Chronic Kidney Disease and Flos Abelmoschus Manihot: What We Have Learnt

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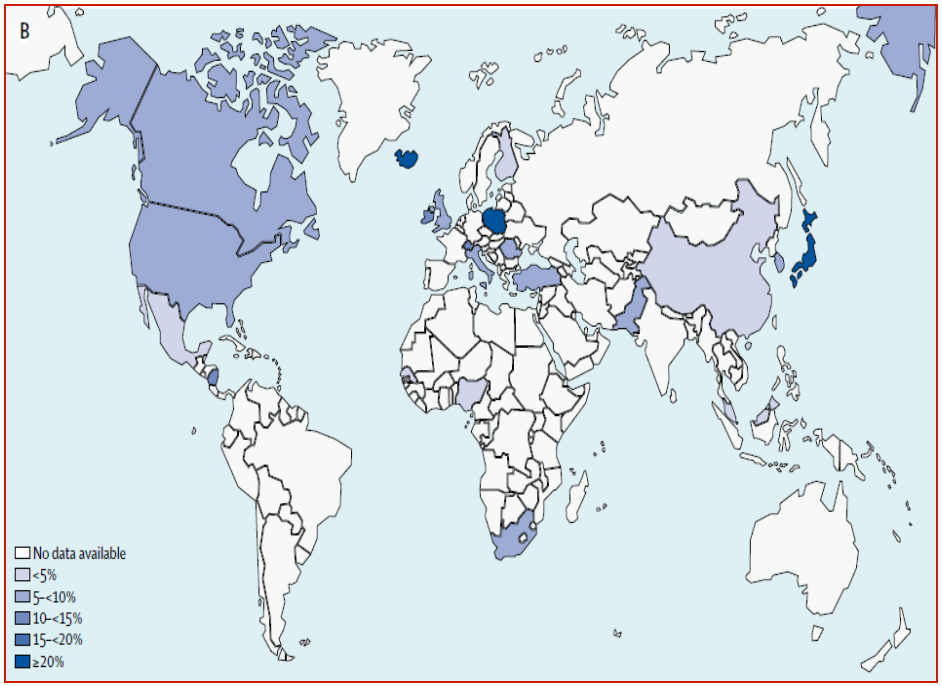
CKD: a major public health issue worldwide



	Kidney function			Albuminuria		CKD prevalence (95% CI)
	eGFR (mL/min per 1·73 m²)	n	Prevalence (95% CI)	n	Prevalence (95% CI)	
1	>90	29 244	65·2 (64·4–66·1)	1877	8·7 (8·0–9·3)	5·7 (5·2–6·1)
2	60–89	16 775	33·0 (32·2–33·9)	1385	10·3 (9·3–11·2)	3·4 (3·1–3·7)
3	30–59	1106	1·6 (1·4–1·8)	221	21·1 (16·1–26·1)	1·6 (1·4–1·8)
3a	45–59	940	1·4 (1·2–1·5)	165	19·5 (14·2–24·98)	1·4 (1·2–1·5)
3b	30–44	166	0·2 (0·1–0·3)	56	31·3 (16·2–46·4)	0·2 (0·1–0·3)
4	15–29	59	0·1 (0·06–0·2)	25	34·3 (9·6–58·9)	0·1 (0·06–0·2)
5	<15	20	0·03 (0·01–0·05)	9	56·6 (22·6–90·5)	0·03 (0·01–0·05)
Total	..	47 204	100	3517	9·4 (8·9–10·0)	10·8 (10·2–11·3)

Albuminuria was defined as a urinary albumin:creatinine ratio >30 mg/g creatinine. CKD was defined as eGFR <60 mL/min per 1·73m² or albuminuria. All prevalences are adjusted for synthesised weights. eGFR=estimated glomerular filtration rate. CKD=chronic kidney disease.

Table 2: Prevalence of indicators of kidney function, by disease stage

Prevalence of Chronic Kidney Disease varies by ethnicity and social determinants of health.

Webster AC Lancet 2017
Zhang L Lancet 2012

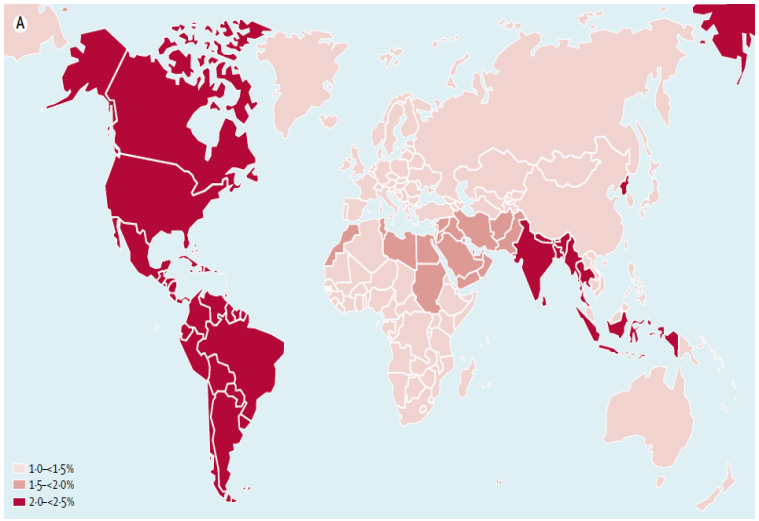
The Burden of CKD is Substantial

- End-stage renal disease(dialysis and transplatation)
- Accelerated cardiovascular disease (CVD)
- Increased risk of mortality(8-10 folds)
- Mineral and bone disease
- Infections
- Adverse metabolic and nutritional consequences
- CKD increases risk of AKI
- Economic burden of CKD(2–6% of the health care/ 0.02-0.03% population)

Nephrol Dial Transplant (2012) 27 (Supple 3): iii32–iii38

How to Improve the outcome of CKD: Still a Big Challenge

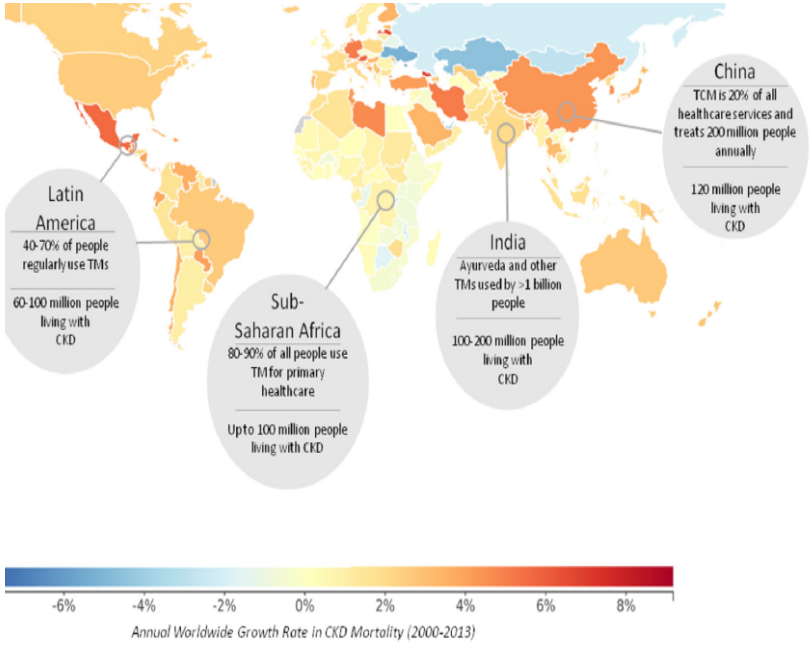
World Health Organization



- CKD accounted for 12.2 deaths per 100 000 people in 2012.
- Ranked fourteenth in the list of leading causes of death,
- Since 1990, only deaths from complications of HIV infection have increased at a faster rate than deaths from CKD.
- the death rate from CKD will continue to increase to reach 14 per 100 000 people by 2030.

http://apps.who.int/gho/data/node.main. PROJRATEWORLD?lang=en

CKD and Traditional Chinese Medicine



•TCM is fully integrated within the Chinese health care system, where it accounts for nearly 20% of all health care services .

•more than 200 million Chinese seek TCM care each year

•TCM has a long history of being used to treat kidney disease

•nearly 120 million people are living with CKD in China

•Most frequently prescribe both biomedicines directed at treating the underlying pathology while prescribing TCMs to restore body balance in China.

Seminars in Nephrology, Vol37,No3,May2017,pp245–259

The Chinese Herbs and CKD

Rheum palmatum

Tripterygium wilfordii

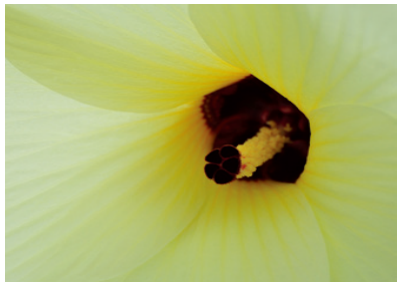
Cordyceps sinensis

A. manihot

A Story about Abelmoschus manihot

A. manihot

The dry corolla



Huangkui capsule

SFDA Z19990040

Huangkui capsule
- Calcium hydrogen phosphate(17%)
- Magnesium stearate(3%)
- the dry extract(80%) → flavonoids
  - Hyperoside(43.2%)
  - hibifolin
  - Isoquercitrin
  - myricetin
  - quercetin
  - gossypetin

Clinical and Experimental Pharmacology and Physiology (2016) 43, 145–148

Efficacy and Safety of *Abelmoschus manihot* for Primary Glomerular Disease: A Prospective, Multicenter Randomized Controlled Clinical Trial

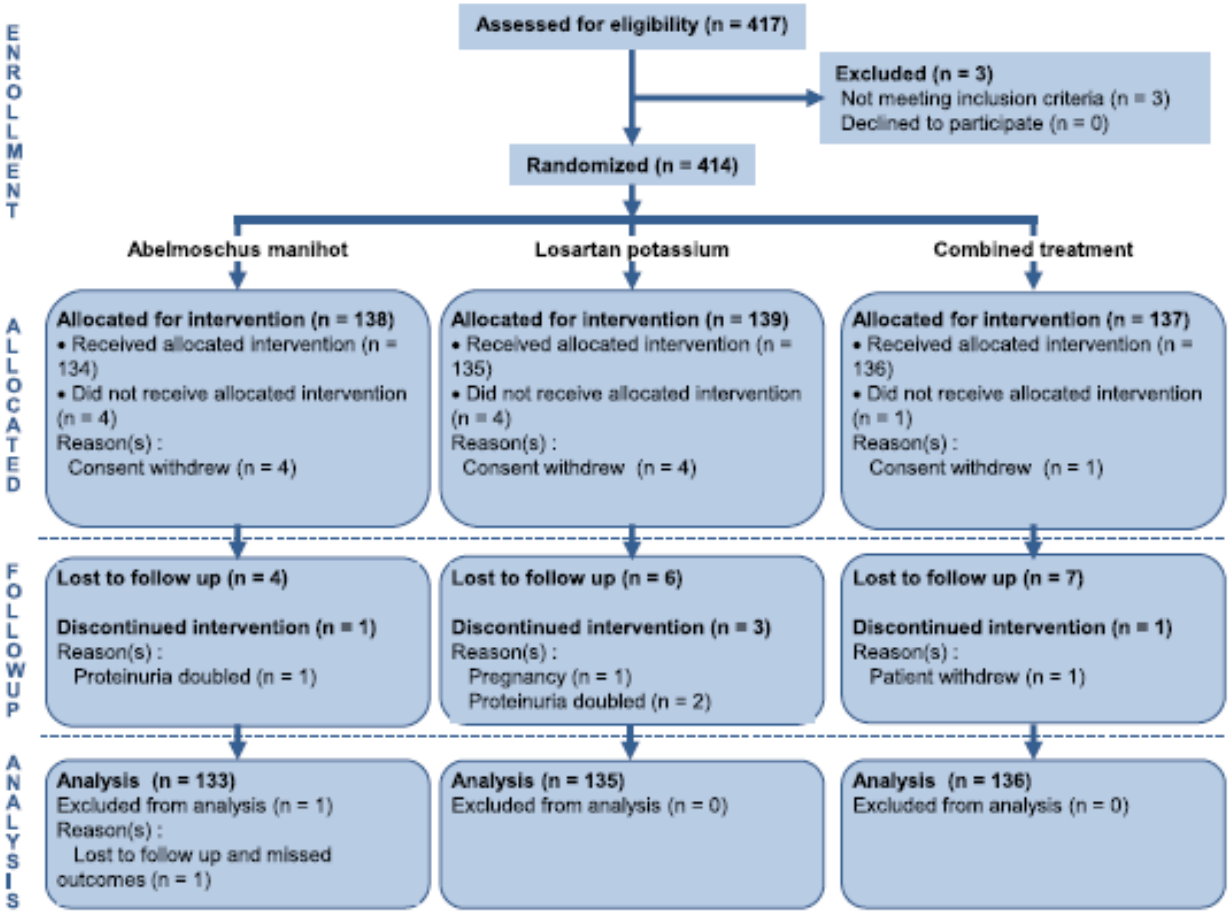


Figure 1. Randomization and flow of patients.

Baseline Participant Characteristics

Table 1. Baseline Participant Characteristics by Treatment Group

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*P*
Age (y)	37.3 ± 12.5	38.1 ± 12.7	37.1 ± 11.1	0.9
Sex				0.6
Male	67 (50.4)	72 (53.3)	64 (47.1)	
Female	66 (50.0)	63 (46.7)	72 (52.9)	
Pathologic classification				0.5
IgAN	60 (45.1)	76 (56.3)	72 (52.9)	
Non-IgAN mesangial proliferative GN	35 (26.3)	28 (20.7)	34 (25.0)	
FSGS	18 (13.5)	16 (11.9)	10 (7.4)	
Minimal-change nephropathy	9 (6.8)	6 (4.44)	10 (7.4)	
Membranous nephropathy	10 (7.5)	8 (5.9)	7 (5.2)	
Mesangial proliferative GN	1 (0.8)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	1 (0.7)	3 (2.2)	
SBP (mm Hg)	120.2 ± 8.6	120.7 ± 8.2	121.0 ± 7.8	0.7
DBP (mm Hg)	74.0 ± 6.0	74.9 ± 5.6	74.7 ± 5.6	0.4
24-h proteinuria (mg)	1,045 ± 420	1,084 ± 453	1,073 ± 439	0.9
Serum creatinine (mg/dL)	0.80 ± 0.22	0.82 ± 0.21	0.81 ± 0.23	0.4
eGFR (mL/min/1.73 m^2)	108 ± 24	106 ± 23	106 ± 24	0.8

Am J Kidney Dis. 2014;64(1):57-65

Primary Outcome Measure: 24-Hour Proteinuria

Table 2. Change From Baseline in 24-Hour Proteinuria Over 24-Week Follow-up Period

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*A manihot* vs Losartan	Combined Treatment vs *A manihot*	Combined Treatment vs Losartan
0 wk	1,045 ± 420	1,084 ± 453	1,073 ± 439	$P = 0.9$	$P = 0.9$	$P = 0.9$
12 wk	762 ± 533	825 ± 706	783 ± 658	$P = 0.7$	$P = 0.7$	$P = 0.5$
Δ 24-h proteinuria	−283 ± 553	−258 ± 701	−290 ± 542	−25 (−177 to 128) $P = 0.9$	−7 (−124 to 139) $P = 0.8$	−32 (−118 to 181) $P = 0.8$
Comparison within group	$P < 0.001$	$P < 0.001$	$P < 0.001$			
24 wk	537 ± 409	708 ± 588	529 ± 509	$P = 0.02$	$P = 0.4$	$P < 0.001$
Δ 24-h proteinuria	−508 ± 457	−376 ± 577	−545 ± 500	−132 (−257 to −7) $P = 0.003$	−36 (−151 to 79) $P = 0.3$	−169 (−298 to −39) $P < 0.001$
Comparison within group	$P < 0.001$	$P < 0.001$	$P < 0.001$			

Am J Kidney Dis. 2014;64(1):57-65

Secondary Outcome Measures: eGFR

Table 3. Change From Baseline in Serum Creatinine and eGFR Over 24-Week Follow-up Period

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*A manihot* vs Losartan	Combined Treatment vs *A manihot*	Combined Treatment vs Losartan
Comparison of Scr						
0 wk	0.80 ± 0.22	0.82 ± 0.21	0.81 ± 0.23	$P = 0.4$	$P = 0.6$	$P = 0.8$
12 wk	0.81 ± 0.22	0.83 ± 0.22	0.85 ± 0.25	$P = 0.4$	$P = 0.07$	$P = 0.3$
24 wk	0.80 ± 0.20	0.85 ± 0.22	0.82 ± 0.24	$P = 0.05$	$P = 0.3$	$P = 0.4$
ΔScr	−0.005 ± 0.19	+0.03 ± 0.18	+0.01 ± 0.17	−0.03 (−6.94 to 1.21); $P = 0.2$	0.02 (−2.37 to 5.47); $P = 0.4$	−0.02 (−5.15 to 2.53); $P = 0.5$
Comparison within group	$P = 0.7$	$P = 0.1$	$P = 0.4$			
Comparison of eGFR						
0 wk	108 ± 24	106 ± 23	106 ± 24	0.5	0.4	0.9
12 wk	108 ± 23	105 ± 23	105 ± 23	0.2	0.2	0.9
24 wk	109 ± 22	104 ± 25	105 ± 23	0.07	0.1	0.7
ΔeGFR	+1 ± 20	−3 ± 19	−1 ± 18	1.6 (−1 to 9); $P = 0.1$	−1.2 (−8 to 2); $P = 0.2$	0.02 (−6 to 3); $P = 0.9$
Comparison within group	$P = 0.5$	$P = 0.1$	$P = 0.07$			

Am J Kidney Dis. 2014;64(1):57-65

Safety Evaluation

Table 4. Summary of Adverse Events by Treatment Group

	Total	*A manihot*	Losartan	Combined Treatment
Dizziness	1	0	0	1
Nausea	1	1	0	0
Diarrhea	1	0	0	1
Tonsillitis	2	0	0	2
Upper respiratory tract infection	13	4	5	4
Gingivitis	1	0	0	1
Pregnancy during treatment	1	0	1	0
Schizophrenia	1	1	0	0
Elevated white blood cell or neutrophil count	2	0	1	1
Anemia	1	0	1	0
Thrombocytopenia	1	0	0	1
Elevated cholesterol or triglycerides	11	5	2	4
Liver injury	4	3	1	0
Total	40	14	11	15

	Adverse events	P value
HK	9(133)	>0.05
Losartan	10(135)	>0.05
combined	11(136)	>0.05

There were no severe adverse events in any of the 3 groups.

Am J Kidney Dis. 2014;64(1):57-65

nature REVIEWS NEPHROLOGY

RESEARCH HIGHLIGHTS

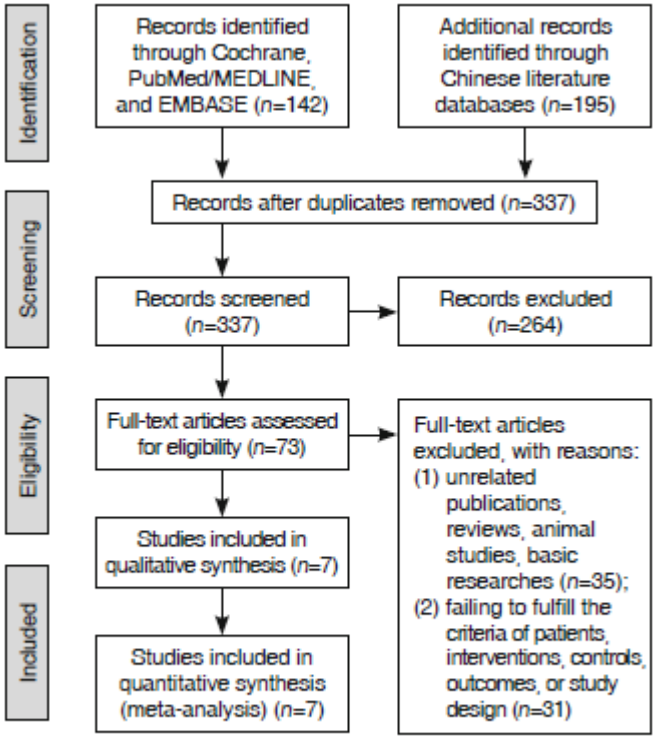
GLOMERULAR DISEASE

Antiproteinuric efficacy of *A. manihot* superior to losartan

"New data from the first randomized controlled trial of the traditional Chinese medicine Abelmoschus manihot suggest that this herb is more effective than the angiotensin-receptor blocker losartan in reducing proteinuria in patients with primary glomerular disease. Standardized traditional Chinese medicines such as A. manihot may have a bright future in the treatment of CKD"

Nature Reviews Nephrology 10, 300

Efficacy and Safety of Flos Abelmoschus Manihot on Type 2 Diabetic Nephropathy: A Systematic Review



First author (Year)	Groups	Sample size (Case)	Age (Year)	Male [Case (%)]	Proteinuria (mg/24 h)
Yu (2011)[41]	*Flos A. manihot* plus candesartan	29	69 (42–82)	–	1570 ± 670
	Candesartan	29		–	1490 ± 560
Ding (2011)[42]	*Flos A. manihot* plus alprostadil	64	50 ± 13	44 (69)	1580 ± 540
	Alprostadil	60	51 ± 13	36 (60)	1650 ± 720
Li (2009)[43]	*Flos A. manihot* plus captopril and candesartan	30	54 (42–71)	–	885 ± 150
	Captopril plus candesartan	31		–	876 ± 235
Li (2009)[44]	*Flos A. manihot* plus fosinopril	40	52 (42–65)	26 (65)	1100 ± 300
	Fosinopril	40		24 (60)	1200 ± 400
Guan (2008)[45]	*Flos A. manihot* plus captopril/enalapril	40	45 ± 12	22 (55)	1460 ± 650
	Captopril/enalapril	40	46 ± 13	21 (53)	1410 ± 630
Li (2007)[46]	*Flos A. manihot* plus benazepril	30	41 ± 12	14 (47)	1480 ± 680
	Benazepril	30	42 ± 12	16 (53)	1450 ± 690
Yu (1995)[47]	*Flos A. manihot* plus captopril	35	55 (44–78)	23 (66)	890 ± 310
	Captopril	33	54 (45–76)	21 (64)	860 ± 330

Seven trials (531 patients) were included

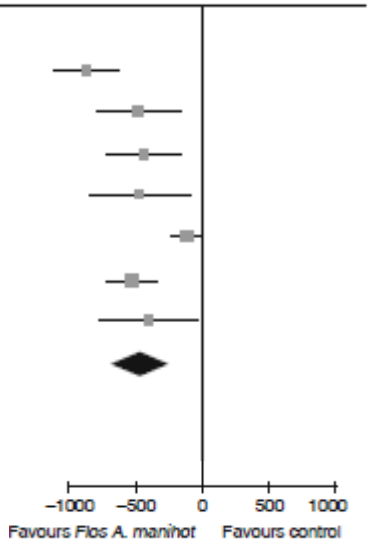
Chin J Integr Med 2015 Jun;21(6):464-472

Flos A. manihot signifificantly decreased proteinuria

	Flos A. manihot			Control				MD	MD
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Total analysis (irrespective of co-interventions)									
Ding LP 2011[42]	640	430	64	1230	510	60	14.7%	−590.00 [−756.59, −423.41]	
Guan ZX 2008[45]	590	420	40	920	510	40	13.5%	−330.00 [−534.74, −125.26]	
Li HY 2009[44]	600	500	40	900	300	40	14.2%	−300.00 [−480.70, −119.30]	
Li YL 2007[46]	650	440	30	970	540	30	12.1%	−320.00 [−569.26, −70.74]	
Li ZF 2009[43]	499	133	30	579	149	31	17.1%	−80.00 [−150.82, −9.18]	
Yu JY 1995[47]	410	260	35	770	240	33	16.1%	−360.00 [−478.85, −241.15]	
Yu ZW 2011[41]	740	480	29	1010	460	29	12.3%	−270.00 [−511.97, −28.03]	
Subtotal (95% CI)			268			263	100.0%	−317.32 [−470.48, −164.17]	

Heterogeneity: Tau^2=34354.43; Chi^2=41.85, df=6 (*P*<0.00001); I^2=86%

Test for overall effect: *Z*=4.06 (*P*<0.0001)



High-quality RCTs are urgently needed to confirm the effect of Flos A. manihot!

Chin J Integr Med 2015 Jun;21(6):464-472

U.S. National Library of Medicine

ClinicalTrials.gov

NCT03016832

A Randomized, Double-blind, Parallel-controlled, Multi-center Clinical Trial of HuangKui Capsule to Treat Diabetic Kidney Disease

Subjects:9 hospitals,414 subjects:Meet the diagnostic criteria of type 2 diabetes and diatetic kidney disease, 300mg/g ≤ ACR <2000mg/g, eGFR>30 mL/min, Glycated hemoglobin ≤8.5%

intervention: Huangkui arm(n=138), irbesatan arm(n=138) and combined treatment arm(n=138).

Primary objective: To evaluate the efficacy of HuangKui capsule on ACR.

Secondary objective: To evaluate the efficacy of HuangKui capsule on 24-hour urinary protein reduce PCR-increase eGFR, improve micro-inflammatory state, and improving Traditional Chinese medicine clinical efficacy

Huangkui capsule attenuates renal fibrosis in diabetic nephropathy rats through regulating oxidative stress and p38MAPK/Akt pathways, compared to α-lipoic acid

SD rats via unilateral nephrectomy and intraperitoneal injection of streptozotocin.

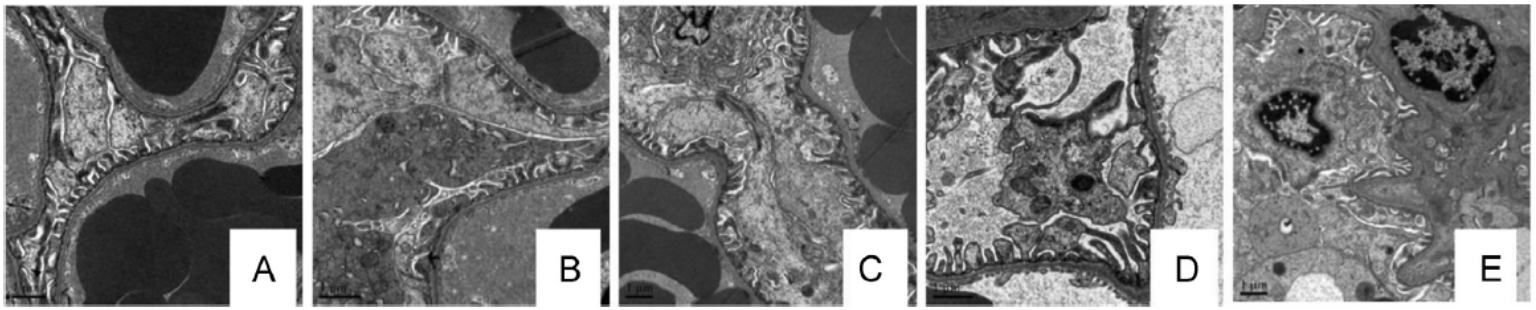
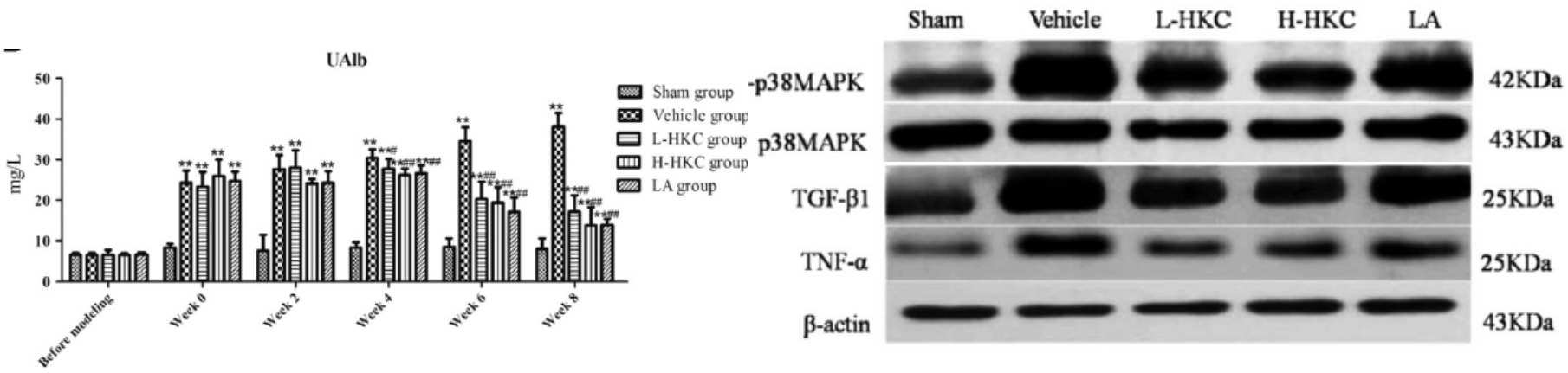
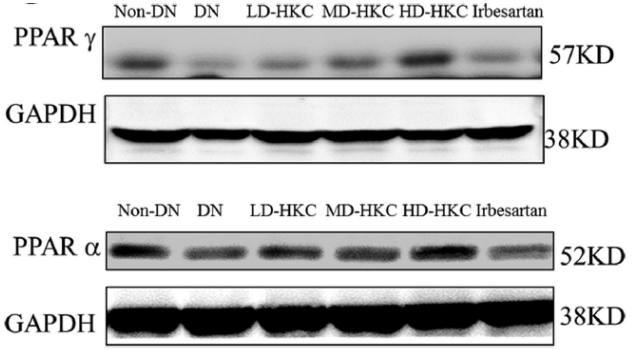


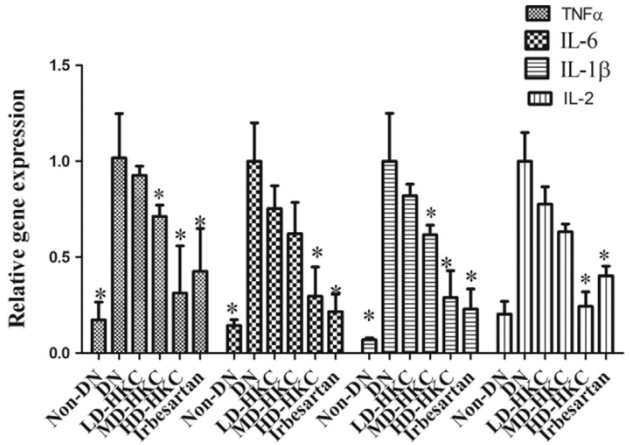
Fig. 7. Podocyte shape among 5 groups (original magnification, 5000 ×). (A)=Sham group; (B)=Vehicle group; (C)=L-HKC group; (D)=H-HKC group; (E)=LA group.

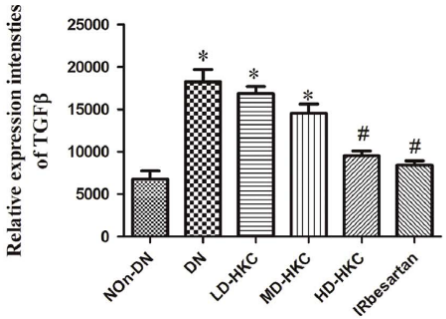


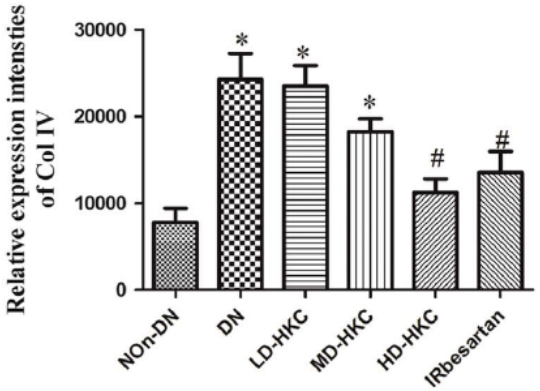
Journal ofEthnopharmacology173(2015)256–265

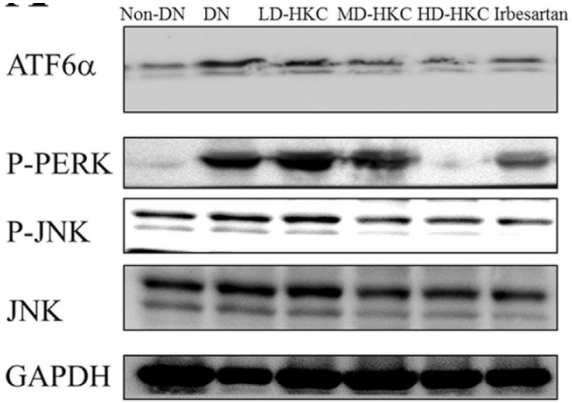
Huangkui capsule,anextract from Abelmoschusmanihot (L.) medic, improves diabetic nephropathy via activating peroxisomeproliferator–activatedreceptor(PPAR)-α/γ and attenuating endoplasmic reticulum stress in rats





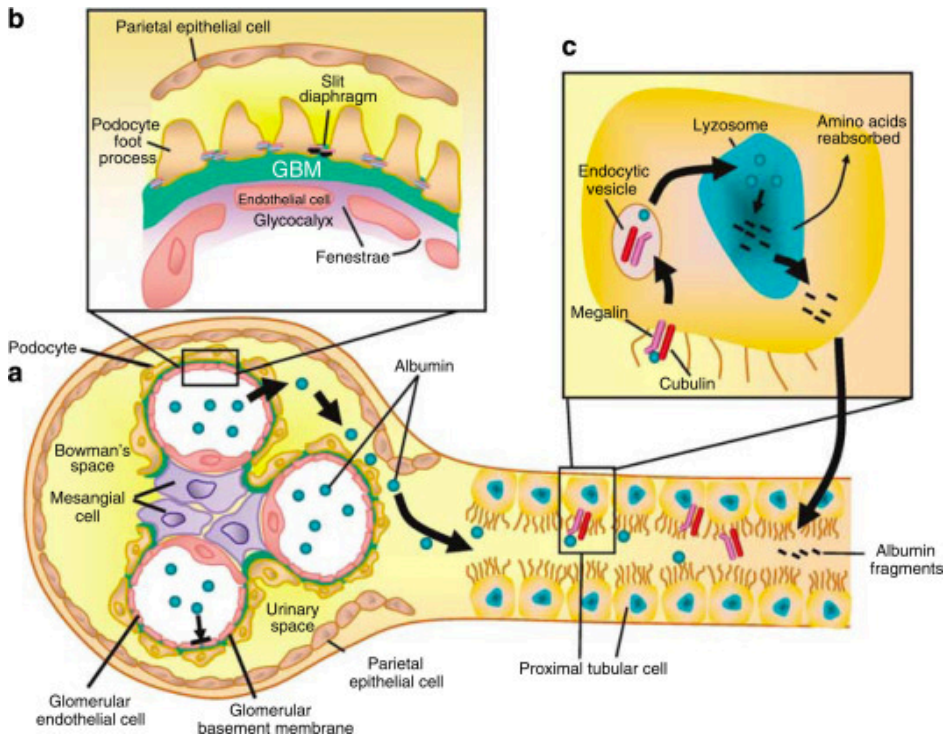






Journal of Ethnopharmacology 189(2016)238–249

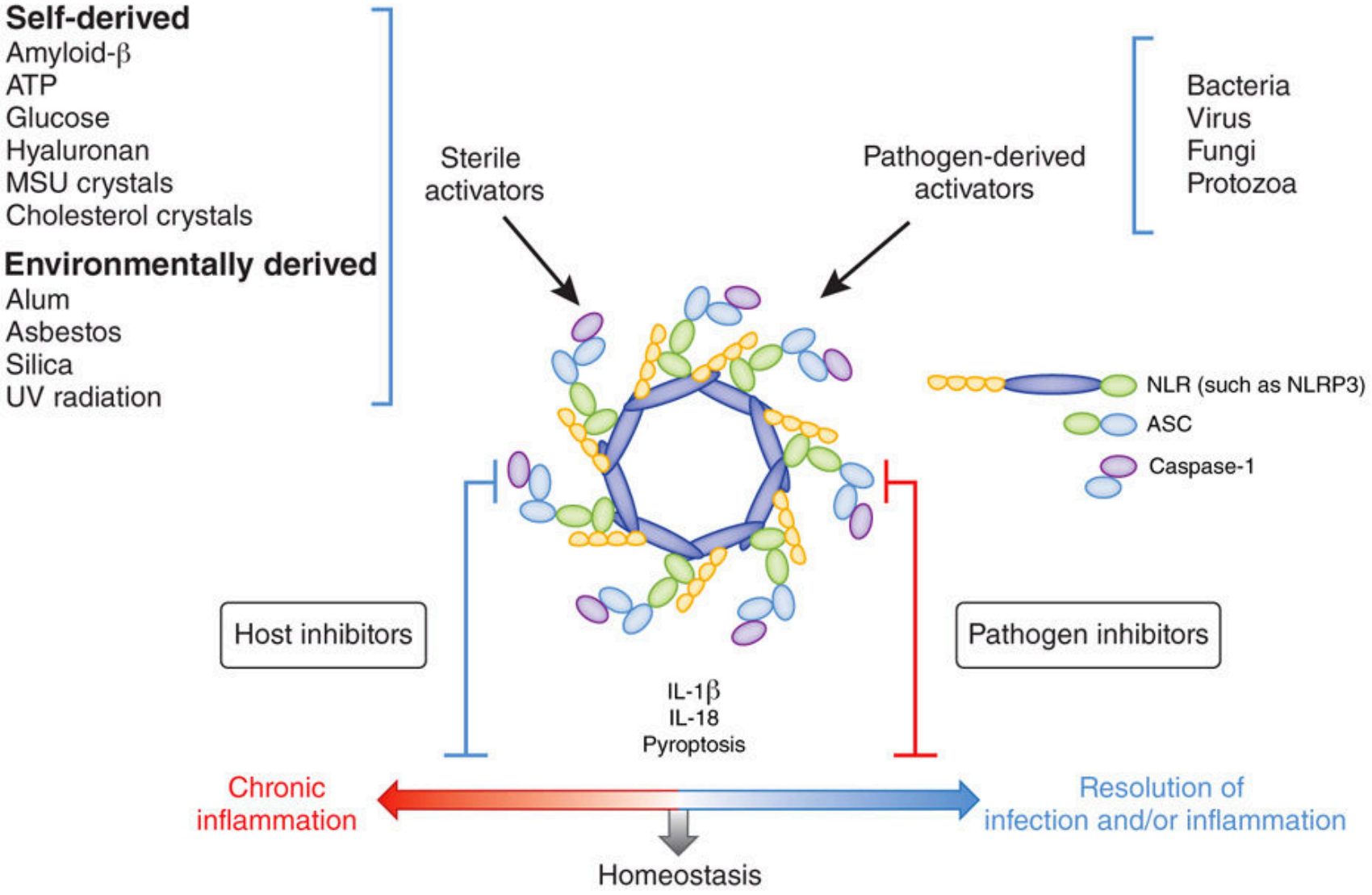
Schematic representation of events underlying progressive glomerular and tubulointerstitial injury of proteinuric nephropathies



- Inflammasome
- ER stress
- apoptosis
- complement
- autophage
- ….

Nephrol Dial Transplant (2015) 30: 706–712

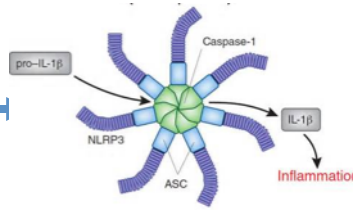
Inflammasome

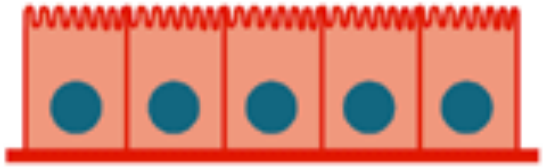


Research Hypothesis

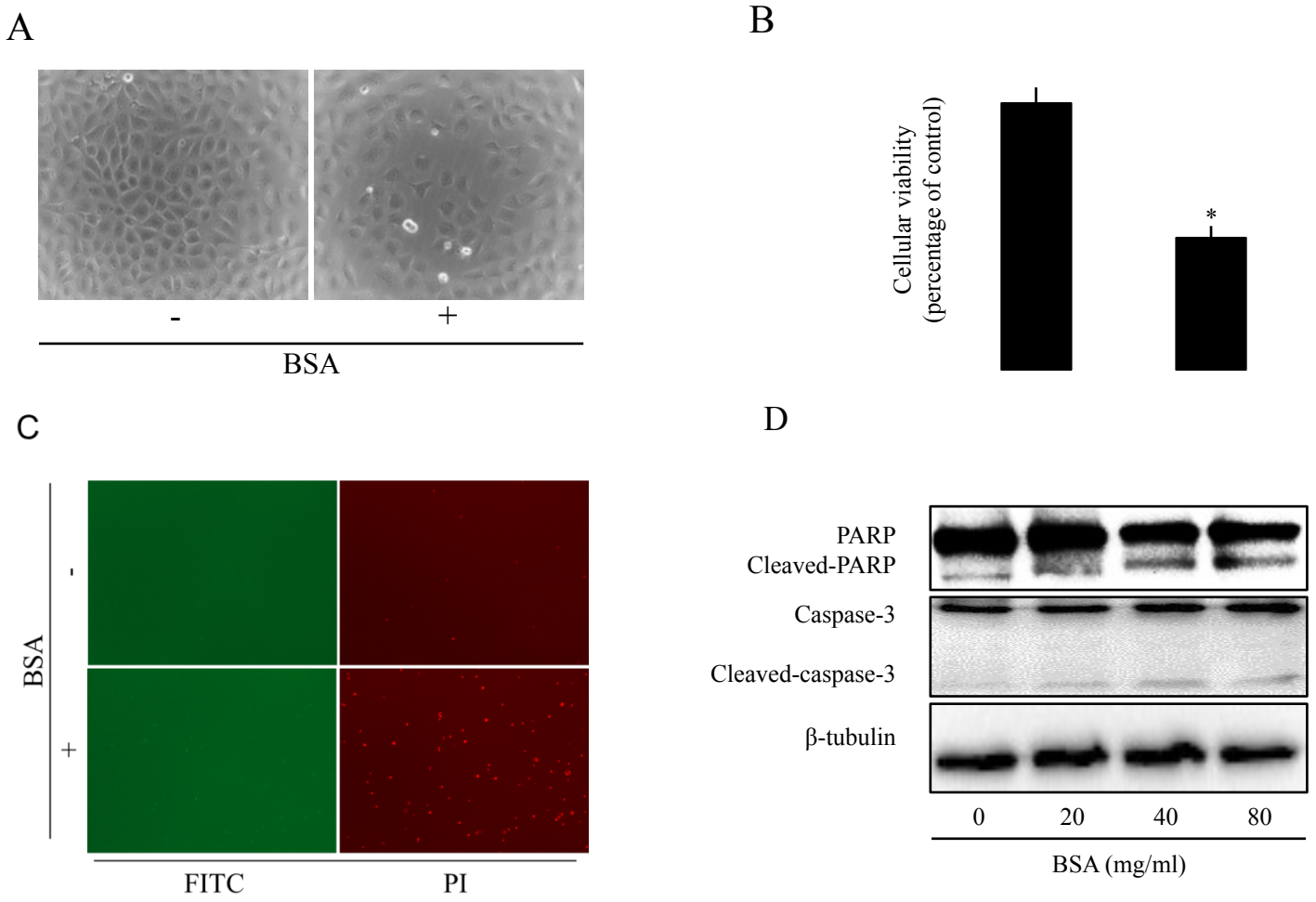
albumin overload

Total flavonoids



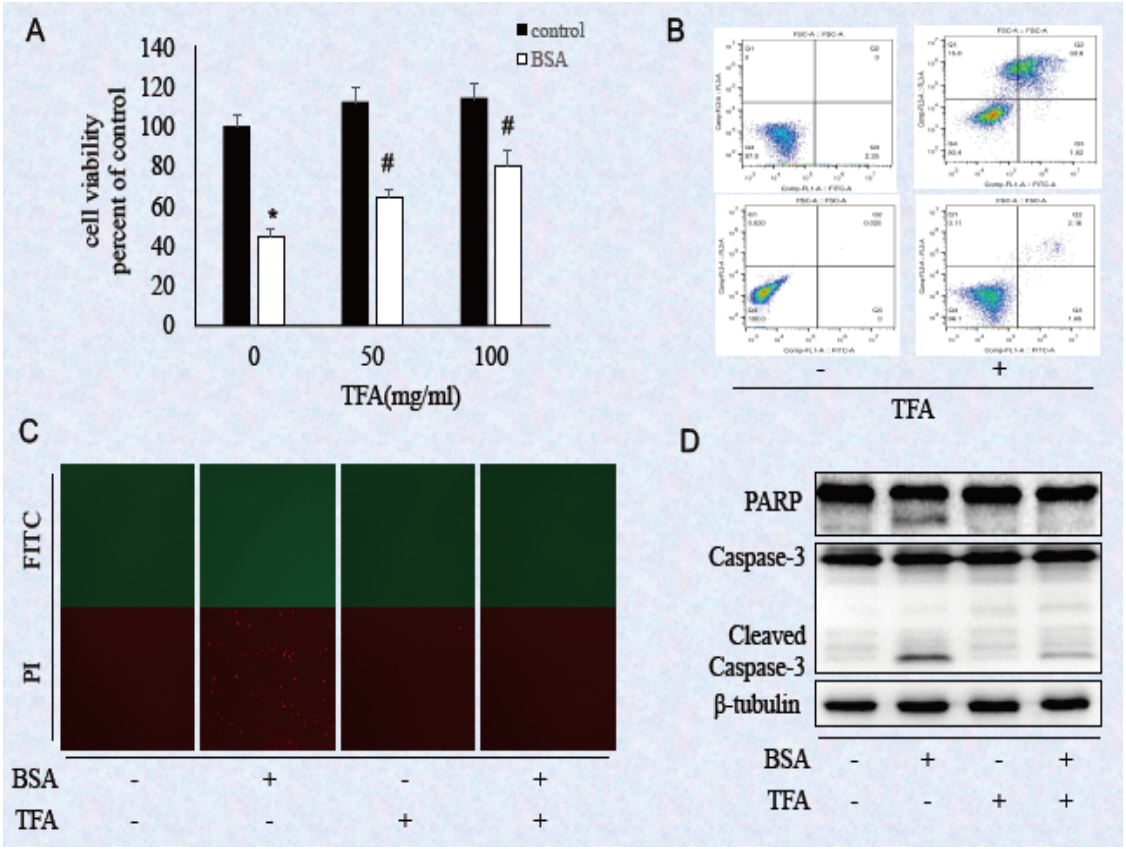


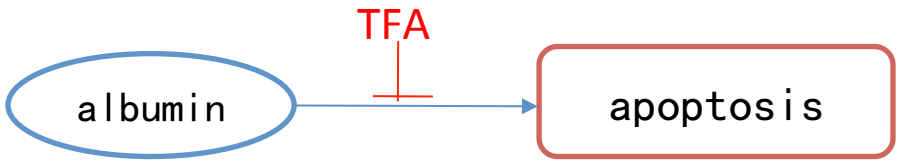
Albumin overload induced renal tubular cell injury



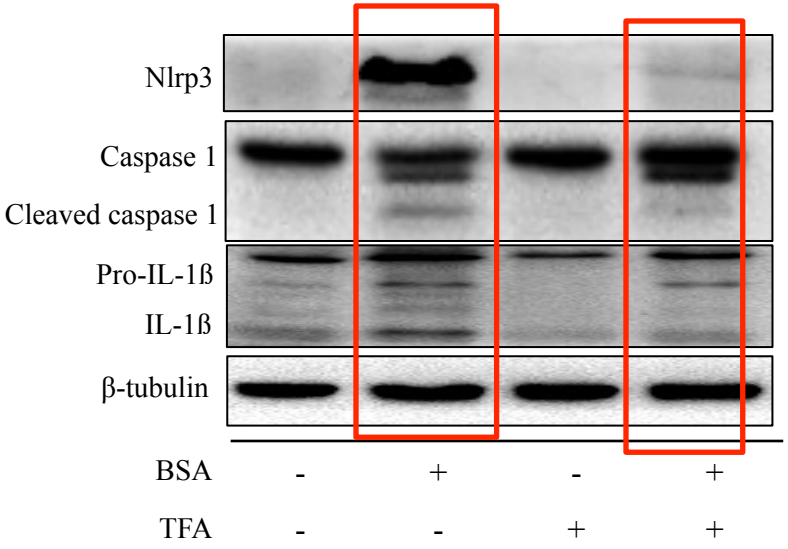
albumin → apoptosis

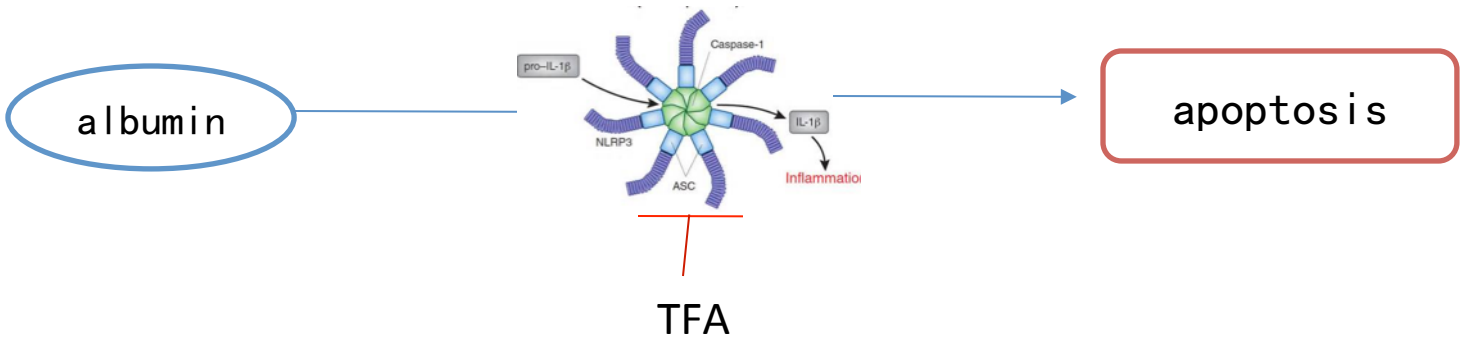
TFA ameliorated Albumin overload-triggered apoptosis





NLRP3 inflammasome was implicated in the role of TFA in BSA-induced cell injury

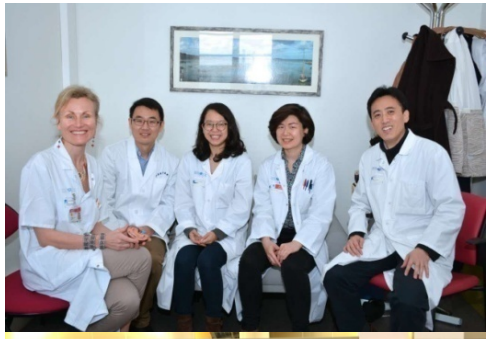


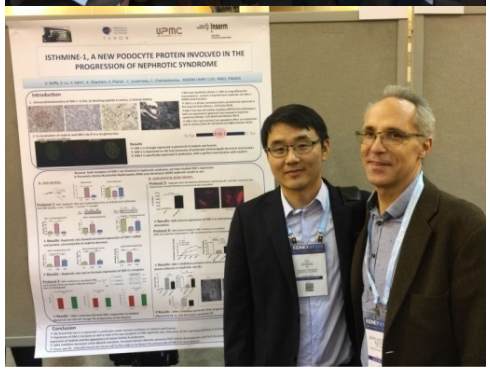


Summary

1. the use of Flos A.manihot to treat CKD has a long history in China
2. The main bioactive constituents of Flos A. manihot are flavonoids
3. the mechanisms underlying the renoprotective effects of flavonoids need to be elucidated
4. Designing and conducting high-quality RCTs with an adequate sample size and long enough follow-up to test the efficacy and safety of Flos A. manihot are of considerable importance..

Acknowledgement





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Collaboration is key to advance shared goals.
- Eleanor Lederer, MD, FASN
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