;

(2) have an impairment of GFR <60 mL/min/1A73 m2 for ‡3 months; or

(3) have had kidney damage for >=3 months, as defined by structural or functional abnormalities of the kidney, manifested by either pathological abnormalities or markers of kidney damage including abnormalities in the blood or urine or imaging tests.

Exclusion

(1) merely stated that their patients had renal disease or renal insufficiency without mentioning baseline data of GFR, Scr, or other indicators of kidney function such as blood or urine tests;

(2) involved patients who have undergone renal transplantation.

(3) Studies of diabetic nephrology were also excluded from the review, because different treatment principles and compositions of herbal formula are normally used for this disease.

(4) Enema therapy using herbal medicine was also excluded, as it is not regarded as a typical topical intervention.

Table 1 Summary of the characteristics of the included studies on topical herbal medicine for CKD.

Study	No. participants (T/C)	Sex, M (%)	Age, years Mean (range)	Mean baseline Scr (μmol/L) (T/C)	Haemo-dialysis treatment	Outcome measures
Herbal paste plus co-interventions vs. placebo plus same co-interventions						
Bai *et al.* (2002)	80 (40/40)	20 (25)	61·87 (32–78)	530/442	Yes	Pruritus, Scr, Ca, P
Herbal paste plus co-interventions vs. the same co-interventions alone						
Wu *et al.* (2004)	27 (13/14)	15 (55·6)	394 (19–68)	1107/1009	No	GFR, Scr, Ca, P, 24 h UPE, TCH
Sun and Sun (2005)*	74 (40/34)	40 (54·1)	408 (20–63)	433·80/423·47	No	PRD, Ccr, Scr, Hb
Ba *et al.* (2006)†	135 (45/45/45)	73 (54·1)	38·65 (18–65)	372·69/374·78/376·13	No	PRD, Ccr, Scr, Hb, 24 h UPE, Alb
Sun *et al.* (2006)	100 (50/50)	57 (57)	514 (32–72)	432·94/425·79	No	PRD, Scr, Hb, Alb
Huo and Chen (2008)‡	90 (30/30/30)	48 (53·3)	34·67 (18–65)	380·17/382·05	No	PRD, Ccr, Scr, Hb, 24 h UPE, Alb
Yang *et al.* (2008)	41 (20/21)	33 (80·5)	44·49 (20–71)	178–707	No	PRD, Hb, 24 h UPE, Alb
Herbal bathing/fuming plus co-interventions vs. the same co-interventions alone						
Zhu (1998)	66 (36/30)	38 (57·6)	547 (25–70)	603·2/556·7	No	PRD, Ccr, Scr
Zhou and Dong (2004)	60 (30/30)	35 (58·3)	531 (NR)	485·93/483·82	No	PRD, Scr
Wang *et al.* (2005)	60 (30/30)	31 (51·7)	51·85 (NR)	484·84/482·76	No	PRD, Scr
Cao *et al.* (2006)	40 (20/20)	21 (52·5)	38·65 (NR)	380·13/384·12	No	Scr, Hb, TC
Guan (2006)	60 (30/30)	32 (53·3)	39·15 (22–72)	459·1/461·5	No	PRD, Scr
Qian *et al.* (2006)	129 (68/61)	78 (60·5)	46 (18–68)	176·8–442	No	PRD
Wang (2006)	120 (60/60)	73 (60·8)	NR (24–68)	546·37/534	No	PRD, Scr
Huang (2007)	60 (30/30)	38 (63·3)	572 (28–73)	>707	No	Pruritus
Yu *et al.* (2008)	100 (50/50)	57 (57)	459 (29–70)	>133	No	PRD
Huang *et al.* (2009)‡	104 (38/30/36)	56 (53·8)	41·98	1122/1132	Yes	Pruritus
Jin (2009)§	121 (30/30/31/30)	67 (55·4)	42·86 (16–71)	354·49/276·23/306·68/324·27	No	PRD, Scr, Hb
Herbal bathing vs. conventional treatment with same co-interventions						
Du *et al.* (2004)	29 (15/14)	14 (48·3)	455 (32–70)	830/840	Yes	Pruritus
Wen (2007)	42 (21/21)	20 (47·6)	484 (23–73)	>707	Yes	Pruritus
Sun *et al.* (2008)	266 (133/133)	142 (53·3)	51·35 (29–76)	536·1/529·5	No	Scr, Hb, Ca, P
Herbal bathing vs. water bathing with same co-interventions						
Lu *et al.* (2001)¶	60 (32/28)	48 (80)	62 (NR)	658/642	Yes	PRD, Scr
Yang (2007)	35 (19/16)	21 (60)	43 (21–79)	>707	Yes	Pruritus

Were the included studies sufficiently valid for the type of question asked?

Randomization 不佳

- The randomized allocation was mentioned in 20 studies but without further elaboration.
- One study reported the simple random number table was used (Yang et al. 2008).
- Two studies stated the simple randomization procedure without further detailed description (Zhou & Dong 2004, Wang et al. 2005).
- One study used the sequence of hospital admission for patient allocation, rendering it a quasi-randomization or systematic allocation (Guan 2006).

Blind 不佳

- The double-blind method was mentioned in one study that used a placebo paste as control, but it was not clear whether the patients, the doctors, or the data collectors were masked.
- No blinding was mentioned in the other remaining studies.

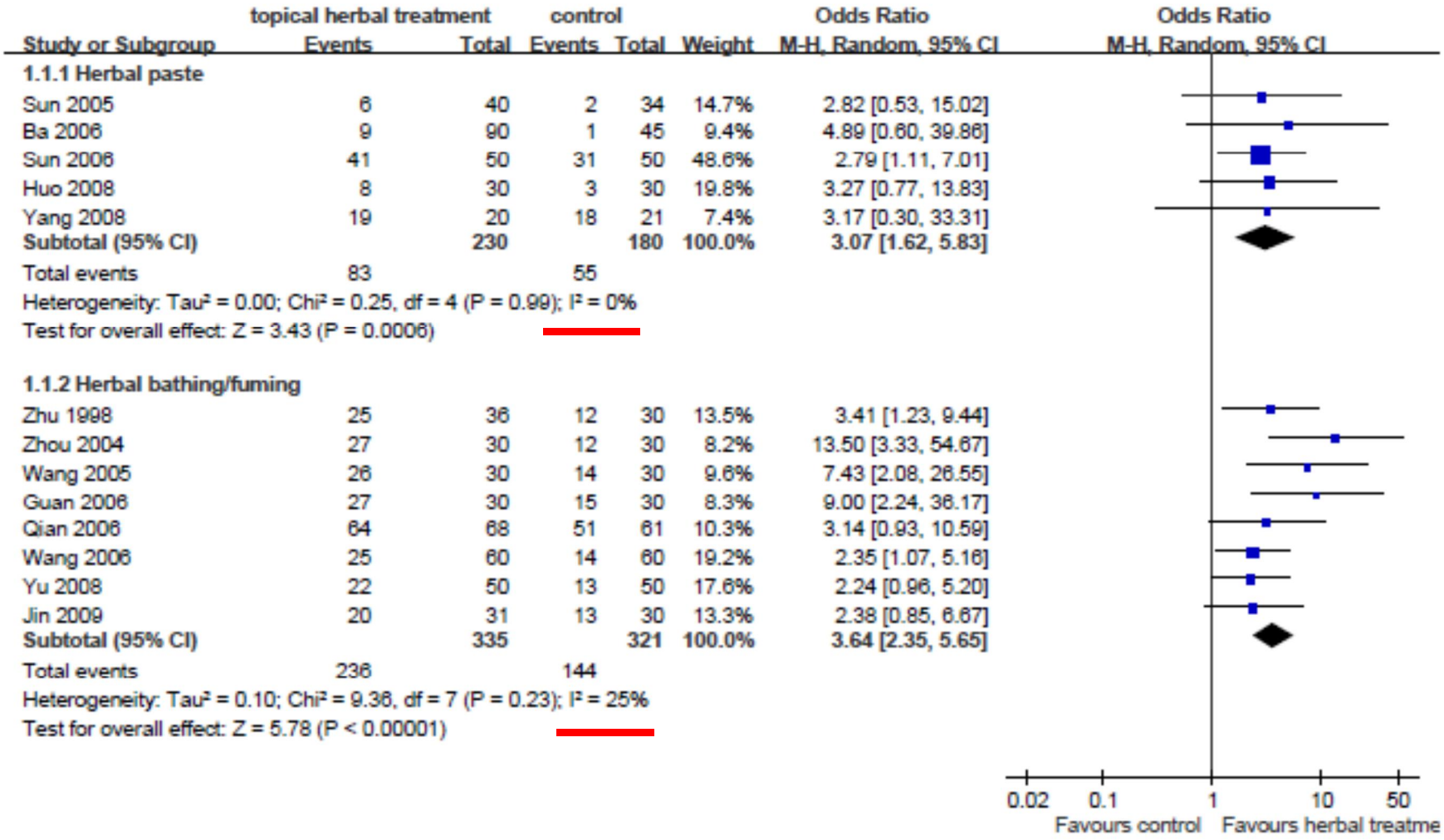
Were the results similar from study to study?

- We used chi-squared test with an alpha of 0.1 for statistical significance and *I^2 test to analyse heterogeneity* across the included studies

- As *the chi-squared test has low power when the included studies have small sample size or are few in number, a P value of 0.10, rather than the conventional level of 0.05*, was used to determine statistical significance.

- *We did not conduct a funnel plot* because the number of included trials was relatively small.

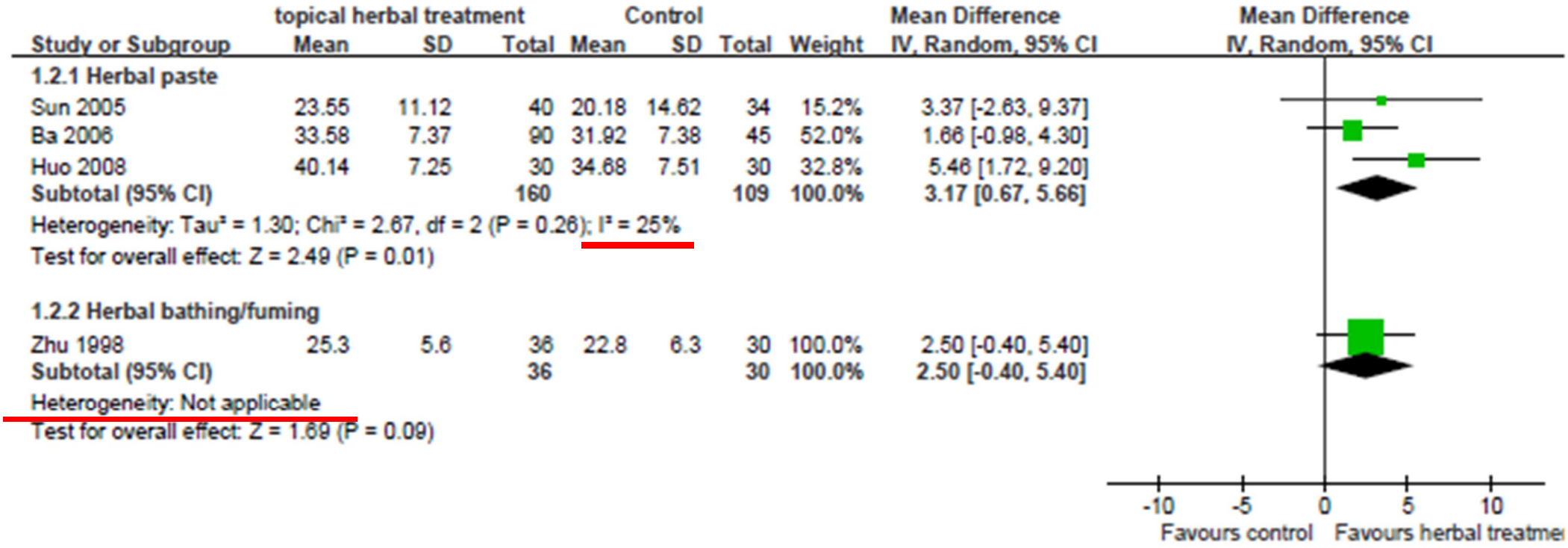
How are the results presented?



Study or Subgroup	topical herbal treatment Events	Total	control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Herbal paste						
Sun 2005	6	40	2	34	14.7%	2.82 [0.53, 15.02]
Ba 2006	9	90	1	45	9.4%	4.89 [0.60, 39.86]
Sun 2006	41	50	31	50	48.6%	2.79 [1.11, 7.01]
Huo 2008	8	30	3	30	19.8%	3.27 [0.77, 13.83]
Yang 2008	19	20	18	21	7.4%	3.17 [0.30, 33.31]
Subtotal (95% CI)		**230**		**180**	**100.0%**	**3.07 [1.62, 5.83]**
Total events	83		55			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 4 (P = 0.99); I² = 0%						
Test for overall effect: Z = 3.43 (P = 0.0006)						
1.1.2 Herbal bathing/fuming						
Zhu 1998	25	36	12	30	13.5%	3.41 [1.23, 9.44]
Zhou 2004	27	30	12	30	8.2%	13.50 [3.33, 54.67]
Wang 2005	26	30	14	30	9.6%	7.43 [2.08, 26.55]
Guan 2006	27	30	15	30	8.3%	9.00 [2.24, 36.17]
Qian 2006	64	68	51	61	10.3%	3.14 [0.93, 10.59]
Wang 2006	25	60	14	60	19.2%	2.35 [1.07, 5.16]
Yu 2008	22	50	13	50	17.6%	2.24 [0.96, 5.20]
Jin 2009	20	31	13	30	13.3%	2.38 [0.85, 6.67]
Subtotal (95% CI)		**335**		**321**	**100.0%**	**3.64 [2.35, 5.65]**
Total events	236		144			
Heterogeneity: Tau² = 0.10; Chi² = 9.36, df = 7 (P = 0.23); I² = 25%						
Test for overall effect: Z = 5.78 (P < 0.00001)						

Figure S1 Effects of herbal paste or herbal bathing/fuming treatment with co-interventions on the progress of renal disease (defined as 20% decrease in Scr or 20% increase in Ccr) when compared with the same co-interventions alone.

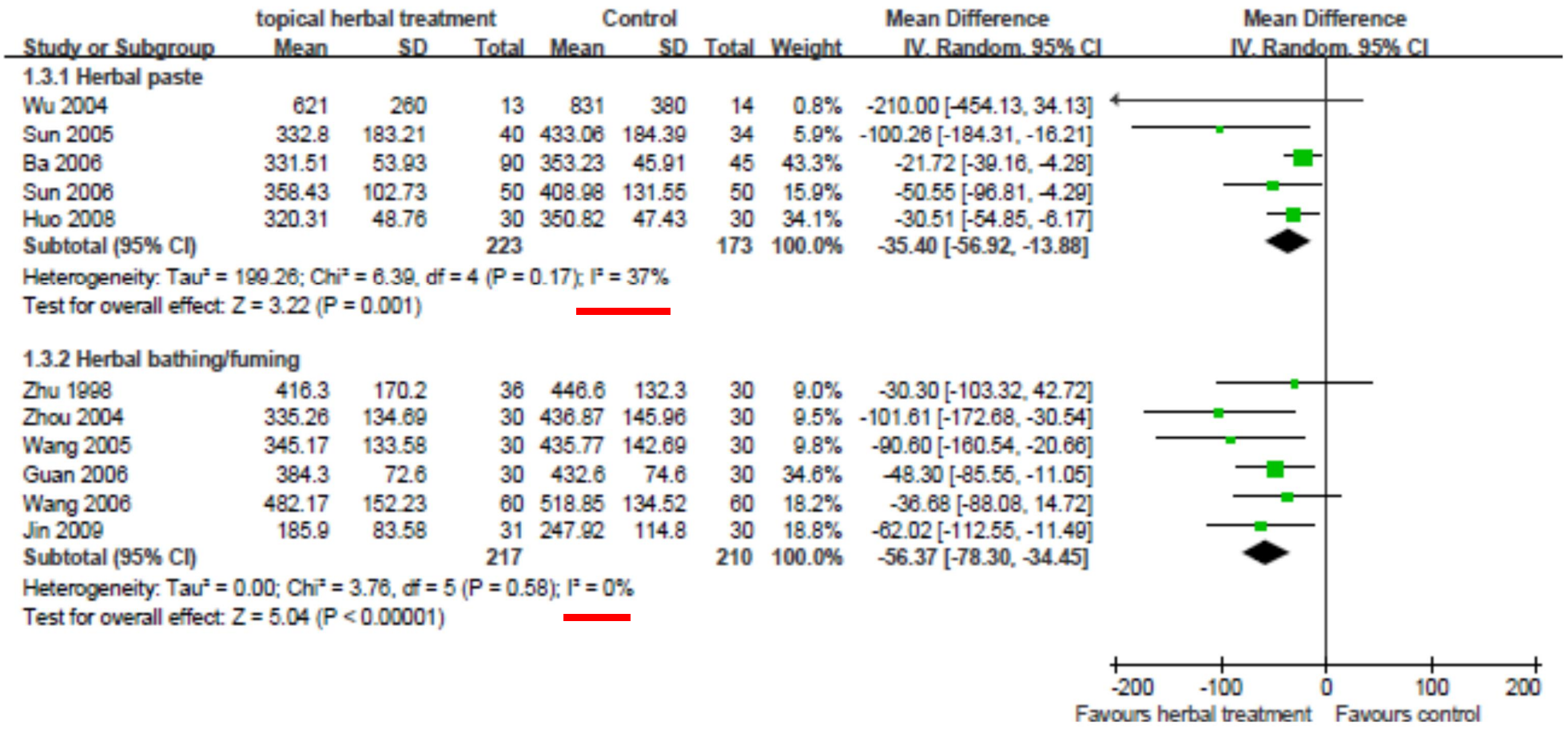
How are the results presented?



Study or Subgroup	topical herbal treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Herbal paste								
Sun 2005	23.55	11.12	40	20.18	14.62	34	15.2%	3.37 [-2.63, 9.37]
Ba 2006	33.58	7.37	90	31.92	7.38	45	52.0%	1.66 [-0.98, 4.30]
Huo 2008	40.14	7.25	30	34.68	7.51	30	32.8%	5.46 [1.72, 9.20]
Subtotal (95% CI)			160			109	100.0%	3.17 [0.67, 5.66]
Heterogeneity: Tau² = 1.30; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%								
Test for overall effect: Z = 2.49 (P = 0.01)								
1.2.2 Herbal bathing/fuming								
Zhu 1998	25.3	5.6	36	22.8	6.3	30	100.0%	2.50 [-0.40, 5.40]
Subtotal (95% CI)			36			30	100.0%	2.50 [-0.40, 5.40]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.69 (P = 0.09)								

Figure S2 Effects of herbal paste or herbal bathing/fuming treatment with co-interventions on creatinine clearance (Ccr) when compared with the same co-interventions alone.

How are the results presented?



Study or Subgroup	topical herbal treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Herbal paste								
Wu 2004	621	260	13	831	380	14	0.8%	-210.00 [-454.13, 34.13]
Sun 2005	332.8	183.21	40	433.06	184.39	34	5.9%	-100.26 [-184.31, -16.21]
Ba 2006	331.51	53.93	90	353.23	45.91	45	43.3%	-21.72 [-39.16, -4.28]
Sun 2006	358.43	102.73	50	408.98	131.55	50	15.9%	-50.55 [-96.81, -4.29]
Huo 2008	320.31	48.76	30	350.82	47.43	30	34.1%	-30.51 [-54.85, -6.17]
Subtotal (95% CI)			223			173	100.0%	-35.40 [-56.92, -13.88]
Heterogeneity: Tau² = 199.26; Chi² = 6.39, df = 4 (P = 0.17); I² = 37%								
Test for overall effect: Z = 3.22 (P = 0.001)								
1.3.2 Herbal bathing/fuming								
Zhu 1998	416.3	170.2	36	446.6	132.3	30	9.0%	-30.30 [-103.32, 42.72]
Zhou 2004	335.26	134.69	30	436.87	145.96	30	9.5%	-101.61 [-172.68, -30.54]
Wang 2005	345.17	133.58	30	435.77	142.69	30	9.8%	-90.60 [-160.54, -20.66]
Guan 2006	384.3	72.6	30	432.6	74.6	30	34.6%	-48.30 [-85.55, -11.05]
Wang 2006	482.17	152.23	60	518.85	134.52	60	18.2%	-36.68 [-88.08, 14.72]
Jin 2009	185.9	83.58	31	247.92	114.8	30	18.8%	-62.02 [-112.55, -11.49]
Subtotal (95% CI)			217			210	100.0%	-56.37 [-78.30, -34.45]
Heterogeneity: Tau² = 0.00; Chi² = 3.76, df = 5 (P = 0.58); I² = 0%								
Test for overall effect: Z = 5.04 (P < 0.00001)								

Figure S3 Effects of herbal paste or herbal bathing/fuming on the mean serum creatinine (Scr) when compared with no treatment.

How are the results presented?

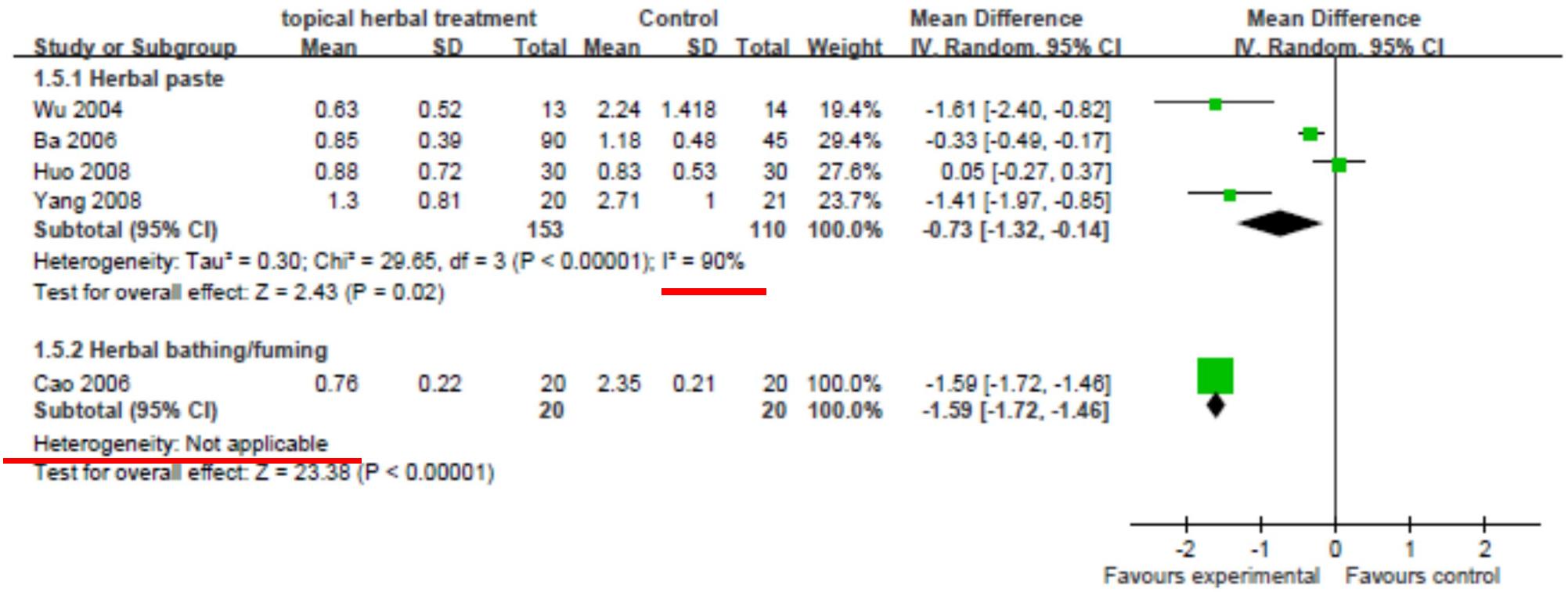


Figure S4 Effects of herbal paste or herbal bathing/fuming plus co-interventions on 24-h UPE when compared with the same co-interventions alone

Topical herbal application as an adjuvant treatment for chronic kidney disease - a systematic review of randomized controlled clinical trials

Are the results of the review valid?

Y
- What question (PICO) did the systematic review address?

Y
- Is it unlikely that important, relevant studies were missed?

N
- Were the criteria used to select articles for inclusion appropriate?

N
- Were the included studies sufficiently valid for the type of question asked?

N
- Were the results similar from study to study?

What were the results?

- How are the results presented?

Small sample size and poor designed studies included

Critical appraisal for therapy articles (RCT)

Are the results of the trial valid? (Internal Validity)

- Was the assignment of patients to treatments randomised?
- Were the groups similar at the start of the trial?
- Aside from the allocated treatment, were groups treated equally?
- Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?
- Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

What were the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

Will the results help me in caring for my patient? (ExternalValidity/Applicability)

The clinical research on serum cystatin-C alteration on stage II chronic kidney disease with gubenquduyishen decoction treatment.

ABSTRACT

Aim of the study: Gubenquduyishen (GBQDYS) decoction, the modified remedy of a classical Chinese prescription named Liuweidihuang decoction, has been clinically employed to treat nephrotic syndrome and chronic nephritis in chronic kidney disease (CKD). The present study was designed to examine whether GBQDYS decoction has a protective effect on renal function associated with the raised level of cystatin-C (Cys-C), serum creatinine (Scr), blood urea nitrogen (BUN) and decreased Glomerular filtration rate (GFR) in stage-II CKD.

Materials and methods: A total of 68 stage-II CKD patients were randomly divided into two groups, the control group and the treatment group who received GBQDYS decoction as an additional therapy supplement.

Results: Following up on a period of 48 months, levels of serum Cys-C, Scr, and BUN were significantly reduced by the treatment of GBQDYS decoction and GFR was elevated in the treated group. Whereas not achieved in the control group, suggesting the nephro-protective activity of GBQDYS decoction.

Conclusions: Taken together, these results demonstrated that GBQDYS decoction is able to protect renal function by delaying the progression of renal failure, and this may be used as an effective alternative treatment for CKD patients.

- GBQDYS decoction：六味地黃丸去丹皮，加丹參、杜仲、黃耆、積雪草、六月雪、大黃、豬苓

- Recently, it has been suggested that GFR can be predicted based on the Cys-C concentrations and that the *Cys-C concentration is not influenced by the gender or the age* (Stefan et al., 2000).

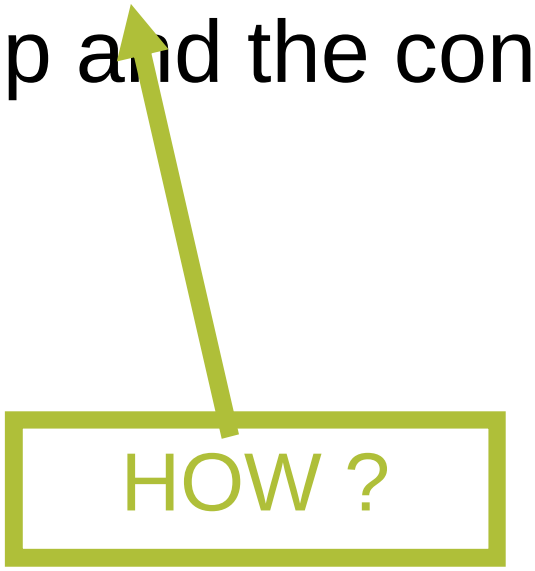
- A recent meta-analysis demonstrated that *Cys-C is a better marker for GFR than Scr* (Tanaka et al., 2007).

- Clinically, it has been demonstrated that *Cys-C can satisfy early detection for both the Stage-I and -II CKD* (Coll et al., 2000).

Was the assignment of patients to treatments randomised?

M&M

- A total of 68 patients identified with stage-II CKD were randomly divided into the treatment group and the control group, 34 patients each.



Were the groups similar at the start of the trial?

Whether differences between groups are statistically significant?

Table 1
Clinical data of the participants.

Group	Treatment Group	Control Group	P-value
Male/female	16/18	17/17	0.8
Age (mean yr ± SD)	57.80 ± 3.52	57.90 ± 3.51	0.9
GFR	66.35 ± 6.25	66.88 ± 6.43	0.75

Table 2
Effect of GBQUYS decoction on stage-II CKD patients in the pre-treatment and post-treatment after 16 courses of treatment.

Index	Treatment group		Control group		Health group
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Cys-C (mg/L)	3.85 ± 1.23♯	2.13 ± 0.83*,Δ	3.89 ± 1.35♯	3.85 ± 1.22	0.96 ± 0.48
Scr (μmol/L)	135.28 ± 39.88♯	95.26 ± 14.69*,Δ	133.82 ± 34.69♯	135.86 ± 33.96	85.56 ± 12.57
BUN (mmol/L)	13.29 ± 4.78♯	6.87 ± 1.26*,Δ	12.96 ± 4.19♯	12.89 ± 4.98	5.89 ± 1.19
GFR (mL/min)	66.35 ± 6.25♯	70.37 ± 6.98Δ	66.88 ± 6.43♯	42.34 ± 3.28♯	112.5 ± 8.61

♯ One-way ANOVA, compared with health group at $p < 0.01$.
* Paired-samples T test, compared with the pre-treatment subgroup in control group at $p < 0.01$.
Δ Independent-samples T test, compared with the post-treatment subgroup of control group at $p < 0.01$.

Aside from the allocated treatment, were groups treated equally?

- Both the control and the treatment groups took on a low protein and low phosphonium diet regimen, and all patients were subjected to physical examination at a total of 16 times throughout the trial.

- In addition, the concentrated extract of GBQDYS decoction was only given to the treatment group, taken after meal at 3 times per day in a package of 100mL for 48 months.

NO PLACEBO!

Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?

- Losses to follow-up should be minimal – preferably less than 20%.

* However, if few patients have the outcome of interest, then even small losses to follow-up can bias the results.

Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?

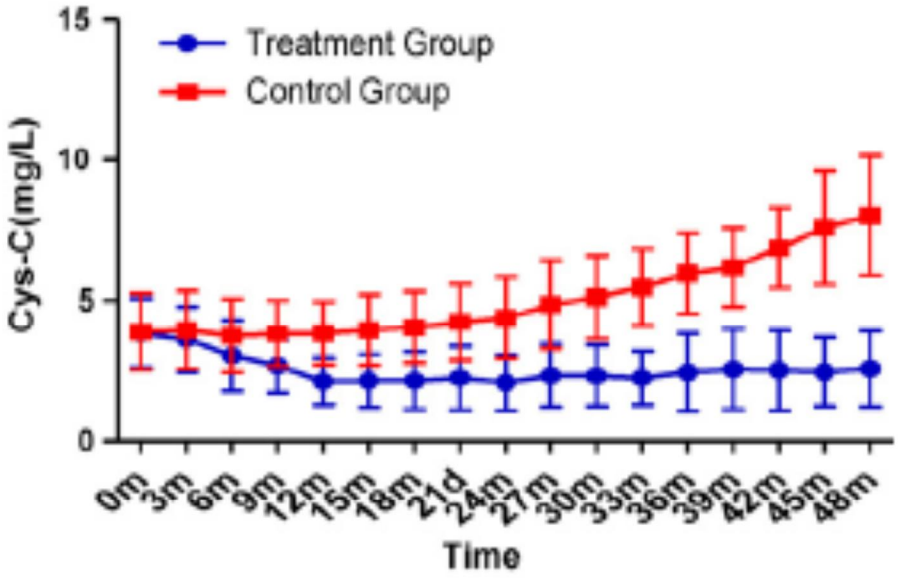
- Total of 68 patients identified with stage-II CKD

- Three months is regarded as one course of treatment, a total 16 courses was completed in this study. *No patient was withdrawn from the study due to intolerability or adverse side effects.*

Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

NO BLIND WAS MENTIONED

How large was the treatment effect?



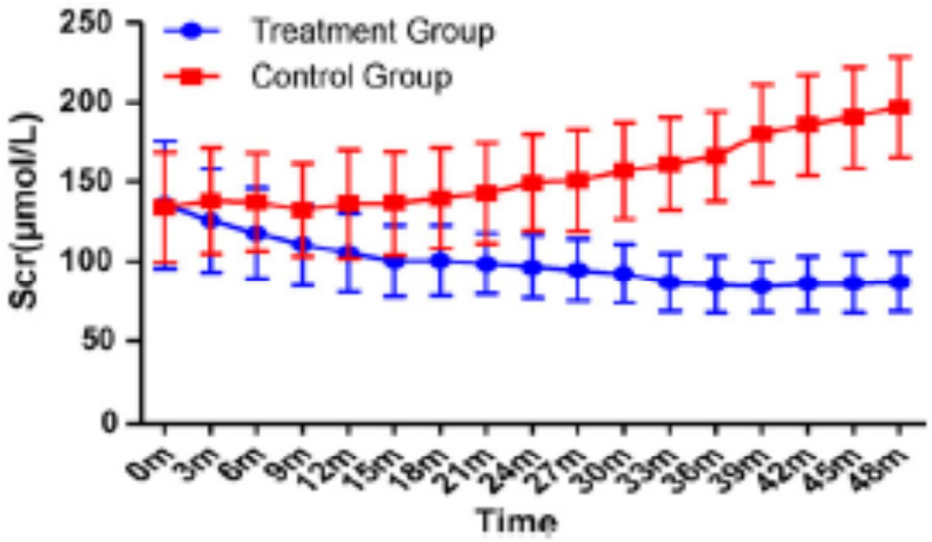


Fig. 1. GBQDYS decoction significantly lowered the levels of serum Cys-C in th treatment group over the period of 48 months when compared to the Control grou Every 3 months, all participants were physically examined and sera were analyze Alteration trendgraph over 48 months' follow up on Cys-C was plotted. A significar difference in the level of Cys-C between the treatment group and control grou ($p < 0.01$) was obtained.

Fig. 2. The serum Scr was significantly reduced in the treatment group over the 48 months period as compared to Control group. The serum Scr levels were similarly analyzed and presented as described in Fig. 1. Compared to the Control group, the GBQDYS decoction treated group had lower levels of Scr and significantly decrease over course of 48 months ($p < 0.01$).

NO Relative Risk, Absolute Risk Reduction, Relative Risk Reduction or Number Needed to Treat were mentioned

How precise was the estimate of the treatment effect?

No confidence interval was presented

Table 2

Effect of GBQUYS decoction on stage-II CKD patients in the pre-treatment and post-treatment after 16 courses of treatment.

Index	Treatment group		Control group		Health group
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	
Cys-C (mg/L)	$3.85 \pm 1.23^{\natural}$	$2.13 \pm 0.83^{*,\Delta}$	$3.89 \pm 1.35^{\natural}$	3.85 ± 1.22	0.96 ± 0.48
Scr (μmol/L)	$135.28 \pm 39.88^{\natural}$	$95.26 \pm 14.69^{*,\Delta}$	$133.82 \pm 34.69^{\natural}$	135.86 ± 33.96	85.56 ± 12.57
BUN (mmol/L)	$13.29 \pm 4.78^{\natural}$	$6.87 \pm 1.26^{*,\Delta}$	$12.96 \pm 4.19^{\natural}$	12.89 ± 4.98	5.89 ± 1.19
GFR (mL/min)	$66.35 \pm 6.25^{\natural}$	$70.37 \pm 6.98^{\Delta}$	$66.88 \pm 6.43^{\natural}$	$42.34 \pm 3.28^{\natural}$	112.5 ± 8.61

$^{\natural}$ One-way ANOVA, compared with health group at $p < 0.01$.

* Paired-samples T test, compared with the pre-treatment subgroup in control group at $p < 0.01$.

$^{\Delta}$ Independent-samples T test, compared with the post-treatment subgroup of control group at $p < 0.01$.

Will the results help me in caring for my patient?

- Is my patient so different to those in the study that the results cannot apply?

No. But lack of Co morbidities data?

- Is the treatment feasible in my setting?

Not so feasible

- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?

Unclear, due to NO PLACEBO!

Critical appraisal for therapy articles

Are the results of the trial valid? (Internal Validity)

How?

Y — Was the assignment of patients to treatments randomised?

- Y — Were the groups similar at the start of the trial?
- Y — Aside from the allocated treatment, were groups treated equally?
- Y — Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?
- N — Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

What were the results?

- N — How large was the treatment effect?
- N — How precise was the estimate of the treatment effect?

Will the results help me in caring for my patient? (ExternalValidity/Applicability)

Unclear, due to NO PLACEBO!

Optimized project of traditional Chinese medicine in treating chronic kidney disease stage 3: a multicenter double-blinded randomized controlled trial.

A B S T R A C T

Ethnopharmacological relevance: Stage 3 is the key phase of chronic kidney disease. Traditional Chinese medicine (TCM) has been used for the treatment of chronic kidney disease. But a large sample trial is desirable.

Materials and methods: A total of 578 Chinese patients with primary glomerulonephritis in CKD stage 3 were randomly assigned to three groups: patients received TCM (TCM group), benazepril (Ben group), TCM combined with benazepril (TCM + Ben group). Patients were followed up for 24 weeks. The primary endpoint was the time to the composite of 50% increased of serum creatinine, end stage renal disease or death.

Results: eGFR in the TCM and the TCM + Ben group were improved (week 24 vs. baseline, $P < 0.05$) while eGFR in the Ben group was decreased (week 24 vs. baseline, $P > 0.05$). 24 h urinary protein excretion (UP) and urinary albumin/creatinine (UAlb/Cr) were decreased in the TCM + Ben (week 24 vs. baseline, $P < 0.05$) and the Ben group (week 24 vs. baseline, $P > 0.05$). UP and UAlb/Cr were increased in the TCM group to week 12, then were stable (week 24 vs. baseline, $P < 0.05$). The hemoglobin in the TCM group was also improved (week 24 vs. baseline, $P < 0.05$). The accumulative survival rate in the TCM + Ben group was higher than that in the TCM group and the Ben group ($P = 0.044$). Side effects in the TCM group were the lowest in these groups ($P < 0.05$). The patients with dry cough in the TCM + Ben group and the Ben group were increased as compared with the TCM group ($P < 0.05$). Hyperkalemia happened less frequently in the TCM group as compared with the other two groups ($P = 0.052$).

Conclusions: For the patients with CKD stage 3, TCM can improve eGFR and hemoglobin with lower side effects. Benazepril significantly decreased the proteinuria. Chinese medicine integrated with benazepril can ameliorate renal function and decrease proteinuria synergistically.

Methods

Patients

- Patients were recruited at 13 hospitals in China.
- Between January 2006 and December 2009,
- Consecutive patients aged from 18 to 65 years old were screening for this study.

Inclusion criteria:

(1)The patients signed written informed consent.

(2) Primary chronic nephritis with eGFR from 30 to 59 ml/min (CKD stage 3).

(a) 24 hproteinuria less than 2 g/d.

(b) Not received ACEI or ARB for at least 2 weeks.

(c) Blood pressure (BP) less than 140/90 mmHg.

Exclusion criteria:

(1) women in pregnancy or lactation.

(2) Patients with severe disease in other organs or cancer, active tuberculosis, positive HBeAg, renal transplantation.

(3) Current treatment with corticosteroid, immunosuppressive agents.

(4) With psychoticdiseases.

(5) Enrolled in other trials.

(6) Hemoglobin (Hb) less than80 g/L.

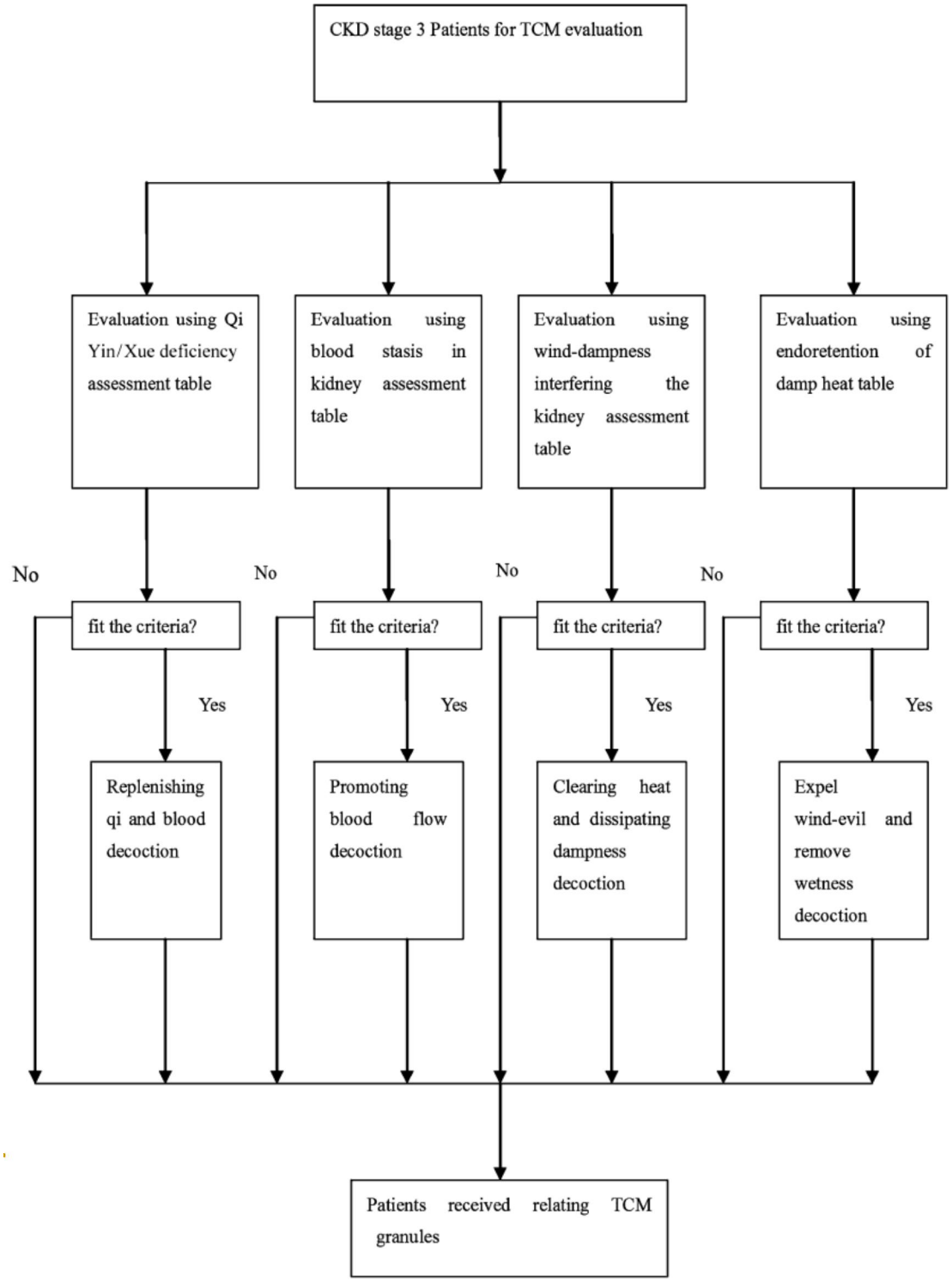
Was the assignment of patients to treatments randomised?

- Eligible patients obtained their sequence numbers from the coordinator and were randomly allocated into three groups according to a computer-generated randomization sequence list

Were the groups similar at the start of the trial?

Baseline characteristics of the patients with chronic kidney disease.[A]

	Ben group (n = 189)	TCM group (n = 192)	TCM + BEN group (n = 191)	P-Value*
Age (yr)	49.04 ± 10.47	47.33 ± 10.93	49.32 ± 11.37	0.16
Female sex-no. (%)	52.38	45.31	52.88	0.25
Weight (kg)	62.45 ± 11.03	63.92 ± 12.29	62.62 ± 10.78	0.39
Height (cm)	164.02 ± 7.27	164.70 ± 7.77	163.31 ± 7.50	0.20
SBP (mmHg)	124.26 ± 10.48	124.78 ± 11.03	125.03 ± 10.49	0.77
DBP (mmHg)	78.89 ± 6.70	80.04 ± 7.04	78.71 ± 7.27	0.13
eGFR (ml/min)	44.50 ± 9.02	45.26 ± 10.12	44.68 ± 9.82	0.72
UP (mg)	690.00 (280.50, 1225.00)	722.00 (300.00, 1450.00)	590.00 (250.00, 1128.00)	0.29
UAlb/Cr (g/mg)	0.31 (0.09, 0.72)	0.30 (0.10, 0.88)	0.30 (0.07, 0.66)	0.56
TCM score	38.04 ± 14.88	38.65 ± 13.91	36.90 ± 13.04	0.46
TCM patterns n (%)[#]				
Qi Yin/Xue	184 (97.4)	183 (95.3)	184 (96.3)	0.57
Blood stasis	127 (67.2)	144 (75.0)	140 (73.3)	0.21
Wind-dampness	138 (73.0)	133 (69.3)	127 (66.5)	0.38
Damp heat	67 (35.4)	72 (37.5)	75 (39.3)	0.74



The TCM syndrome patterns of CKD patients were classified into

- **Qi yin/Xue Deficiency (氣陰/血兩虛),**

*** Blood stasis in kidney(腎瘀),**

- **Wind-dampness interfering in the Kidney(風濕干腎)**

- **Endoretention of damp heat (濕熱內鬱)**

(Zhen et al., 2010).

Qi-yin(blood) deficiency in the kidney assessment table

Syndrome		Major syndrome				score
qi-yin(blood) deficiency in the kidney	waist soreness and feeble	None				0
		Feel debility occasionally, can do some light physical labor, or with a little foam in urine				4
		Feel debility intermittently , can do daily work reluctantly, or with a little foam in urine				8
		Feel debility persistently even at rest, can not do any work, or with a little foam in urine				12
	Minor syndrome					
	Shortness of breath and disinclination to talk	None	0	suscepti -ble to the cold	None	0
		Feeble, tired after over speech	4		Be susceptible to the cold	4
		Feeble ,shortness of breath, and disinclination to talk	8		Catch cold once a quarter	8
		Intermittent and low voice,too feeble to talk	12		Catch cold twice a quarter	12
	Spontaneous perspiration/ night sweat	None	0	Dry throat	None	0
		Slightly sweating	4		Occasionally, relieve after drinking a little water	4
		Always sweating	8		Frequently, relieve with drinking water always	8
		Aalways sweating to soaked clothes	12		Seriously and can't relieve by drinking water	12
	Feverish sensation in the palms and soles	None	0	Dizziness and tinnitus	None	0
		Feverish sensation in the palms and soles	4		Occasionally and not influence daily work	4
		Feverish sensation in the palms and soles with vexation	8		Frequently, relieve after rest	8
		Feverish sensation in the palms and soles, desire to catch cold objects, with vexation all the day	12		Seriously and can't relieve, influence the daily work	12
	Dry eyes	None	0	Nocturia	None	0
		Occasionally	4		Once a night	4
		Frequently	8		Twice a night	8
		Seriously and unbearable	12		More than Three times a night	12
Total score						

- (a) Qi Yin/Xue deficiency patterns (當歸補血湯加減): Astragalus membranaceus, Radix Pesudostellariae, Radix angelicae sinensis, Fructus ligustri lucidi 黃耆 太子參 當歸 女貞子.
- (b) Blood stasis in the kidney patterns (下瘀血湯加減): Radix salviae miltiorrhizae, Semen persicae, Herba centellae, Radix et rhizoma rhei 丹參 桃仁 積雪草 大黃.
- (c) Wind-dampness interfering in the kidney patterns (防己黃耆湯加減): Tripterygium wilfordii Hook. F, Radix Stephaniae Tetrandrae, Winged Euonymus Twig 雷公藤 防己 鬼箭羽 .
- (d) Endoretention of damp heat (土茯苓湯): Rhizoma polygoni cuspidati, Rhizoma coptidis, Rhizoma smilacis glabrae, Serissa serissoides (DC.) Druce 虎杖 黃連 土茯苓 白馬骨.

Aside from the allocated treatment, were groups treated equally?

Treatment

- All these patients received general therapy for chronic renal failure as follows:

  (1) **protein intake** (50% was high quality protein) was 0.6 g/(kg d) with sufficient calorie supply (30–35 kcal/kg).

  (2) **Antihypertensive agents** except ACEI or ARB was given to the patients with BP > 140/90 mmHg. The patient will not be enrolled in this study until his/her BP was less than 140/90 mmHg.

  (3) Patients received **antihyperlipidemic agents** including fenofibrate and/or atorvastatin for hyperlipoidemia.

Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?

- Losses to follow-up should be minimal – preferably less than 20%.

* However, if few patients have the outcome of interest, then even small losses to follow-up can bias the results.

- Shed criteria. (These patients cannot go on receiving the therapy of the research, but they will be followed up to the end of the trial.) :

  (1) Severe side events.

  (2) Severe complications.

  (3) Violate the trial regimen.

  (4) Significantly increased proteinuria.

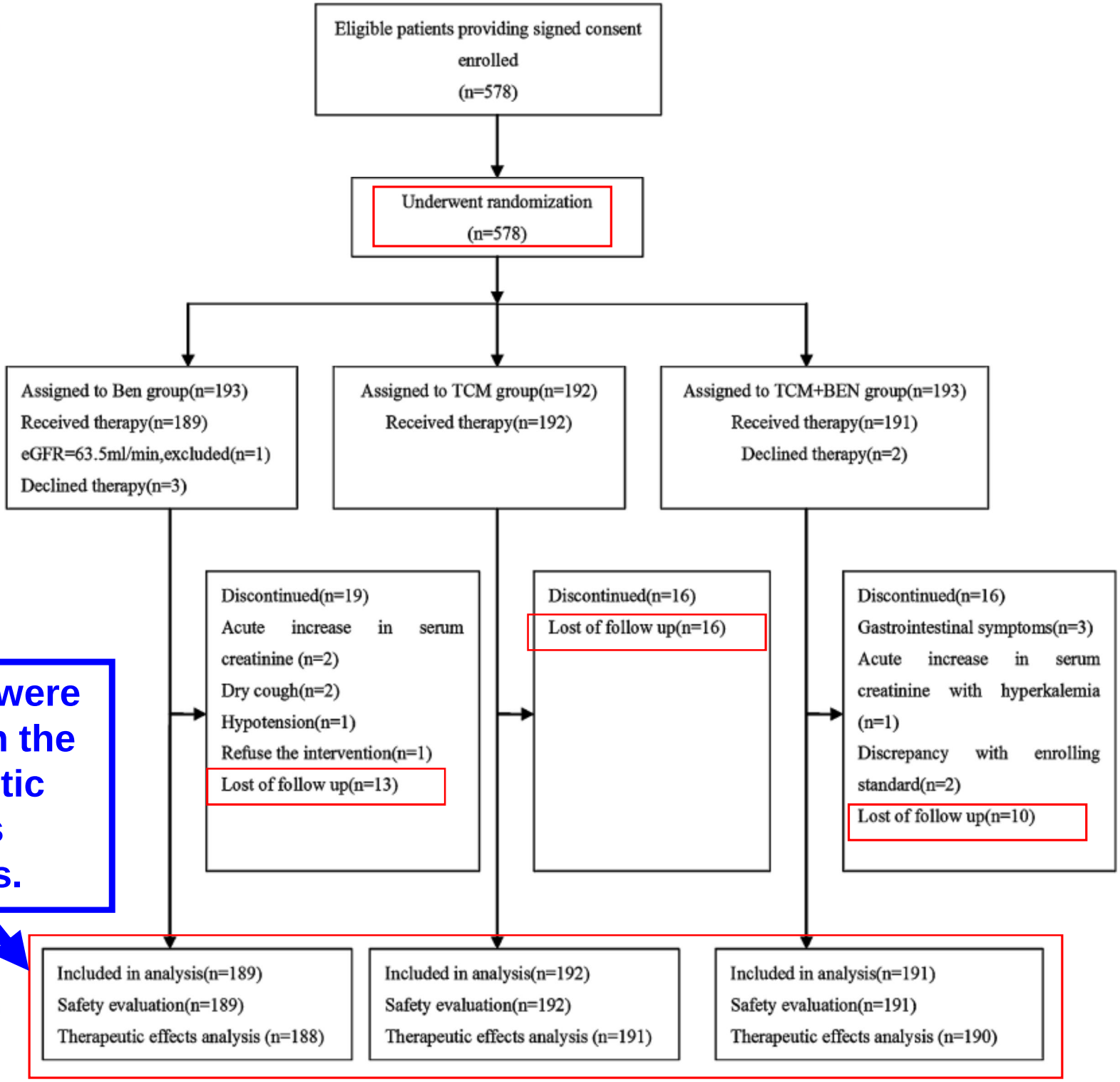
  (5) Lose to follow up.

  (6) Pregnancy.

- Rejection criteria. (The patients have undergone randomization but will be excluded)

  (1) Refuse to take the medicine of this trial.

  (2) Without any follow up data.



569 cases were included in the therapeutic effects analysis.

Fig. 2. Patients' enrollment and randomization.

Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

- This was a prospective, multicenter, **double blinded** and randomized controlled study.

- We conducted the study in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the international Conference on Harmonization, and local regulatory requirements.

- The study protocol was approved by the ethics committee at each participating center.

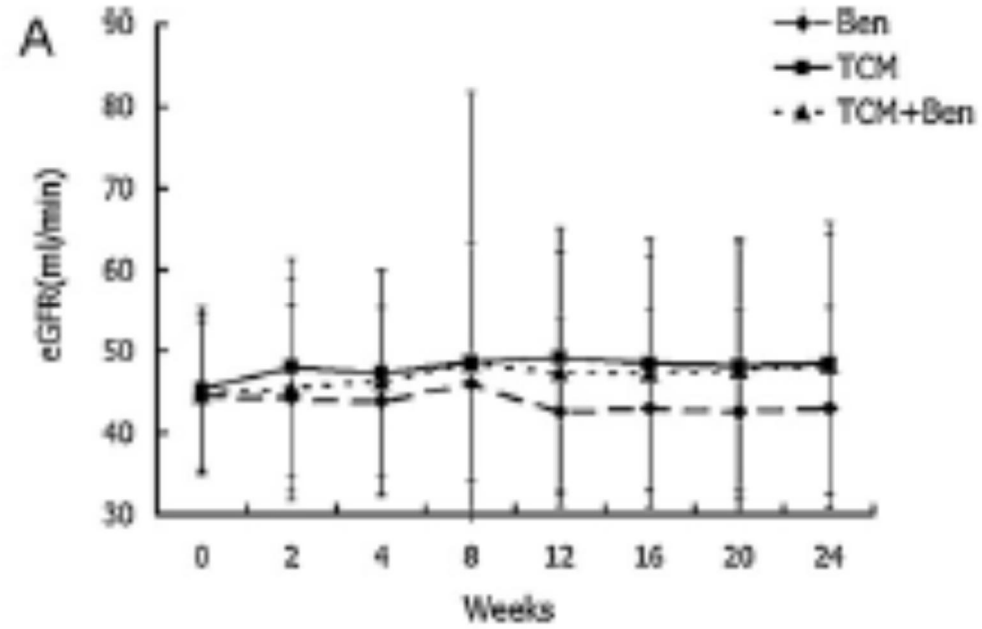
- Benazepril placebo was made of lactose, starch, carboxymethyl starch sodium and magnesium Stearate capsulated in a capsule that was comparable to the Benazepril capsule.

- TCM placebo granules separated to four TCM patterns were made of lactose, starch, edible colorant and bitter taste agents capsulated in a little tin foil bag that was the same as the four kinds of TCM granules.

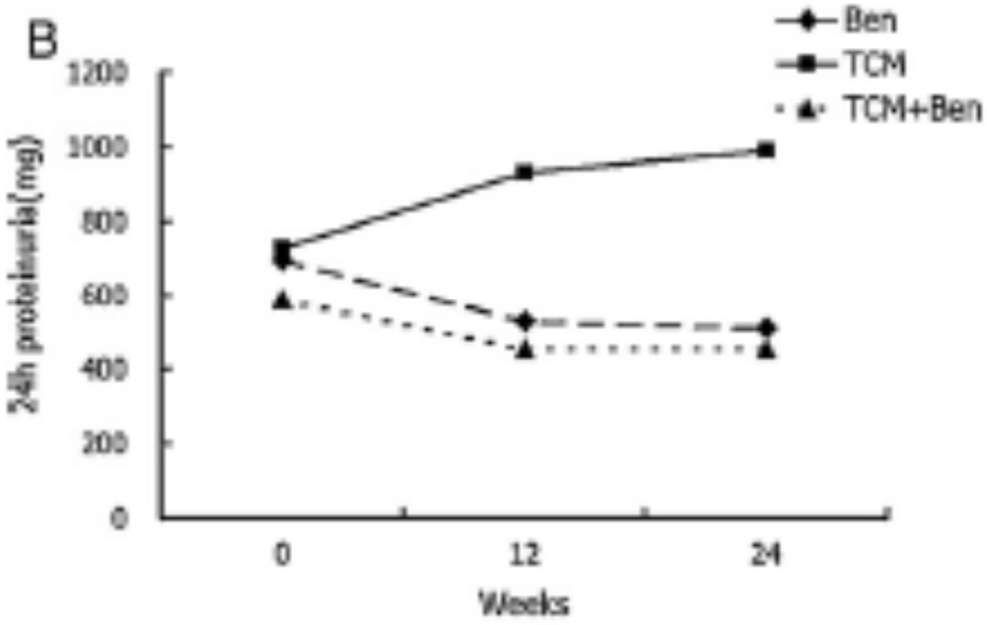
消失的**PLACEBO**組!!!

How large was the treatment effect?

NO Relative Risk, Absolute Risk Reduction, Relative Risk Reduction or Number Needed to Treat were calculated

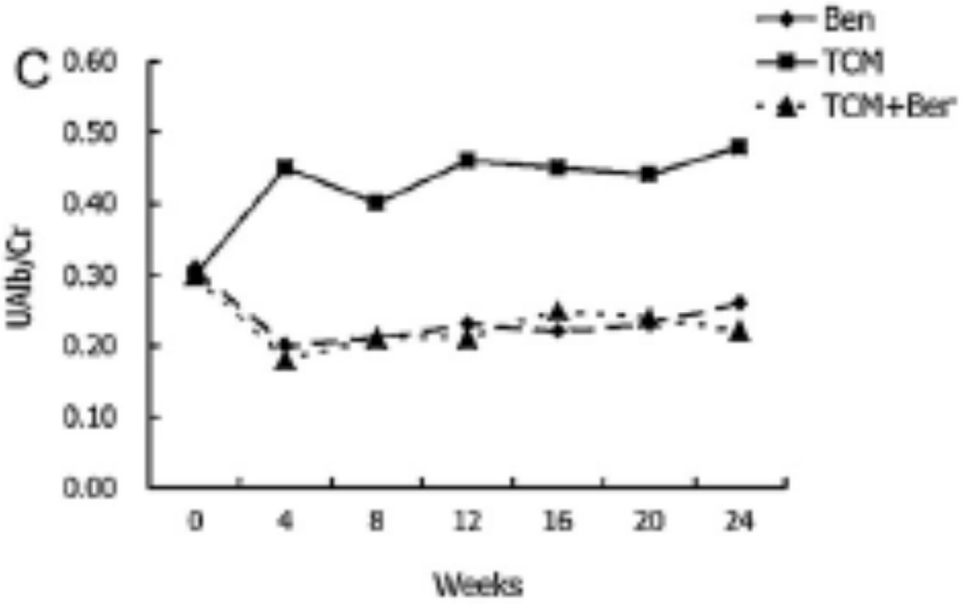


In the end of observation, eGFR in the **TCM** and the **TCM + Ben group** were higher than the Ben group ($P < 0.05$).

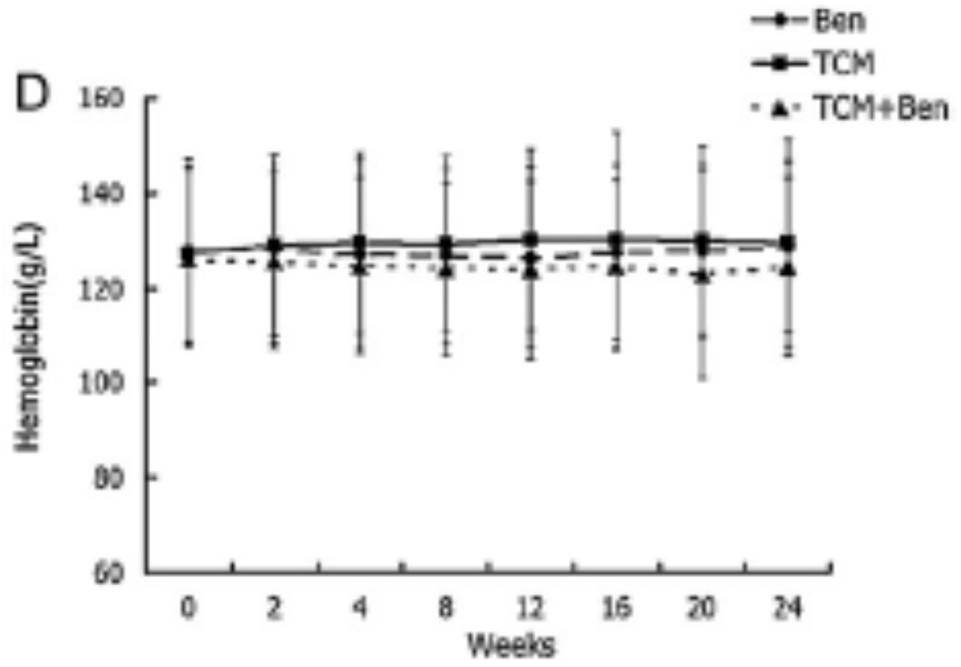


In the end of observation, 24 h proteinuria in TCM group was increased at week 12, and remained stable at week 24.

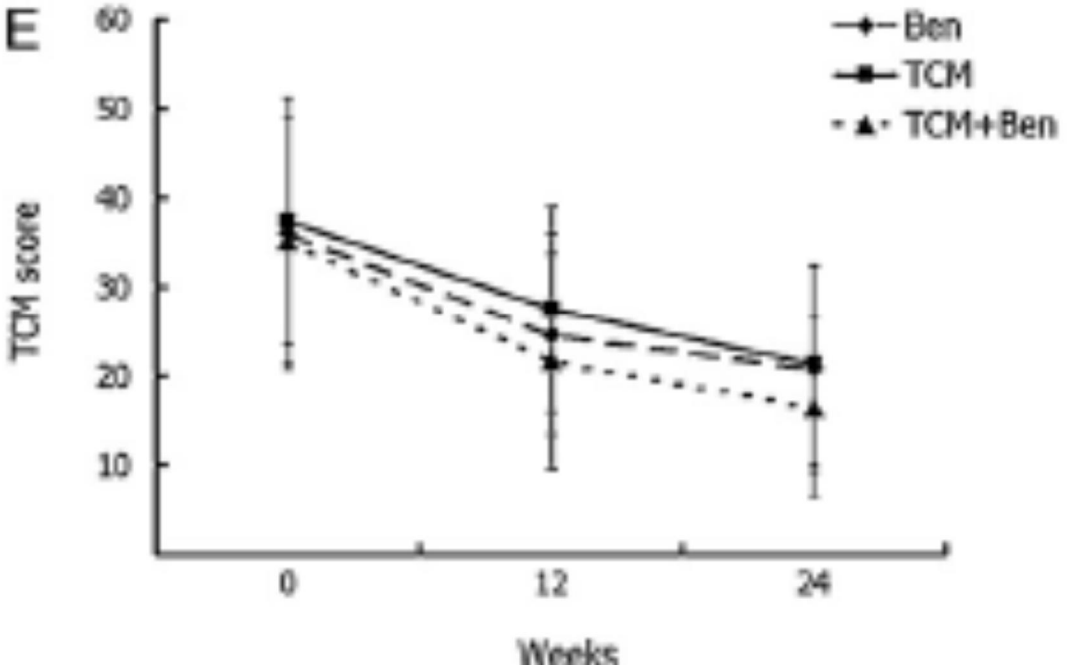
24 h proteinuria in **TCM + Ben** and **Ben group** was decreased as compared with TCM group ($P < 0.05$).



In the end of observation, UAlb/Cr in TCM group was increased from week 4 to week 12, and remained to the end.
UAlb/Cr in **TCM + Ben** and **Ben group** was decreased as compared with TCM group
($P < 0.05$). UAlb/Cr in TCM + Ben group was also lower than Ben group ($P > 0.05$).



In the end of observation, Hb in TCM group was increased as compared with baseline. Hb in **TCM group** was higher than Ben and TCM + Ben group ($P < 0.05$).



The TCM score in each group were all decreased at week 24 as compared with baseline.

TCM score in **TCM + Ben group** was decreased significantly as compared with the other two groups ($P < 0.05$).

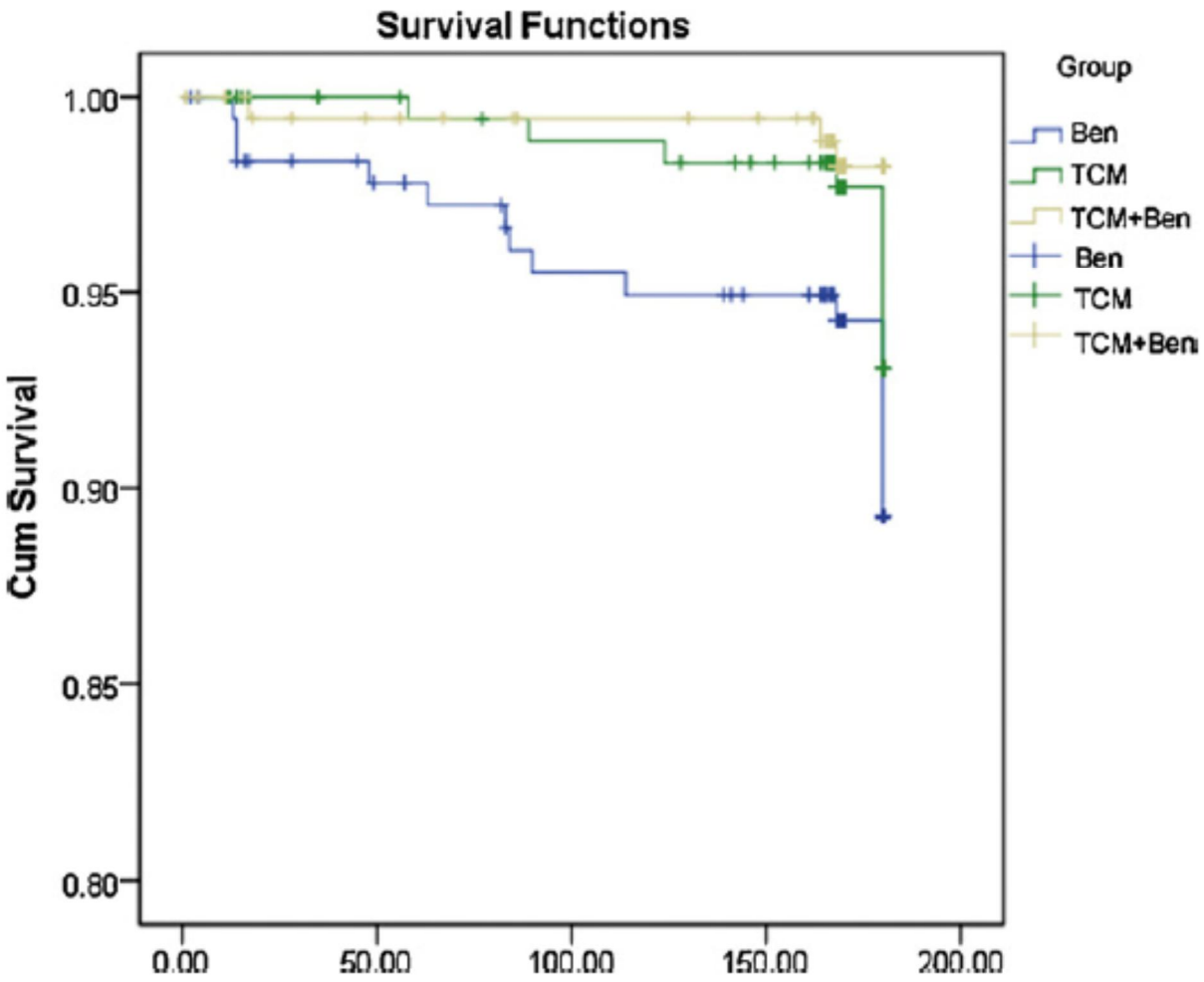


Fig. 4. Kaplan–Meier estimates of the percentage of patients not reaching the primary composite end point of a 50% increase of the serum creatinine, end-stage renal disease, or death.

The primary endpoint was the time to the composite of 50% increased of serum creatinine, end stage renal disease or death.

11 patients in the Ben group reached the primary end point compared with 5 patients in the TCM groups and 4 patients in the TCM + Ben groups (P = 0.044) (Fig. 4), indicating that the patients reached the primary end points in the TCM + Ben group was significantly lower as compared with the Ben group.

Table 3
Adverse events in each group.

Adverse event	Ben group ($n = 189$)	TCM group ($n = 192$)	TCM + Ben group ($n = 191$)	*P*-Value
Liver injury	9	2	5	0.087
Hyperkalemia	10	7	18	0.052
Dry cough	5	0	6	0.01
Hypotension	1	0	0	0.33
Anemia	8	7	6	0.85
Upper respiratory tract infection	5	8	8	0.66
Gastrointestinal symptoms	1	1	3	0.48
Total	39	25	46	0.019

As a whole, side effects events were lowest in the TCM group as compared with the other two groups ($P < 0.05$).

How precise was the estimate of the treatment effect?

- We can gauge how close this estimate is to the true value by looking at the confidence intervals (CI) for each estimate.
- If the confidence interval is fairly narrow

then we can be confident that our point estimate is a precise reflection of the population value.

No confidence interval was presented

Will the results help me in caring for my patient?

- Is my patient so different to those in the study that the results cannot apply?

NO

- Is the treatment feasible in my setting?

Maybe feasible

- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?

Unclear, where is the placebo group?

Critical appraisal for therapy articles

Are the results of the trial valid? (Internal Validity)

Y
- Was the assignment of patients to treatments randomised?

Y
- Were the groups similar at the start of the trial?

Y
- Aside from the allocated treatment, were groups treated equally?

Y
- Were all patients who entered the trial accounted for? – and were they analysed in the groups to which they were randomised?

Y
- Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?

What were the results?

N
- How large was the treatment effect?

N
- How precise was the estimate of the treatment effect?

Will the results help me in caring for my patient? (ExternalValidity/Applicability)

Unclear, due to NO PLACEBO!

Author's opinion

- In summary, this first RCT study about the effects of Chinese decoctions on CKD stage 3 patients with chronic glomerulonephritis following the differentiation of symptoms and signs demonstrated that Chinese decoctions can protect renal function, improve anemia.

- Chinese decoctions combined with benazepril can synerigisticly decrease proteinuria and increase GFR as compared with either TCM decoctions to improve GFR or benazepril to reduce proteinuria, respectively.

Step 4- Apply(用)

一、嚴謹的臨床研究相當不足，造成systemic review所能提供的資訊有限。

二、對於 CKD stage 3的18~65歲患者

- 根據證型給予相應中藥治療，可能可以改善半年內eGFR的惡化。
- 中藥合併ACEi治療，可能可以增強ACEi對於減少尿蛋白的作用。
- 中藥可能可以改善血紅素偏低的狀況。
- 中藥合併ACEi治療，可能可以改善CKD患者的預後。

Step 4- Apply(用)

三、中藥治療對於其他stage的CKD患者，或者年齡小於18歲或大於65歲的患者，或者伴隨其他co morbidities的療效，仍需進一步研究觀察。

四、將來進行中藥double blind RCT或許可以此模式進行，但須注意placebo group的設計與分析。

Step 5- Auditing(審)

- 我提出的問題是否具有臨床重要性？
  我是否明確的陳述了我的問題？
- 我是否已盡全力搜尋？
  我是否從大量的資料庫來搜尋答案？
- 我是否盡全力做評讀了？
  評讀後，我是否做出了結論？
- 我是否覺得這個進行實證醫學的過程是值得的？
- 我還有那些問題或建議？

~The END~

請多多指教