Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials

Supplementary Appendix

Table S1: Search Strategy of MEDLINE

Search Block	Search terms
Intervention	Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Chinese Medicine Herb OR Herbal Medicine OR Herbs
Condition	Diabetic Nephropathies OR Diabetic Nephropathy OR Diabetic Kidney Disease OR Diabetic Kidney Diseases OR Kimmelstiel Wilson Syndrome OR Kimmelstiel Wilson Disease OR Diabetic Glomerulosclerosis OR Nodular Glomerulosclerosis OR Intracapillary Glomerulosclerosis OR albuminuria OR Microalbuminuria OR proteinuria OR Glomerulosclerosis OR Glomerulonephritis OR Kimmelstiel wilson nephropathy OR diabetic nephrosclerosis
Study design	Systematic[sb] OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[sh] OR "randomly"[tiab] OR "trial"[tiab] OR "groups"[tiab] OR "cohort studies"[mesh] OR "case-control studies"[mesh] OR "comparative study"[pt] OR "risk factors"[mesh] OR "cohort"[tw] OR "compared"[tw] OR "groups"[tw] OR "case control"[tw] OR "multivariate"[tw] OR "case series"[tw]

Note: The three search blocks were connected with Boolean operators ‘AND’ to build the overall search terms.

Table S2: Subgroup Analysis of Primary Outcomes

Outcome or Subgroup	Studies	Pts	Statistical Method	Effect Estimate (95%CI)	I^2	*p* value
Urinary albumin excretion						
Subgroup-CHM formulae						
Qiwei Granules	2	104	MD	-70.06 [-88.84, -51.28]	0%	p<0.0001
Arctiin Granules	2	595	Std. MD	-0.38 [-0.56, -0.20]	0%	p<0.0001
Tang shen ning Formulae group	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
Subgroup-Measurements						
CHM vs placebo-AER	1	186	MD	-149.48 [-362.79, 63.83]	NA	p=0.17
CHM vs placebo-ACR	2	124	MD	-30.53 [-76.59, 15.53]	66%	p=0.19
CHM vs placebo-UAE	5	711	MD	-60.91 [-76.82, -45.01]	53%	p<0.0001
CHM vs placebo + ACEi/ARB-AER	1	119	MD	-48.85 [-53.30, -44.40]	NA	p<0.0001
CHM vs placebo + ACEi/ARB-UAE	2	330	MD	-48.16 [-55.12, -41.20]	95%	p<0.0001
24-hour proteinuria						
Subgroup-baseline UP						
CHM vs placebo-baseline UP < 0.5g/d	2	453	MD	-378.34 [-649.90, -106.77]	63%	p=0.006
CHM vs placebo-baseline UP > 0.5g/d	2	246	Std. MD	-1.49 [-3.97, 0.99]	97%	p=0.24
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP < 0.5g/d	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline UP > 0.5g/d	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-CHM formulae						
Qiwei Granules	2	104	Std. MD	-2.47 [-3.11, -1.83]	21%	p<0.0001
Arctiin Granules	2	595	MD	-407.65 [-732.24, -83.05]	45%	p=0.01
Tang shen fang group	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
Subgroup-Measurements						
CHM vs placebo-g/24h	1	60	MD	-0.93 [-1.13, -0.73]	NA	p<0.0001
CHM vs placebo-mg/24h	3	639	MD	-324.42 [-485.15, -163.69]	30%	p<0.0001

CHM + ACEi/ARB vs placebo + ACEi/ARB-g/24h	2	205	MD	0.11 [-0.67, 0.88]	74%	p=0.79
CHM + ACEi/ARB vs placebo + ACEi/ARB-mg/24h	2	284	MD	-31.30 [-68.61, 6.02]	61%	p=0.10
Serum creatinine level						
Subgroup-baseline Scr						
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr normal	3	227	MD	-2.12 [-6.48, 2.23]	0%	p=0.34
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline Scr abnormal	2	368	MD	-9.99 [-17.71, -2.26]	0%	p=0.01
CHM vs placebo + ACEi/ARB-baseline Scr normal	3	434	MD	-4.07 [-6.13, -2.01]	0%	p=0.0001
CHM vs placebo + ACEi/ARB-baseline Scr abnormal	1	156	MD	-2.84 [-18.18, 12.50]	NA	p=0.72
Subgroup-CHM formulae						
Tang shen fang group	2	286	MD	-6.06 [-14.60, 2.47]	0%	p=0.16
Tang shen ning Formulae group	2	330	MD	-3.96 [-6.13, -1.78]	6%	p=0.0004
Glomerular filtration rate						
Subgroup-baseline GFR						
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR>90	2	249	MD	9.38 [1.07, 17.70]	4%	p=0.03
CHM + ACEi/ARB vs placebo + ACEi/ARB -baseline GFR<90	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
CHM vs placebo + ACEi/ARB-baseline GFR>90	1	90	MD	-9.99 [-13.62, -6.36]	NA	p<0.0001
CHM vs placebo + ACEi/ARB-baseline GFR<90	3	452	MD	4.48 [-1.32, 10.28]	70%	p=0.13
Subgroup-CHM formulae						
Tang shen fang group	2	286	MD	5.22 [0.69, 9.74]	0%	p=0.02
Tang shen ning Formulae group	2	330	MD	-0.89 [-18.62, 16.85]	99%	p=0.92

Subgroup-Measurements						
CHM + ACEi/ARB vs placebo + ACEi/ARB-Ccr	1	144	MD	5.80 [1.01, 10.59]	NA	p=0.02
CHM + ACEi/ARB vs placebo + ACEi/ARB-eGFR	3	391	MD	7.13 [-0.29, 14.56]	11%	p=0.06
CHM vs placebo + ACEi/ARB-Ccr	2	246	MD	-4.14 [-15.81, 7.53]	93%	p=0.49
CHM vs placebo + ACEi/ARB-eGFR	2	296	MD	5.25 [-4.65, 15.15]	46%	p=0.30

Abbreviation: Pts, patients; CI, confident interval; NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MD, mean differences; Std, standard.; AER, albuminuria excretion rate; ACR, albuminuria to creatinine ratio; UAE, urinary albuminuria excretion; UP, urinary proteinuria; GFR, glomerular filtration rate; Scr, serum creatinine concentration; Ccr, creatinine clearance.

Table S3 Meta-analysis Results of Secondary Outcomes

Outcome	Studies	Participants	Effect Estimate (95% CI)	I^2	*p* value
Fasting blood sugar	9	962	-0.45 [-1.15, 0.25]	93%	p=0.21
Haemoglobin A1c	8	901	0.04 [-0.17, 0.24]	59%	p=0.73
Total cholesterol	8	815	-0.96 [-1.70, -0.21]	95%	p=0.01
Triglyceride	8	815	-0.60 [-1.01, -0.19]	90%	p=0.004
Low-density lipoprotein	7	696	-0.51 [-0.93, -0.09]	92%	p=0.02
High-density lipoprotein	8	815	0.14 [-0.04, 0.33]	93%	p=0.12
Systolic blood pressure	3	252	0.64 [-0.90, 2.17]	0%	p=0.43
Diastolic blood pressure	3	252	0.14 [-2.02, 2.29]	52%	p=0.90
Diabetes quality of life score	2	461	0.07 [-3.87, 4.00]	54%	p=0.97

Note: All outcomes analysed with mean difference. Abbreviation: CI, confident interval

Table S4: Sensitivity Analysis of Primary Outcomes

Outcomes	Studies	Participants	Statistical Method	Effect Estimate (95% CI)	I^2	*p* value
Urinary albumin excretion						
CHM vs placebo	4	798	Std. Mean Difference	-0.54 [-0.85, -0.22]	73%	p=0.0009
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	330	Std. Mean Difference	-0.56 [-1.04, -0.08]	64%	p=0.02
24-hour proteinuria						
CHM vs placebo	2	595	Mean Difference	-407.65 [-732.24, -83.05]	45%	p=0.01
CHM+ACEi/ARB vs placebo+ACEi/ARB	3	429	Std. Mean Difference	-0.12 [-0.60, 0.37]	81%	p=0.63
CHM vs placebo+ACEi/ARB	2	260	Std. Mean Difference	0.00 [-0.32, 0.32]	26%	p=1.00
Serum creatinine level						
CHM vs placebo	1	41	Mean Difference	10.31 [-2.26, 22.88]	NA	p=0.11
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	-5.59 [-10.61, -0.58]	0%	p=0.03
CHM vs placebo+ACEi/ARB	2	260	Mean Difference	-6.23 [-19.51, 7.05]	0%	p=0.36
Glomerular filtration rate						
CHM+ACEi/ARB vs placebo+ACEi/ARB	4	535	Mean Difference	6.28 [2.42, 10.14]	0%	p=0.001
CHM vs placebo+ACEi/ARB	2	212	Mean Difference	1.50 [-3.08, 6.09]	0%	p=0.52

Abbreviation: NA, not applicable. CHM, Chinese herbal medicine; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; Std, standar