

中医药治疗糖尿病肾病

卫计委中日友好医院 李平

汇报提纲

中医药治疗糖尿病肾病文献分析

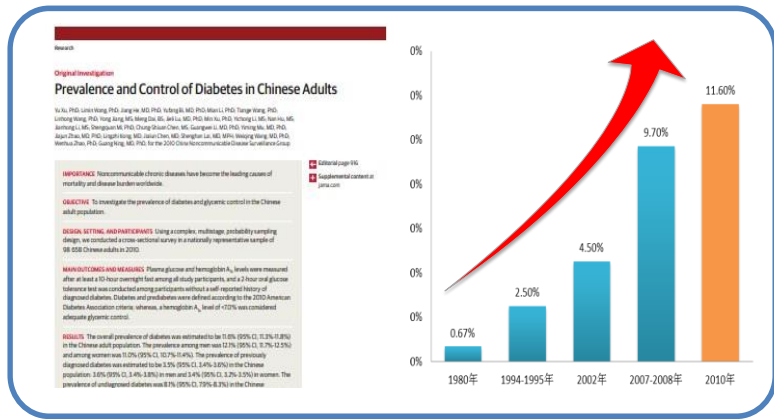
中医药治疗现状梗概

中药治疗糖尿病肾病机制研究

糖肾方临床研究介绍

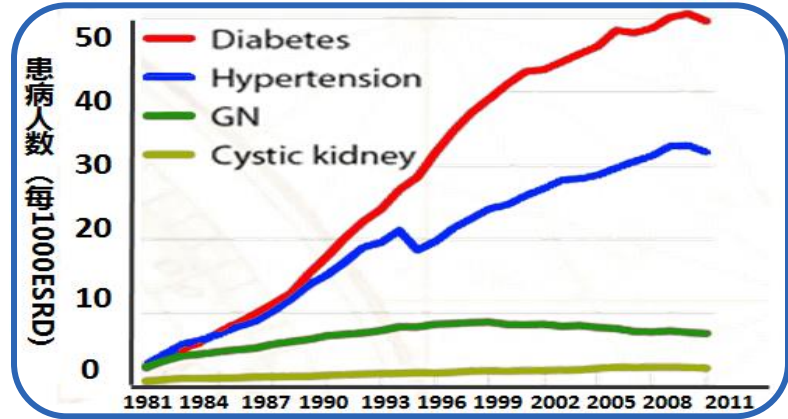
糖尿病肾病防治面临的严峻挑战

我国已成为糖尿病大国



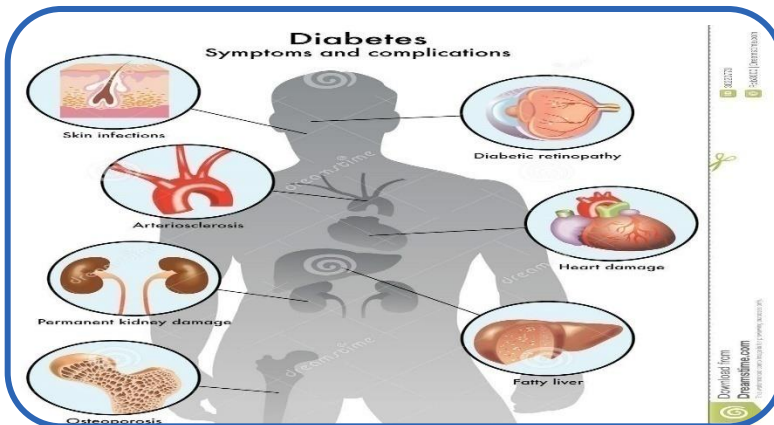
JAMA, 2013, 310(9):948-959

糖尿病肾病为发达国家ESRD的首位病因

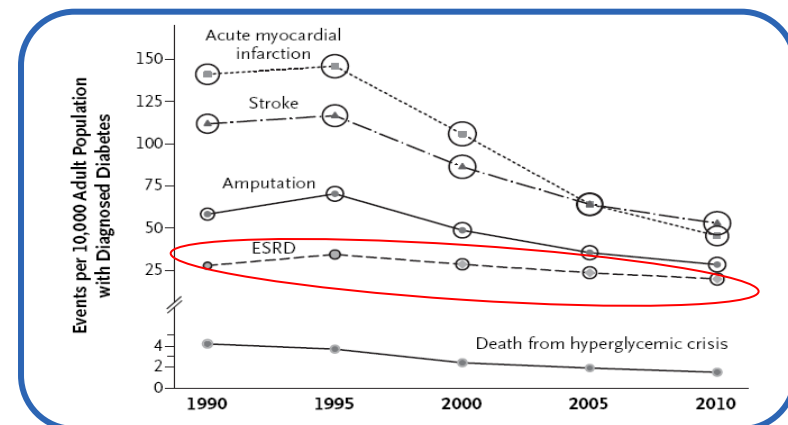


USRDS 2013 ADR

糖尿病肾病并发多器官损害



20年来唯独糖尿病肾病致死率未见改善!



N Engl J Med. 2014, 370(16):1514-23

文献检索策略

■ 数据库：中国知网学术文献总库（CNKI）、万方数据库（Wanfang data）、中文科技期刊全文数据库（VIP）、中国生物医学文献数据库（CBM）、PubMed、Cochrane Library和EMBASE七个数据库。

■ 时间：建库-2015年8月15日

■ 中文检索词：糖尿病肾病、糖尿病肾脏疾病、消渴肾病、糖尿病肾小球硬化症、糖尿病肾小球疾病、中医药、中西医、中草药、草药、汤药、注射液、中成药、植物药、中药提取物、外治、针灸、针法、灸法、刺法、刮痧、拔罐、中药灌肠、随机、对照、系统评价、meta分析。

■ 英文检索词：diabetic kidney disease、diabetic renal disease、diabetic nephropathies、diabetic renopathy、diabetic proteinuria、diabetic albuminuria、diabetic microalbuminuria、diabetic macroalbuminuria、herbal medicine、alternative medicine、complementary medicine、Chinese medicine、Chinese herbal medicine、Traditional Chinese medicine、Chinese medicine、alternative medicine、Randomized、clinical trial。

✓ 根据不同资料库的特征分别进行主题词联合自由词、关键词进行综合检索。

CNKI ; CBM
Wanfang ; VIP

Pubmed
Cochrane library
Embase

共检索文献 (n=5891)

排除：
重复文章(n=2506)
报纸文章(n=60)
会议论文(n=106)
学位论文(n=226)
非临床试验(n=111)
综述类(n=295)

初步纳入文献
(n=2587)

剔除：
重复发表(n=23)
研究对象DKD分期与尿蛋白水平不符(n=498)
干预措施不符合(n=611)
观察指标不符合(n=422)
Jadad评分为0分(n=101)

最终纳入文献
(n=932)

文献方法学质量评价

采用改良Jadad评分法评价RCT方法学质量。
0-3分视为低质量，4-7分视为高质量。

条目	描述及说明	分值	评分
1) 随机序列的产生			
恰当	计算机产生的随机数字或类似方法	2分	
不清楚	随机试验但未描述随机分配的方法	1分	
不恰当	采用交替分配的方法如单双号	0分	
2) 随机化隐藏			
恰当	中心或药房控制分配方案、或用序列编号一致的容器、现场计算机控制、密封不透光的信封或其他使临床医生和受试者无法预知分配序列的方法	2分	
不清楚	只表明使用随机数字表或其他随机分配方案	1分	
不恰当	交替分配、病例号、星期日数、开放式随机号码表、序列编码信封以及任何不能防止分组的可预测性的措施	0分	
未使用	-	0分	
3) 盲法			
恰当	采用了完全一致的安慰剂或类似方法	2分	
不清楚	试验陈述为盲法，但未描述方法	1分	
不恰当	未采用双盲或盲的方法不恰当，如片剂和注射剂比较	0分	
4) 撤出与退出			
	描述了撤出或退出的数目和理由	1分	
	未描述撤出或退出的数目或理由	0分	
			总计：

Jadad评分结果

Jadad评分	篇数	百分比
7~4	10	1.07 %
3	66	7.08 %
2	42	4.51 %
1	814	87.34 %

目前文献的特点

- ✓ 研究设计欠规范
- ✓ 研究方法学质量较差
- ✓ 样本量小，没有计算依据
- ✓ 试验报告不规范
- ✓ 结局指标是替代指标，没有硬终点



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✓ RCT类研究文献

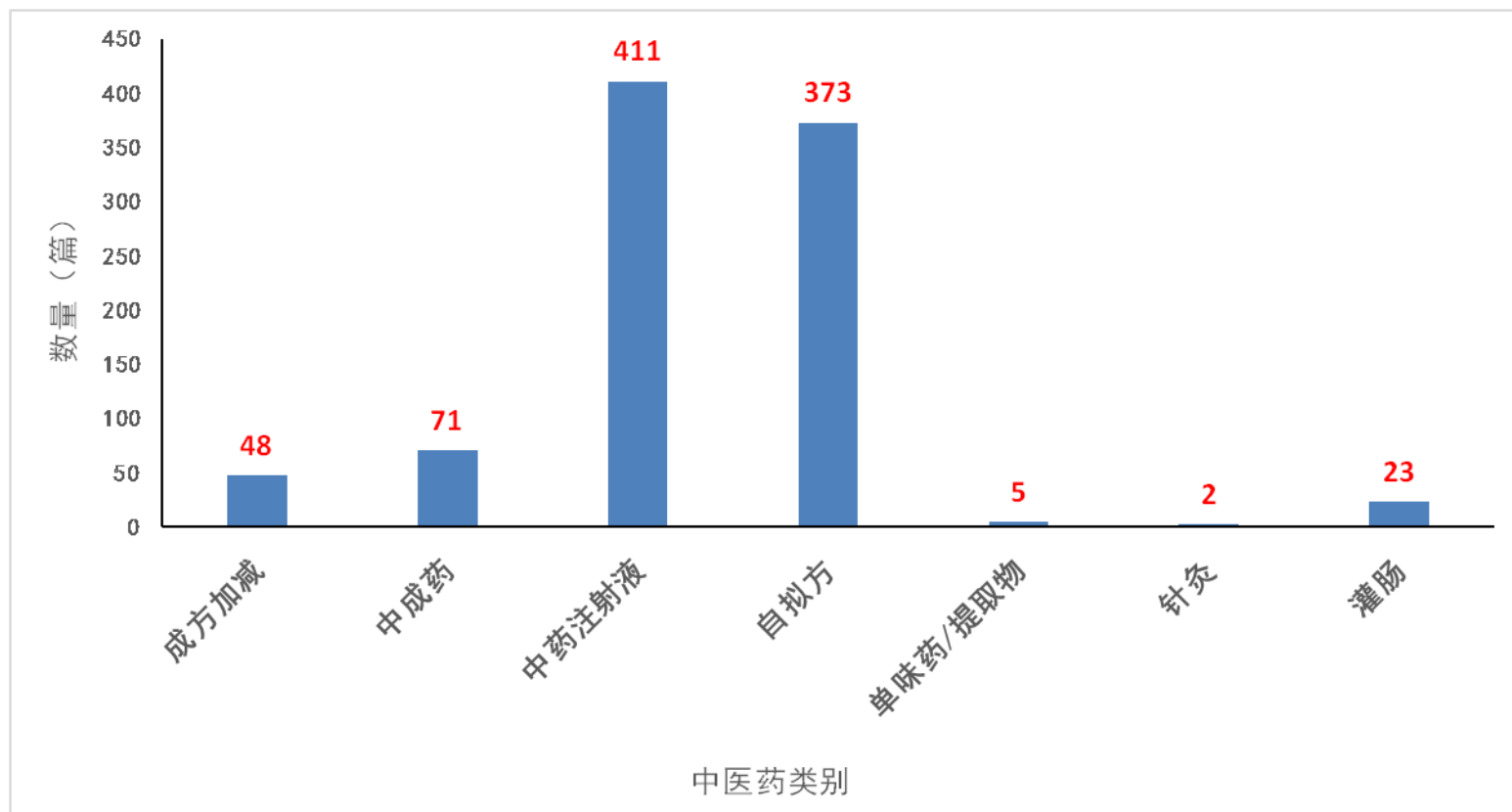
均是**加载设计**：在西医常规治疗基础上，使用中医药。

其中使用ACEI/ARB类情况如下：

	篇数	百分比
明确指出使用ACEI/ARB类药物	480	51.5%
明确指出不使用ACEI/ARB类药物	60	6.4%
未明确说明是否使用	392	42.1%

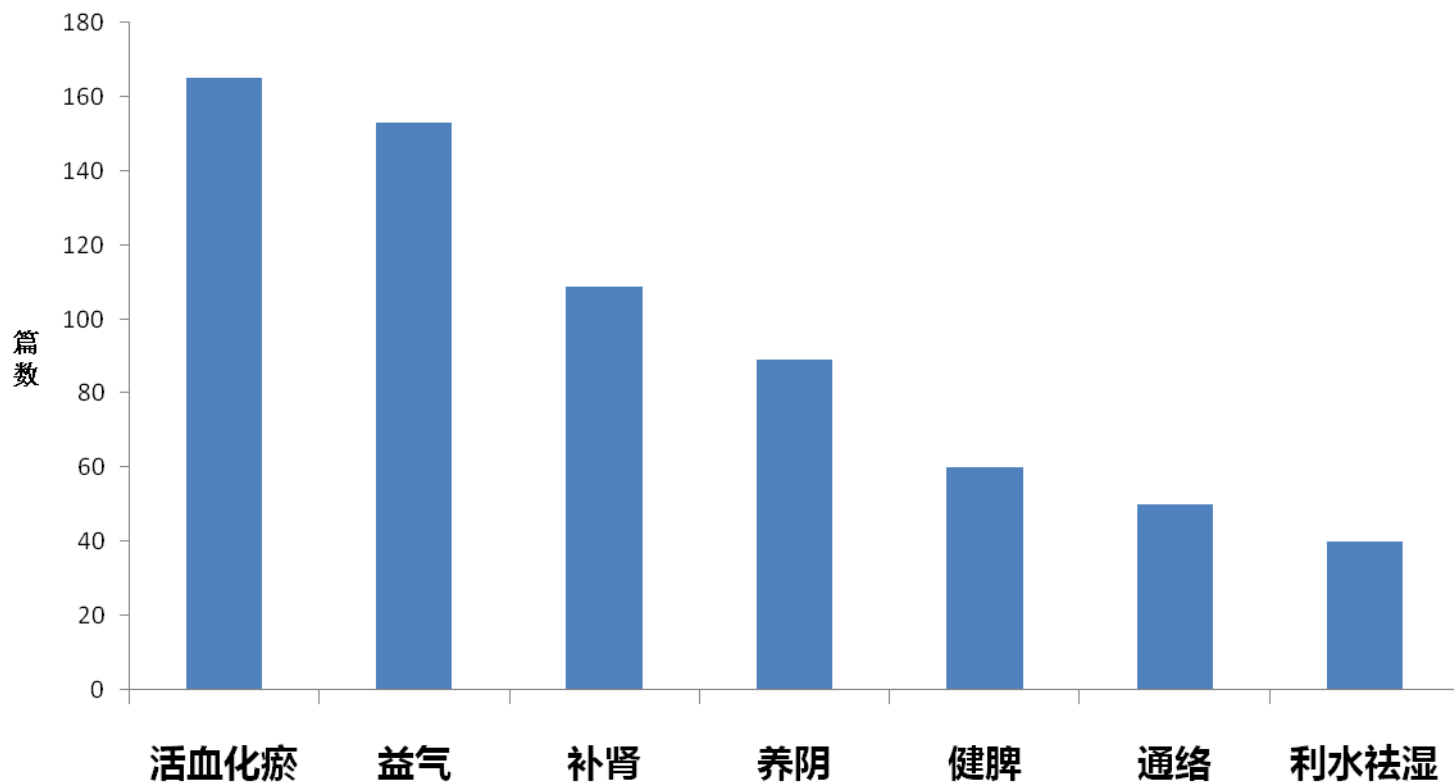
中医药治疗现状分析

✓ 所采用的中医药干预措施情况为：



中医药治疗治则

✓ 根据文献中明确指出治则的文献，频次大于40次的治则为：



国际注册的糖肾临床试验

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Semi-structured Chinese Medicine Treatment as an Adjuvant Therapy to the Management of Diabetic Nephropathy

This study is not yet open for participant recruitment. (see [Contacts and Locations](#))

Verified June 2015 by The University of Hong Kong

Sponsor:

The University of Hong Kong

ClinicalTrials.gov Identifier:

NCT02488252

First received: June 25, 2015

Last updated: June 29, 2015

Last verified: June 2015

A: spleen and kidney Qi deficiency, B: spleen and kidney Yang deficiency, C: spleen and kidney Qi and Ying deficiency, D: liver and kidney Ying deficiency, E: Ying and Yang deficiency

Drug: Semi-individualised **Chinese Medicine** treatment

A: Panax ginseng, Atractylodes macrocephala, Pinellia ternate, Pericarpium citri reticulatae, Herba Pogostemonis, Glycyrrhiza uralensis, Rehmannia-6 decoction

B: Cortex magnoliae officinalis, Atractylodes macrocephala, Common Floweringquince Fruit, Common Vladimiria Root, Tsaoko Amomum Fruit, Palmae Fruit, Radixaconiti laterlis perparata, Zingiber officinale Rosc., Glycyrrhiza uralensis, Rehmannia-8 decoction

C: Root of Pilose Asiabell, Astragalus membranaceus, Rehmannia glutinosa, Common Macrocarpium Fruit, Dioscorea opposita, Barbary Wolfberry Fruit, Cortex eucommiae,

Chinese Angelica, Glycyrrhiza uralensis

D: Rehmannia-6 decoction, Fructus Ligustri Lucidi, Yerbadetajo Herb

E: Rehmannia-8 decoction, Fructus Ligustri Lucidi, Yerbadetajo Herb

目前我国药监局注册的临床试验



国家食品药品监督管理总局药品审评中心

CENTER FOR DRUG EVALUATION, CFDA

CFDA CDE

药物临床试验登记与信息公示平台

序号	登记号	试验状态	药物名称	适应症	试验通俗题目
1	CTR20150138	进行中 招募完成	厄贝沙坦片	本品适用于治疗原发性高血压，合并高血压的2型糖尿病肾病的治疗。	厄贝沙坦片 单次空腹给药人体生物等效性试验
2	CTR20140661	进行中 招募中	Atrasentan (ABT-627)	糖尿病肾病	Atrasentan的糖尿病肾病研究
3	CTR20140437	进行中 招募完成	厄贝沙坦片	治疗原发性高血压。合并高血压的2型糖尿病肾病的治疗。	厄贝沙坦片人体生物等效性试验
4	CTR20132925	进行中 招募中	芪黄胶囊	糖尿病肾病	芪黄胶囊III期临床试验
5	CTR20132259	已完成	糖降肾康颗粒	糖尿病肾病	糖降肾康颗粒3期临床实验研究
6	CTR20132102	已完成	冻干重组人胰岛素原C肽	1型糖尿病肾病	冻干重组人胰岛素原C肽单次给药药代动力学试验
7	CTR20132101	已完成	冻干重组人胰岛素原C肽	1型糖尿病肾病	冻干重组人胰岛素原C肽单次给药安全耐受性试验

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糖肾方临床研究介绍

Example 1

糖肾方 Tangshen Formula

- Tangshen Formula is developed on the basis of the three senior doctors' experiences, which includes seven herbal drugs
- Replenishing Qi and Yin and Removing blood stasis

(君)

黄芪

甘温，益气生津，利水消肿

补肺脾之气

(臣)

生地

甘寒，清热凉血，养阴生津

滋肝肾之阴

山萸肉

酸温，补益肝肾，生津止渴

三七

甘温，化瘀止血；活血定痛

活血通络不伤正
瘀血去而新血生

(佐)

熟大黄

苦寒，泻热降浊，逐瘀通经

鬼箭羽

辛寒，破血通经，解毒消肿

枳壳

辛温，理气行滞，化痰消积

防补药之滋腻
助动药之通络

益气养阴、活血通络



Prof. Zhu Shen-Yu

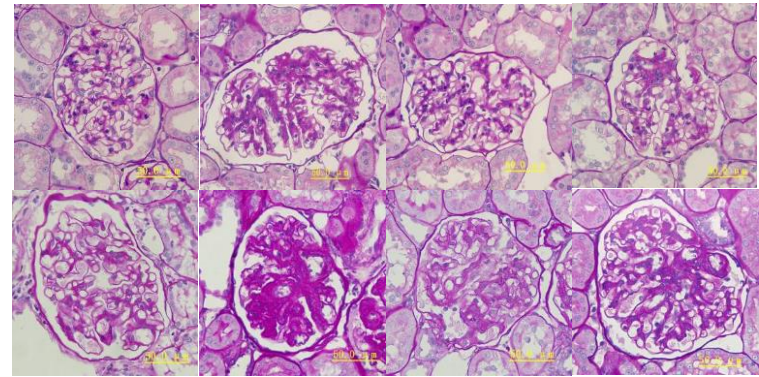
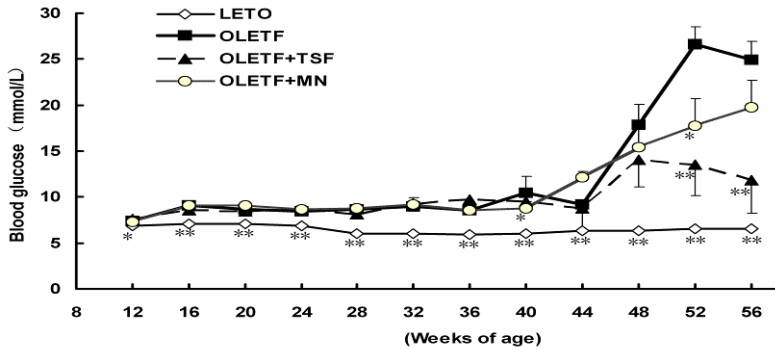


Prof. Shi Zheng-Sheng

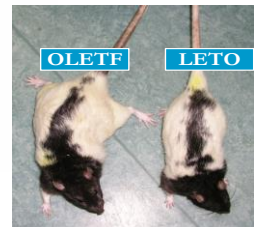
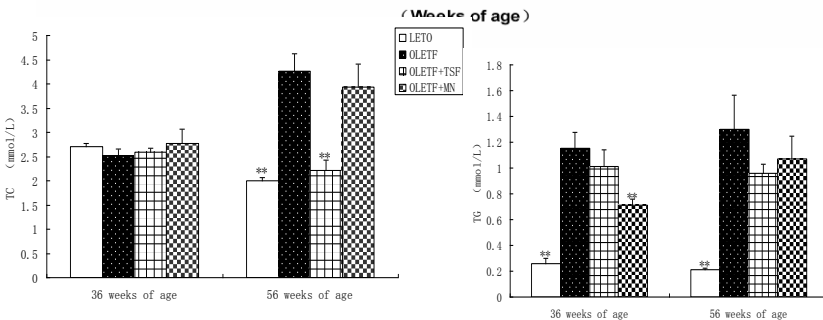
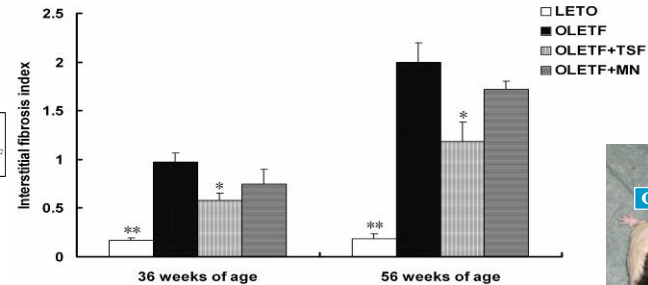
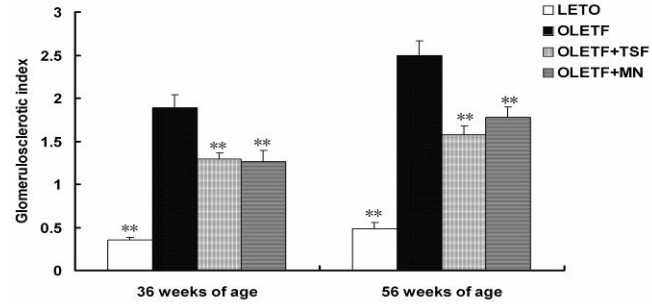
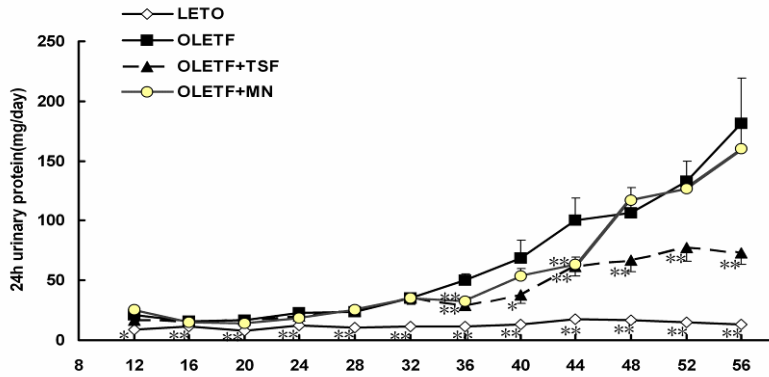


Prof. Lv Ren-He

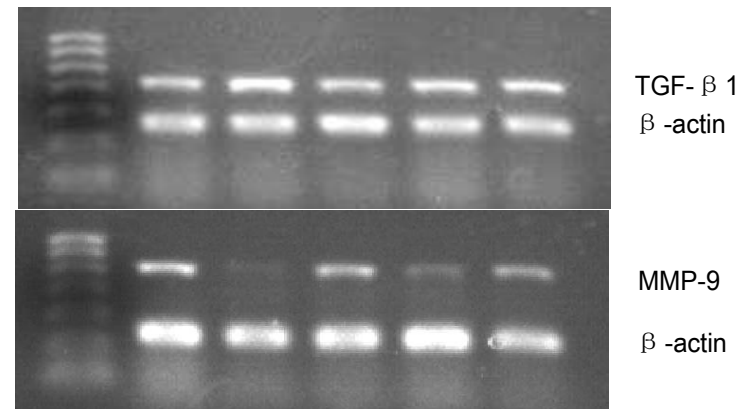
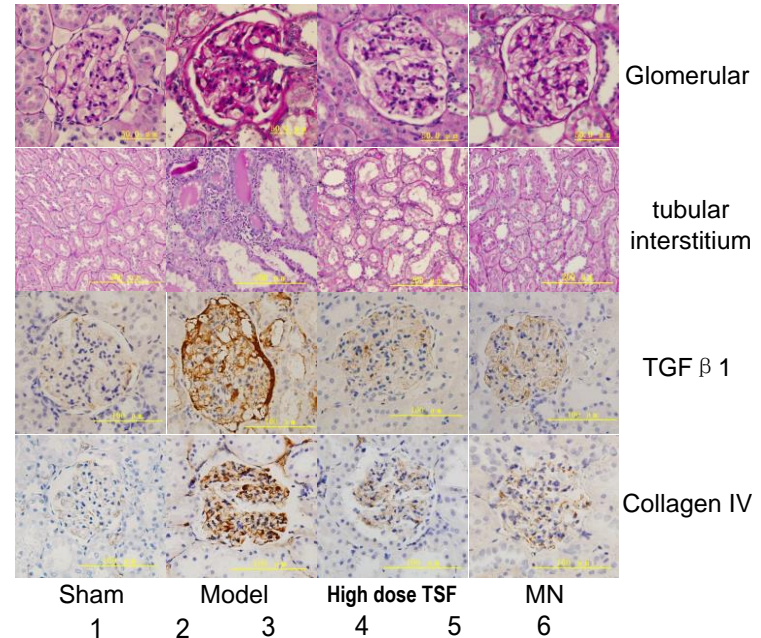
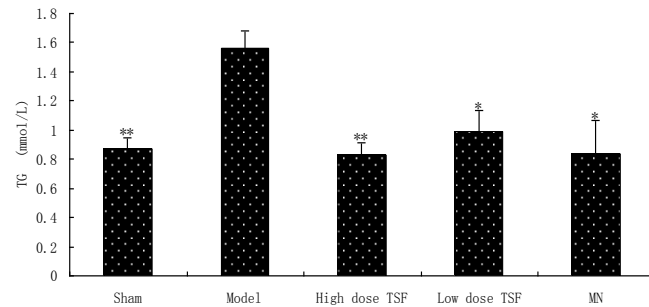
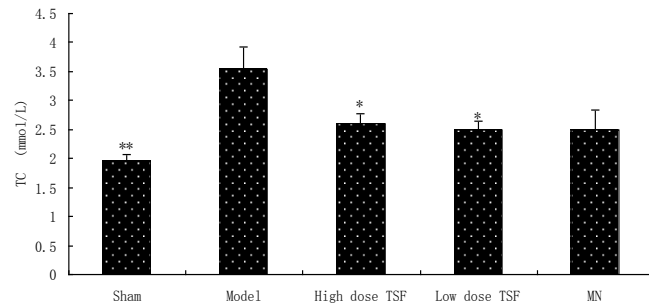
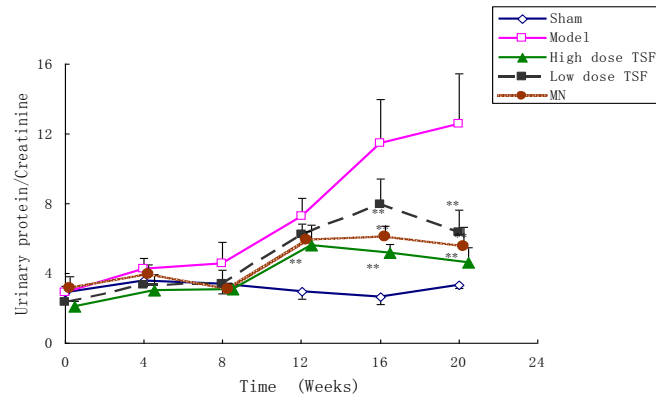
Effect of Tangshen Formula on type 2 DN rats (OLETF)



LETO OLETF OLETF+TSF OLETF+MN



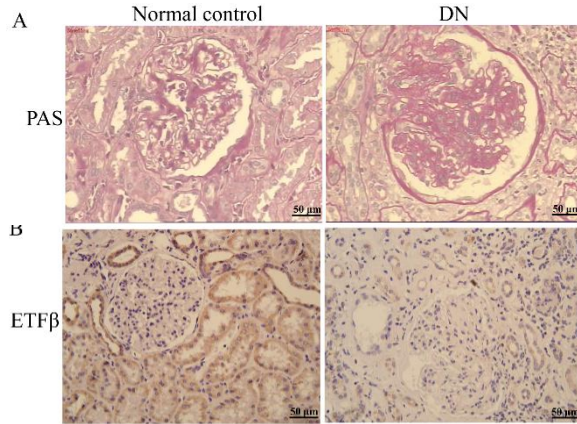
Effect of Tangshen formula on DN rats induced by STZ



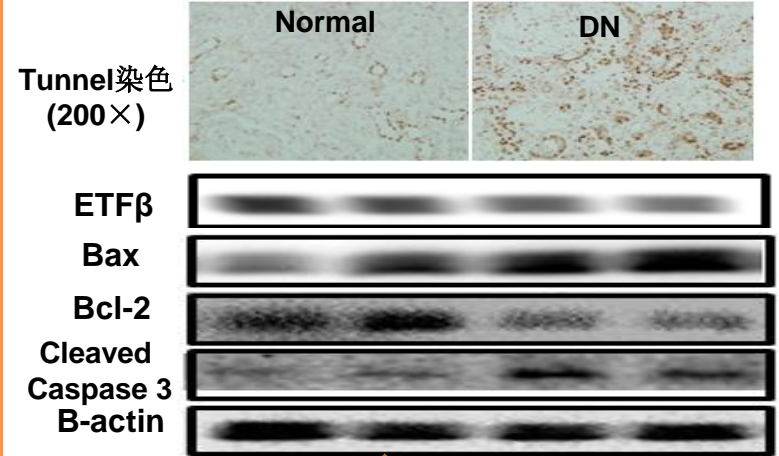
1. DNA Marker 2. Sham 3. Model
4. High dose TSF 5. Low dose TSF 6. MN

糖尿病肾病肾小管损伤早期标志物——ETFβ

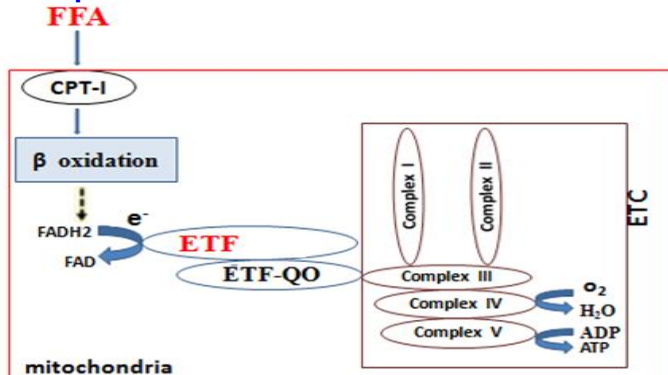
1. DN临床肾活检样本发现ETFβ表达下调



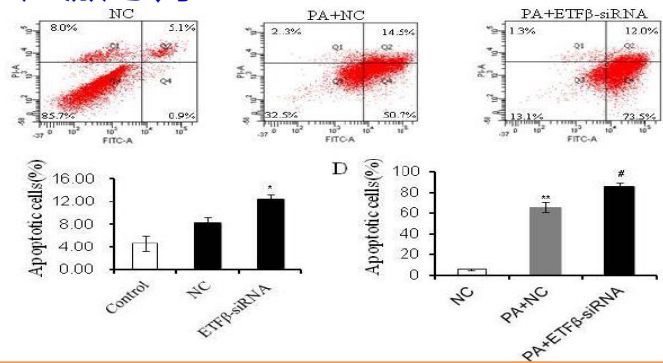
4. 与TEC凋亡密切相关



2. ETFβ参与线粒体氧化应激



3. ETFβ敲降导致肾小管上皮细胞(TEC)氧化应激与凋亡



Example 2

柴黄益肾颗粒

Chaihuang-Yishen granule (CHYS)

- developed on the combination of the modern research with senior doctors' experiences
- includes seven herbal drugs: *bupleurum root*, *astragalus membranaceus*, *angelica sinensis*, *dioscorea niponica*, *polyporus umbellatos* and *pyrrosia petiolosa*
- **Replenishing Qi, Removing blood stasis**
- **Activating Qi, Discharging Water**



Radix stellariae
柴胡



Astragalus membranaceus
黄芪

Active chemical ingredients of CHYS

Herbal components	Dosage (mg/kg)	Main active ingredients
Bupleurum chinense	0.18	Saikosaponin-a Saikosaponin-b2 Saikosaponin-c Saikosaponin-d
Astragalus mongholicus	0.24	Astragaloside 1
Angelica sinensis	0.14	Ferulic acid Succinic acid Adenine
Dioscorea niponica	0.18	Diosgenin Trillin
Polyporus umbellatos	0.18	Ergosterol Biotin
Pyrrrosia petiolosa	0.18	Isomangiferin

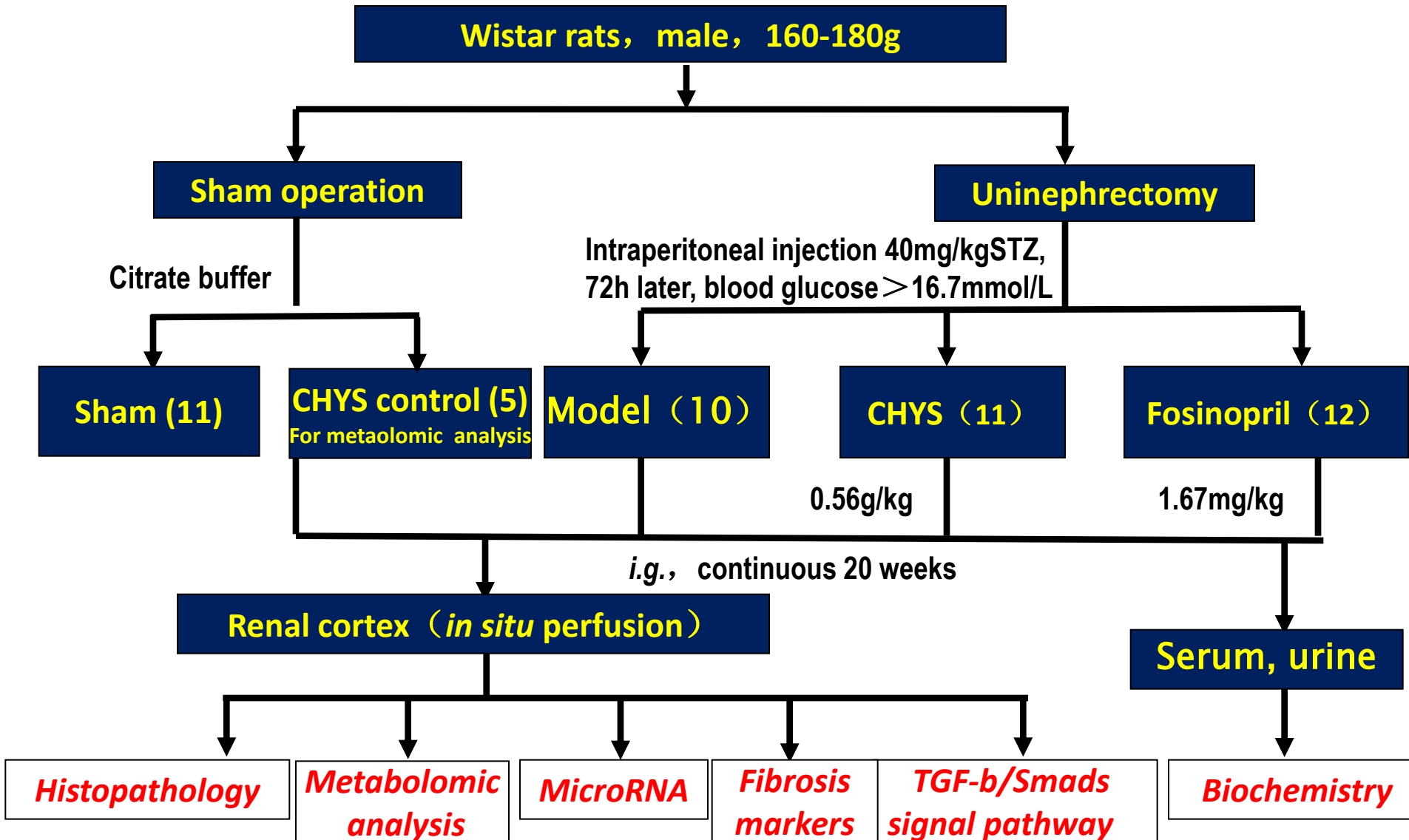


Angelica Sinensis
当归



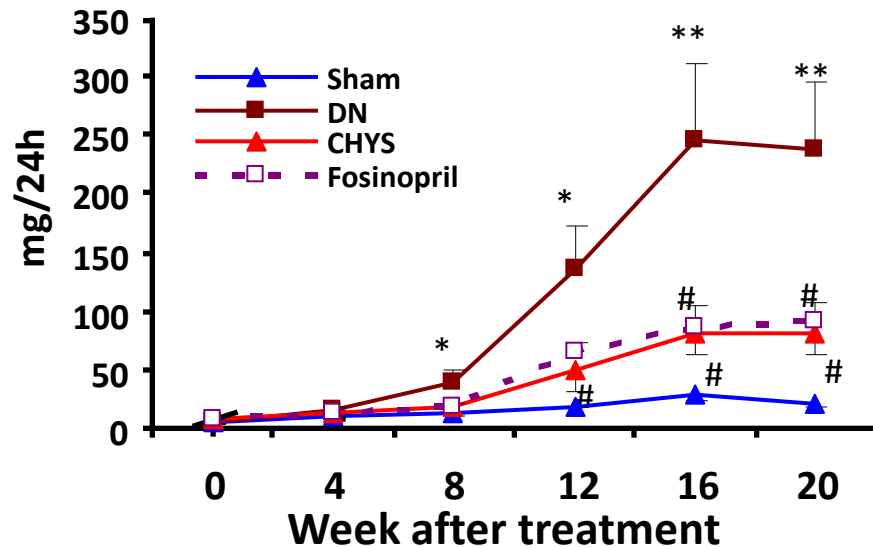
Hirude nipponica
水蛭

Study design

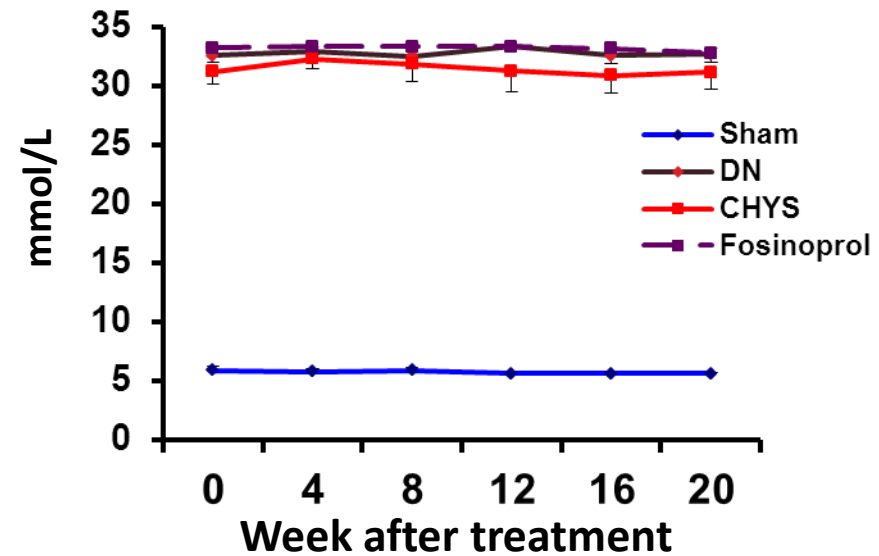


CHYS Treatment Attenuates Urinary Protein in Diabetic Nephropathy

24h urinary protein

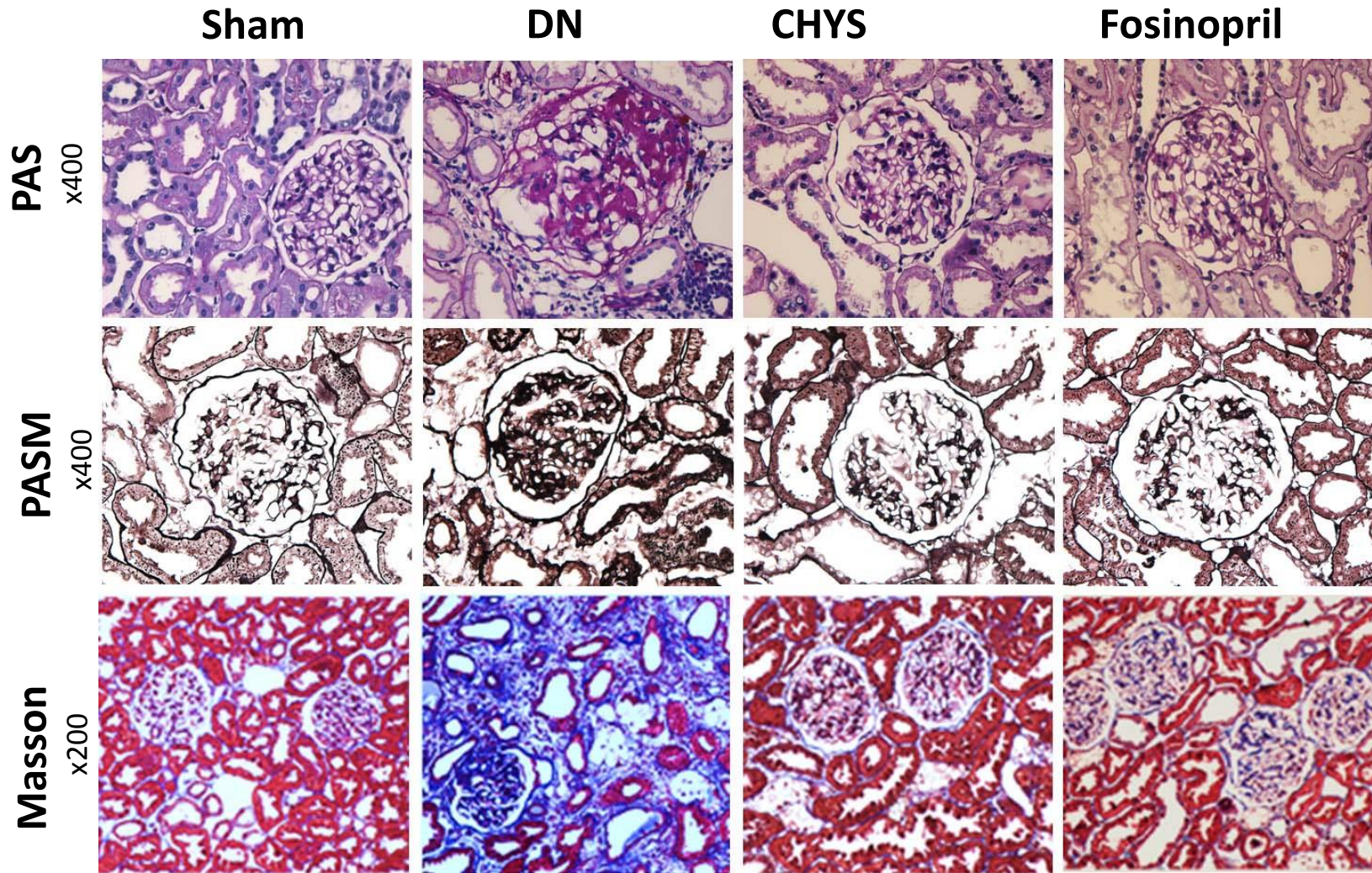


Blood glucose

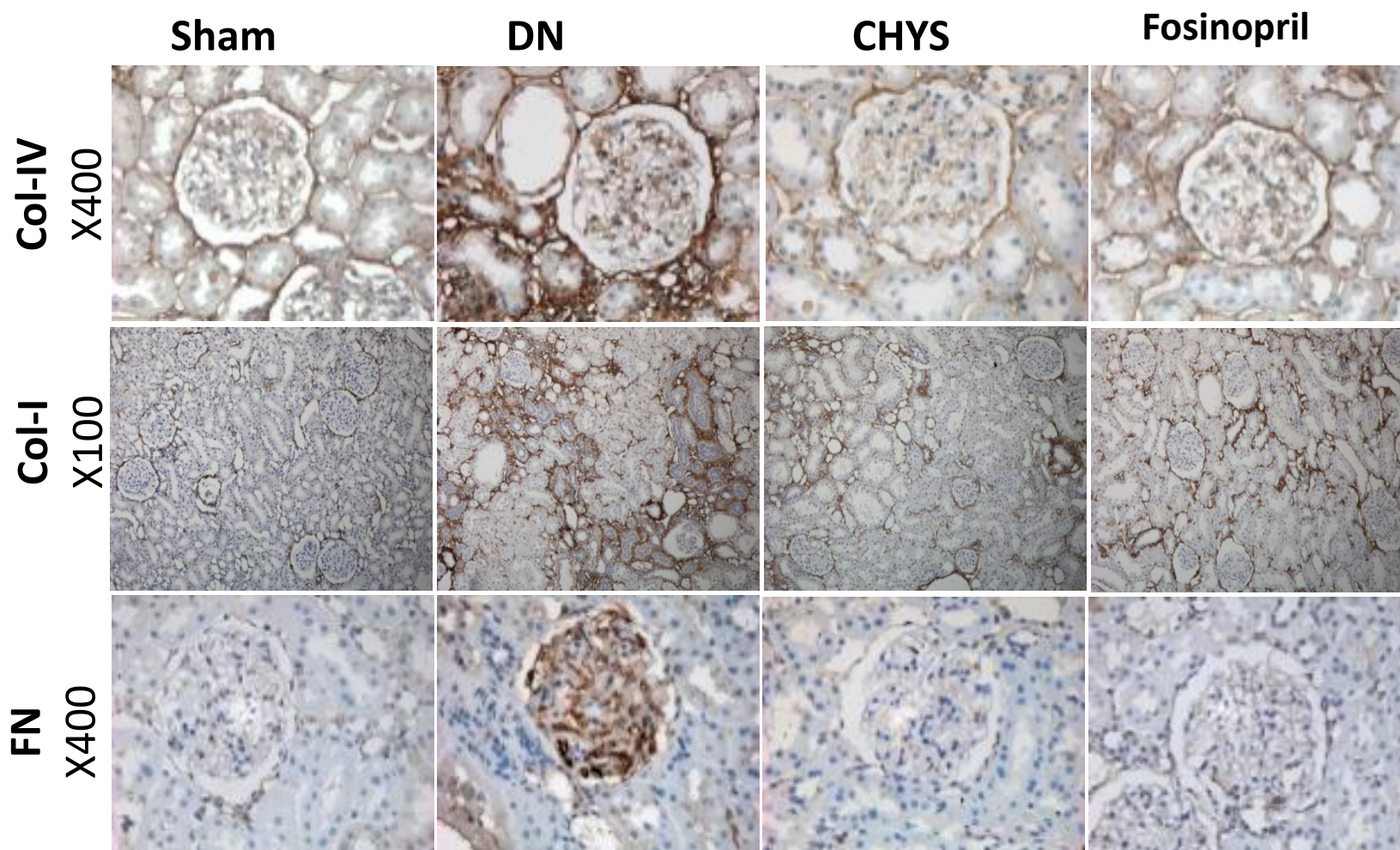


N=6, *P < 0.05, **P < 0.01, ***P < 0.001 vs. sham group, #P < 0.05, ##P < 0.01 vs. DN group.

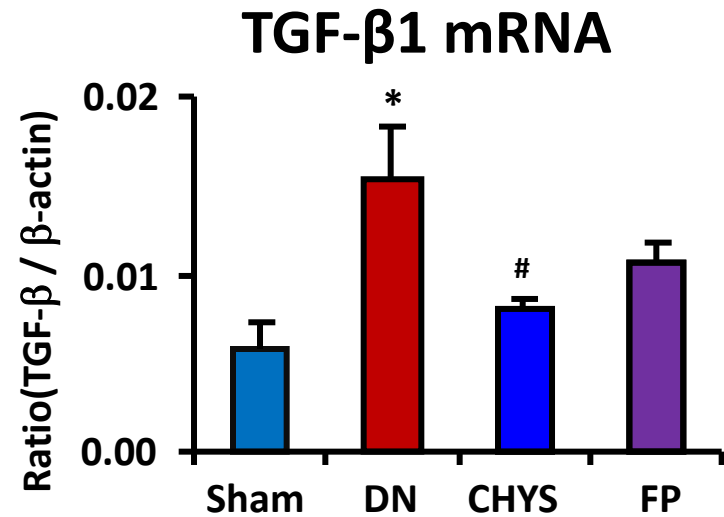
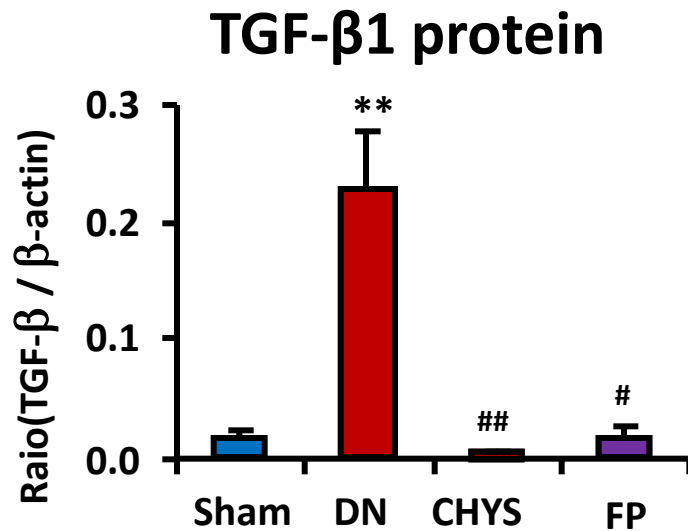
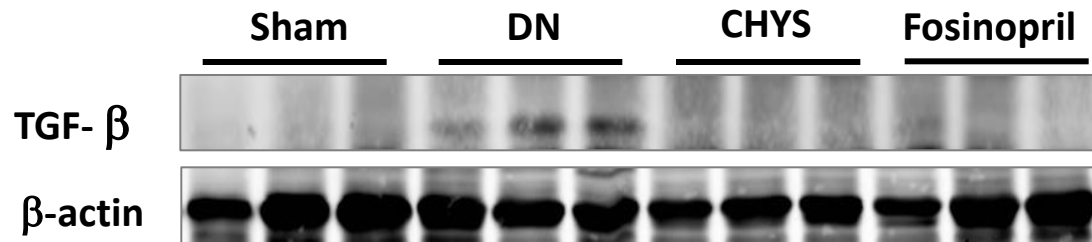
CHYS treatment Inhibits Renal Fibrosis in Diabetic Nephropathy.



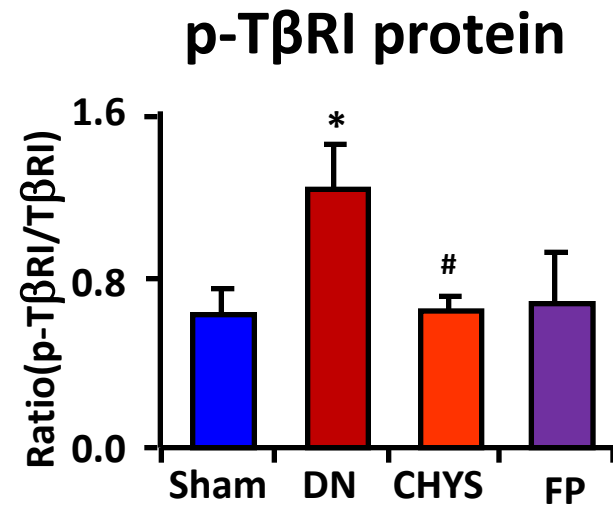
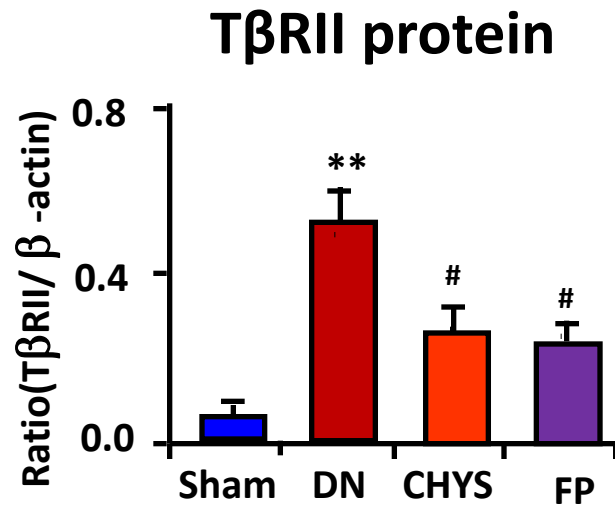
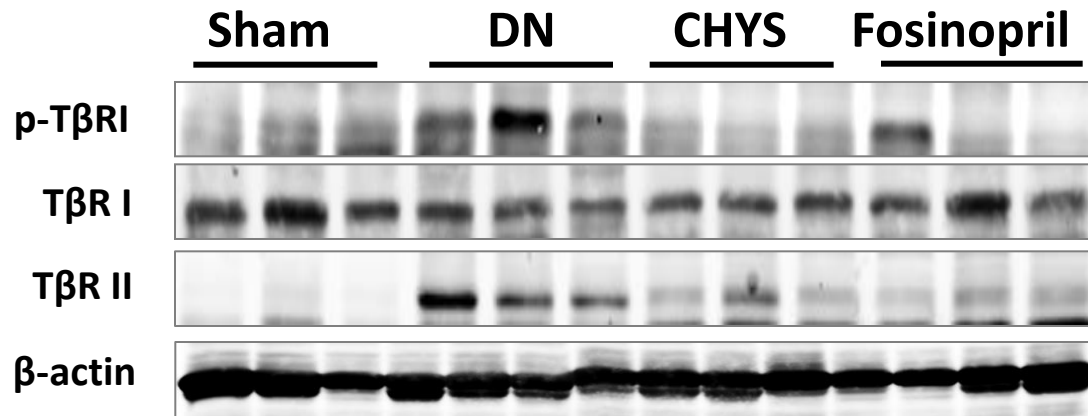
CHYS treatment Inhibits Renal Fibrosis in Diabetic Nephropathy.



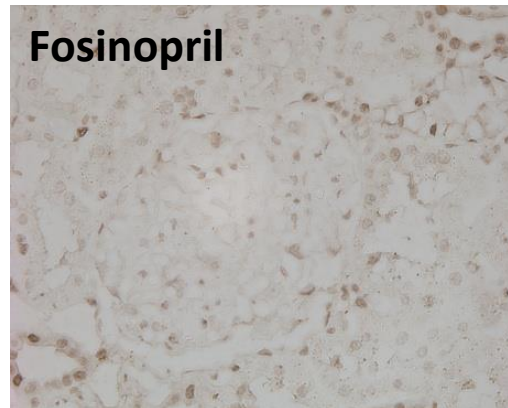
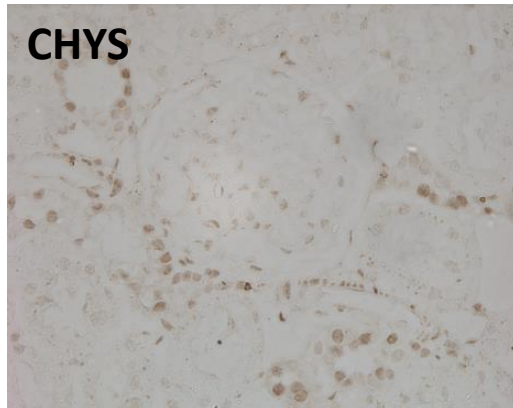
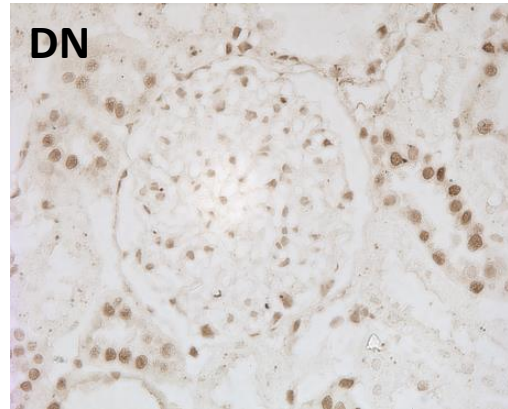
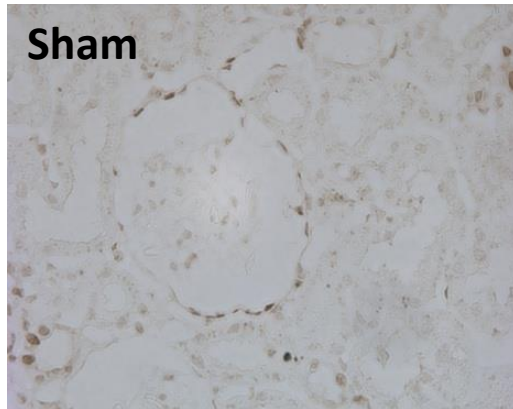
CHYS Blocks Activation of TGF- β / Smad Signaling Pathway in DN



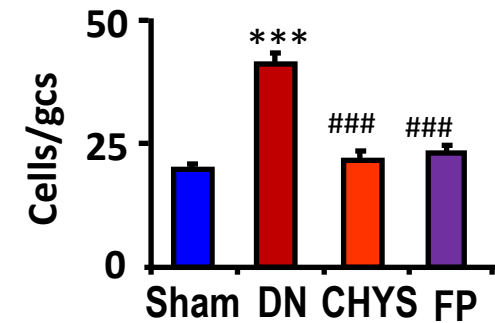
T β R I and T β R II



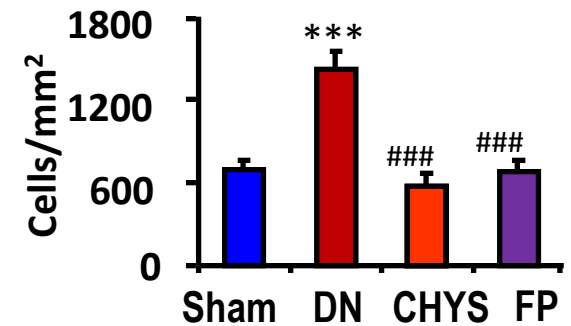
p-Smad2/3-IHC



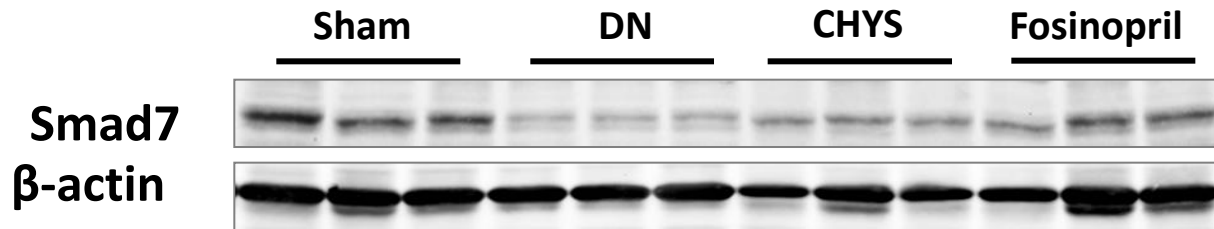
p-Smad2/3 in glomeruli



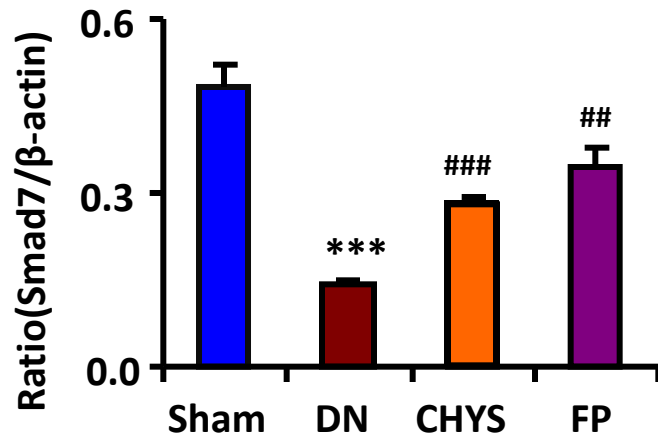
p-Smad2/3 in tubulointerstitium



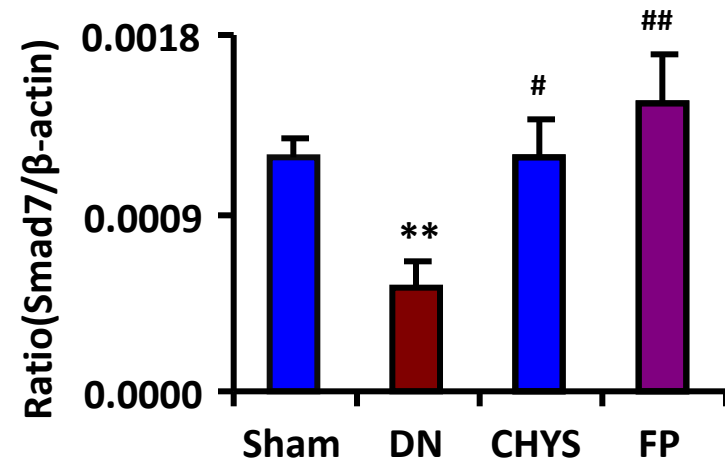
Smad7



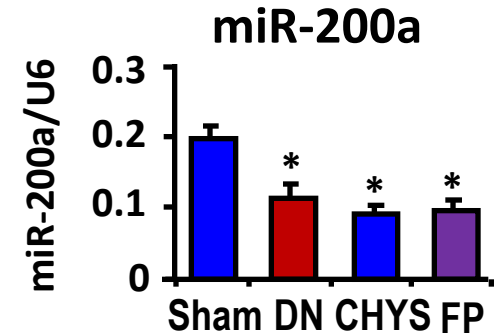
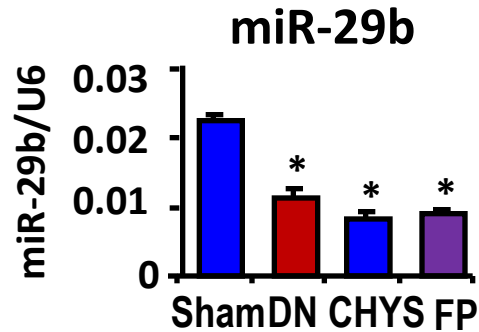
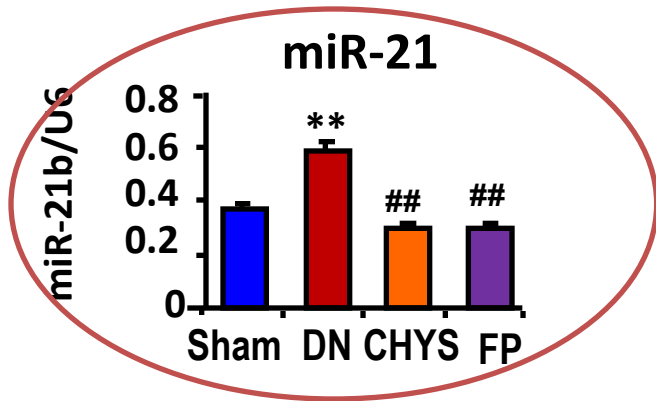
Smad7 protein



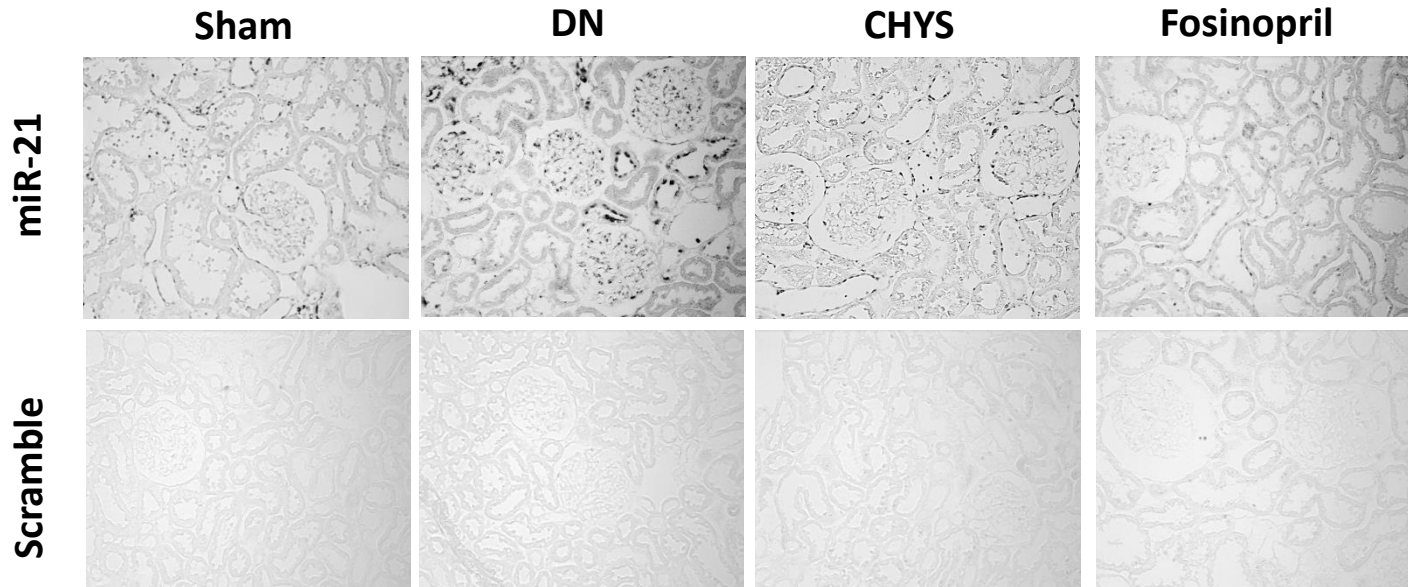
Smad7 mRNA



CHYS Downregulates microRNA-21 Expression in the Kidney of DN



In situ hybridization (x200)



汇报提纲

中医药治疗糖尿病肾病文献分析

中医药治疗现状

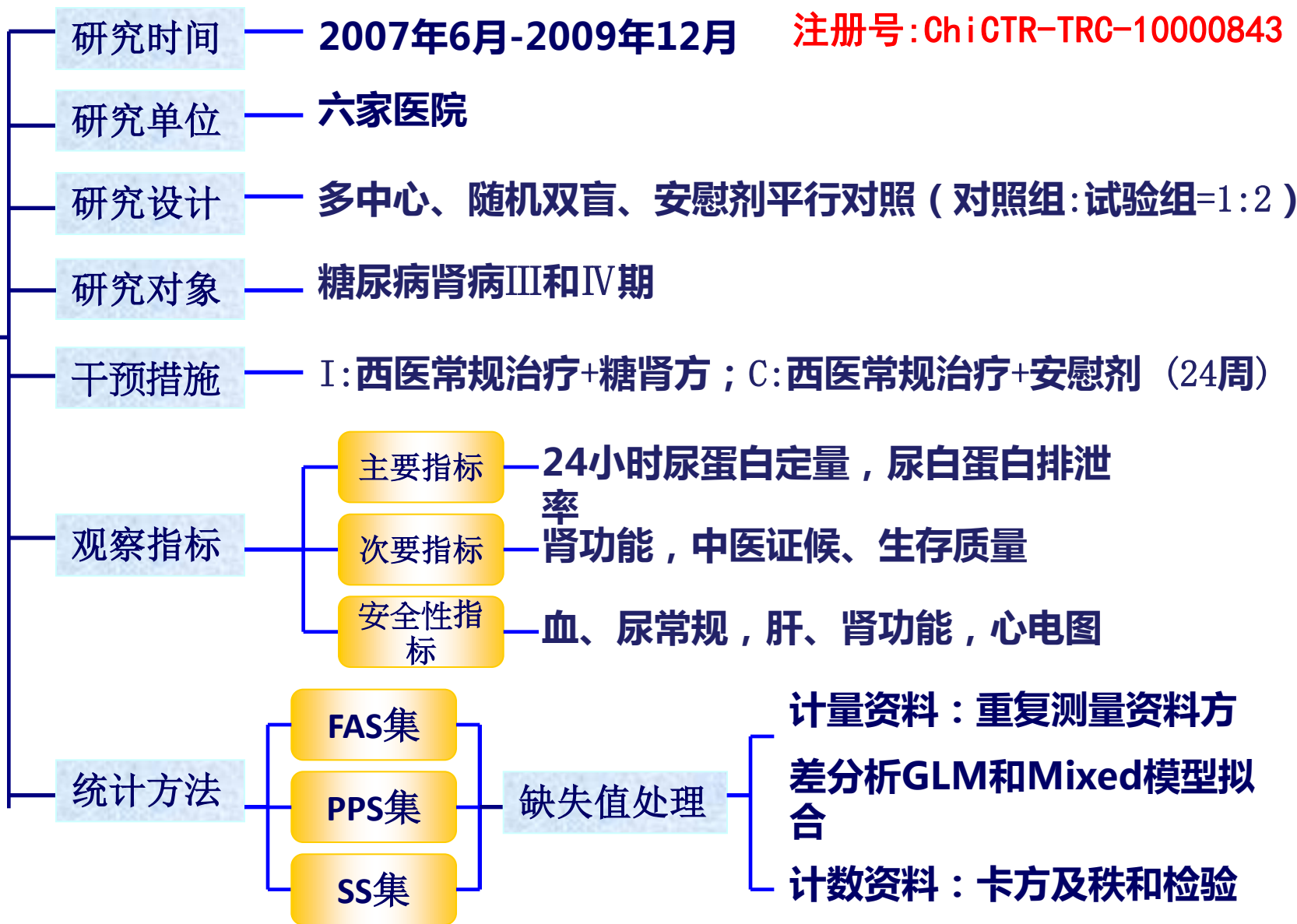
中药治疗糖尿病肾病机制研究

糖肾方临床研究介绍

糖肾方治疗糖尿病肾病RCT研究

伦理委员会批准号：2006-059
注册号：ChiCTR-TRC-10000843

研究方案



病例选择

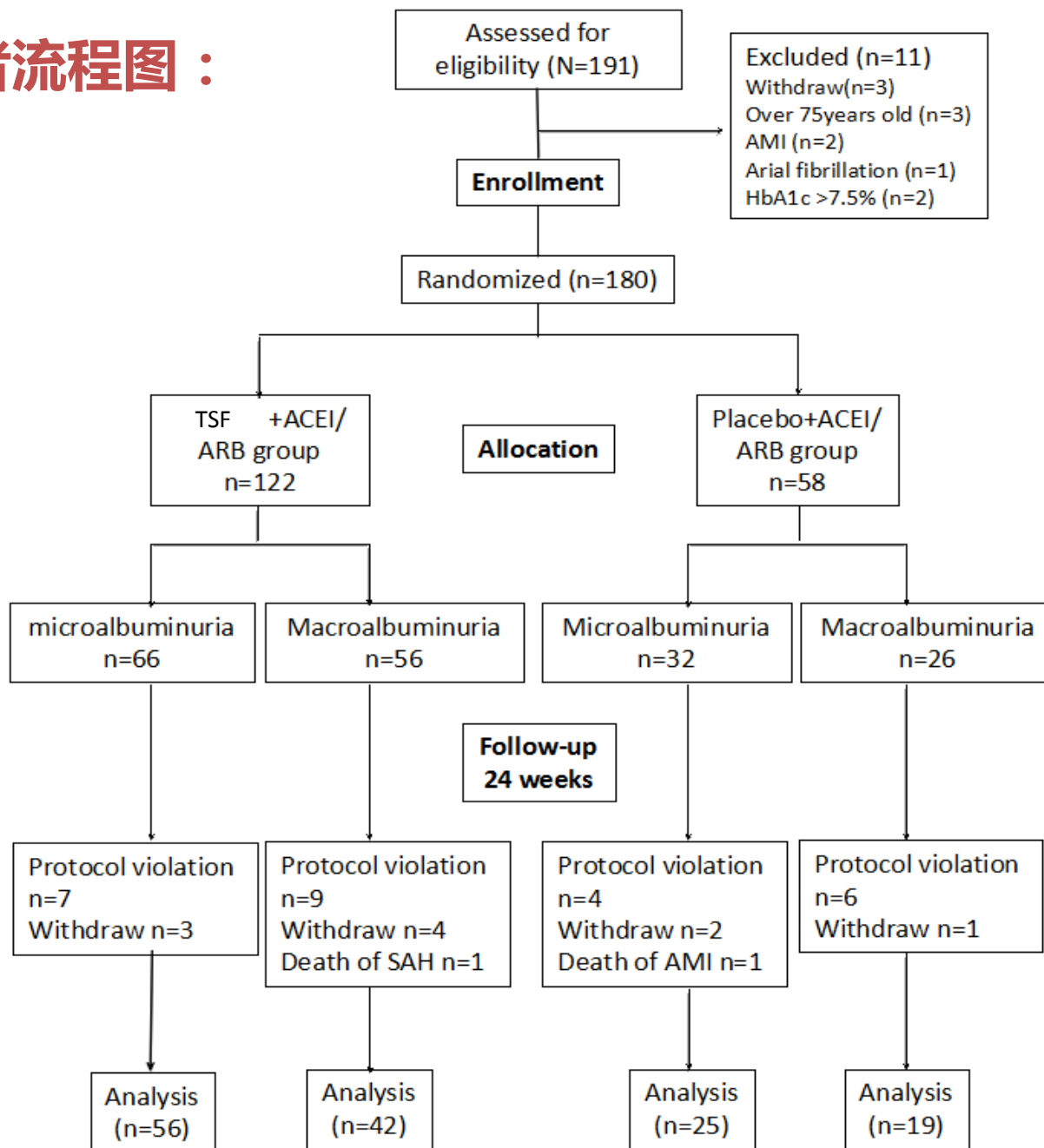
■ 纳入标准：

- 1、2型糖尿病；
- 2、糖尿病肾病Ⅲ和Ⅳ期；
- 3、**GFR60-130ml/min**；蛋白尿水平**2g/d**以下；
- 4、**血压 \leq 140/90mmHg**；**FBG \leq 7.8mmol/L**，**HbA1c \leq 7.5%**
- 5、中医辨证符合气阴两虚夹瘀者；

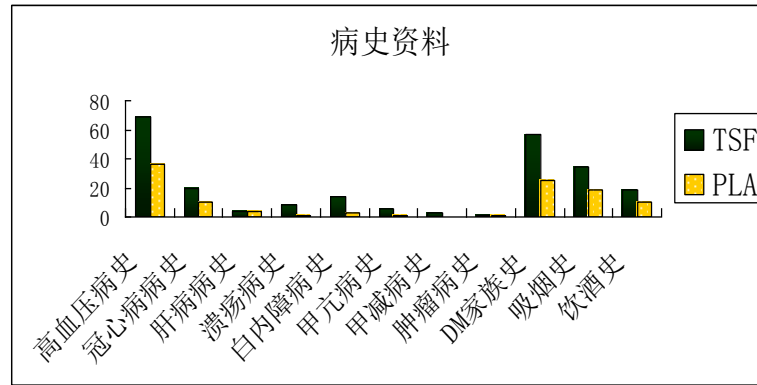
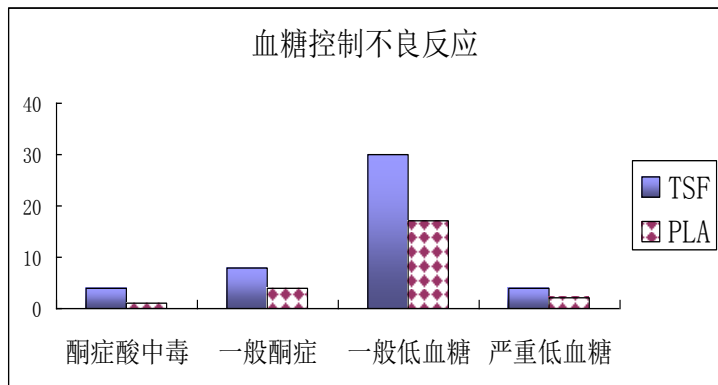
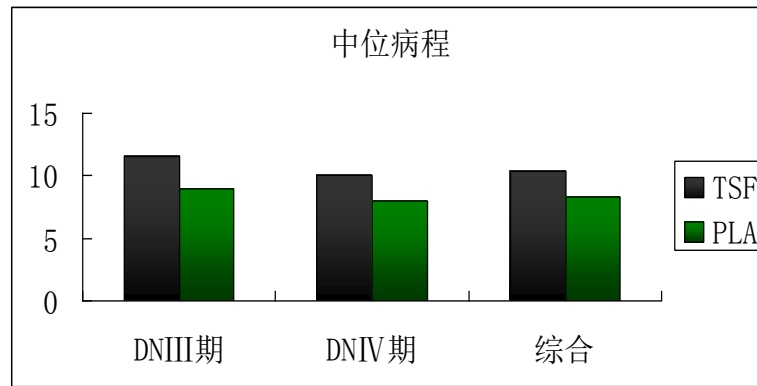
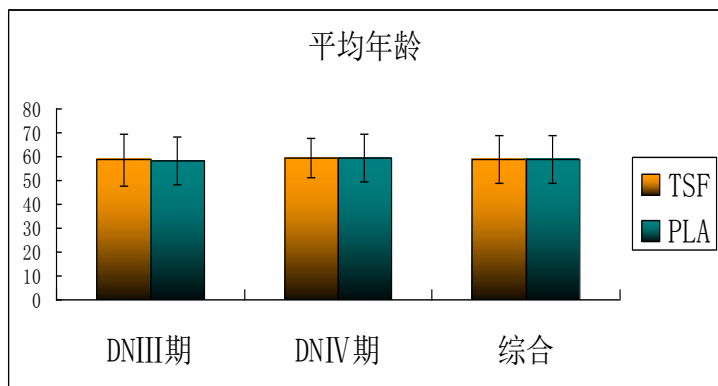
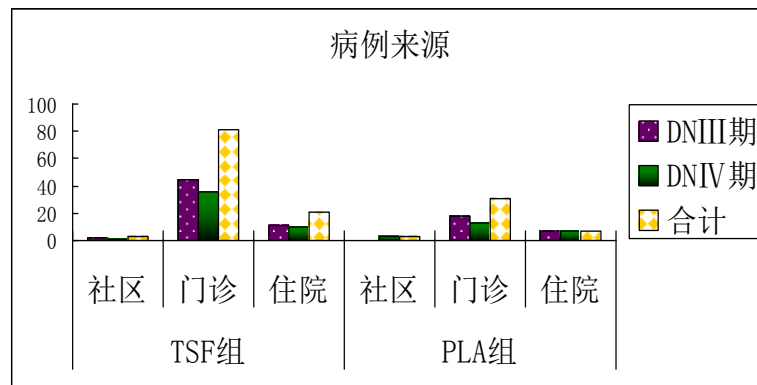
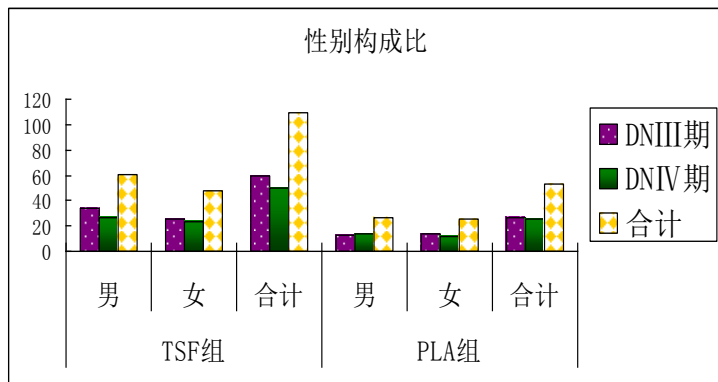
■ 排除标准：

- 1、有严重糖尿病并发症及现有大血管事件者
- 2、近期内（4周内）有各种感染者
- 3、妊娠或哺乳期妇女，对试验药物过敏者、精神障碍患者
- 4、原发性肾脏疾病、其他继发性肾脏疾病，血液系统疾病、其他内分泌代谢疾病。

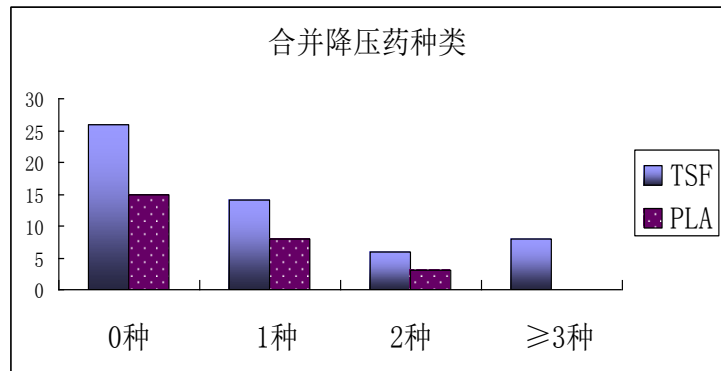
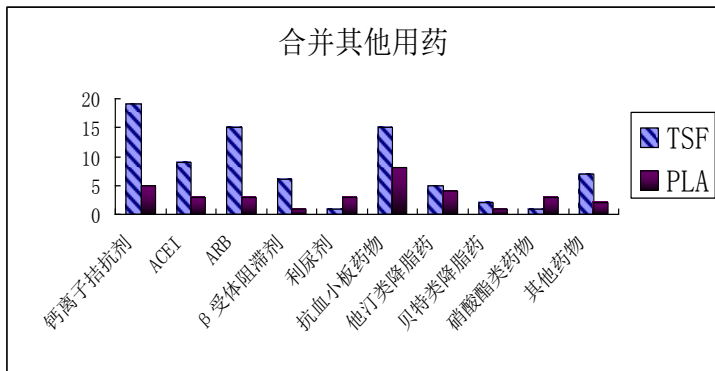
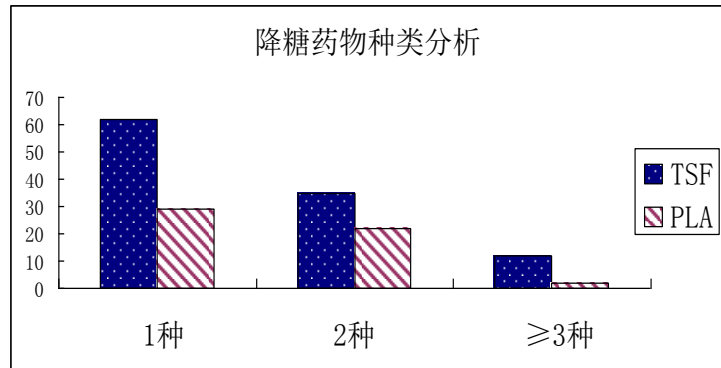
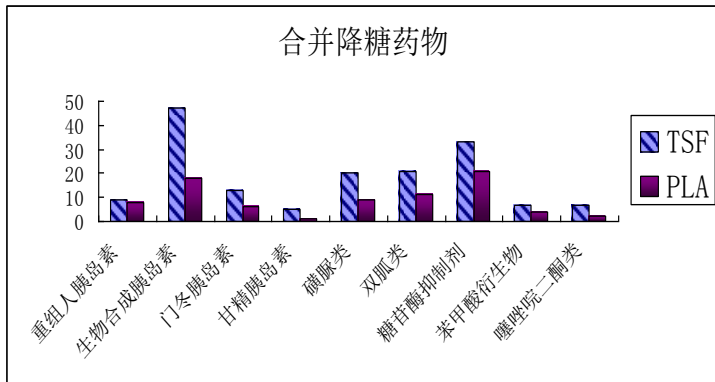
临床受试者流程图：



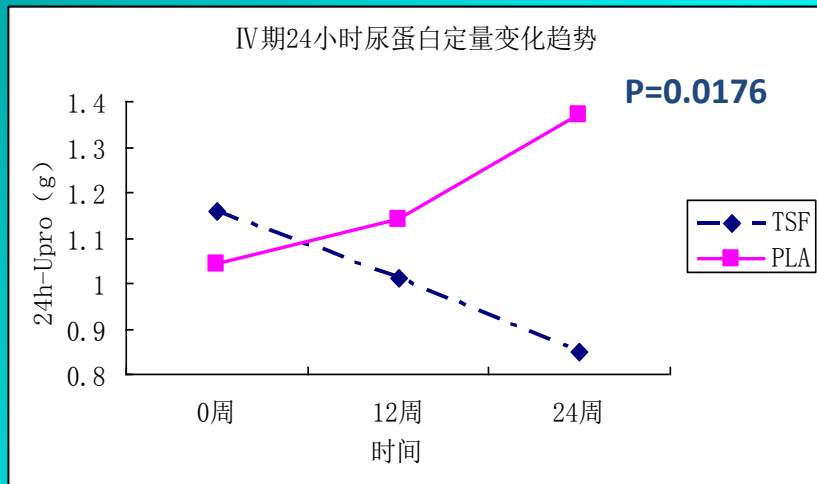
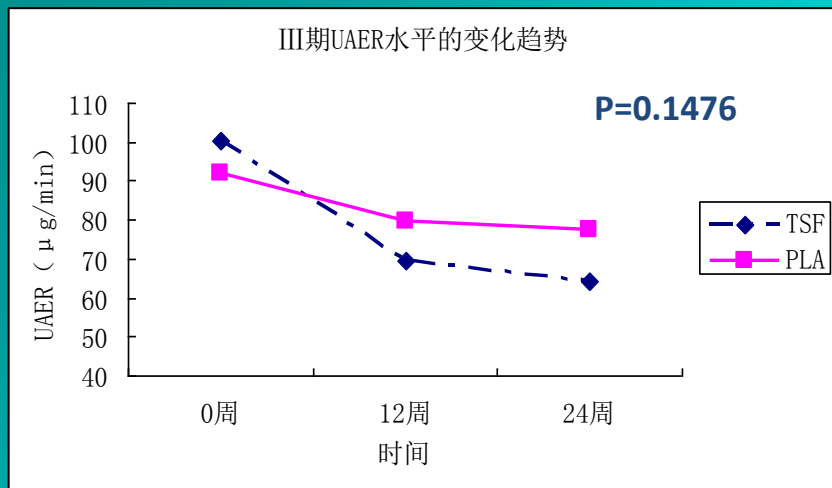
基线水平分析 (1)



基线水平分析 (2)



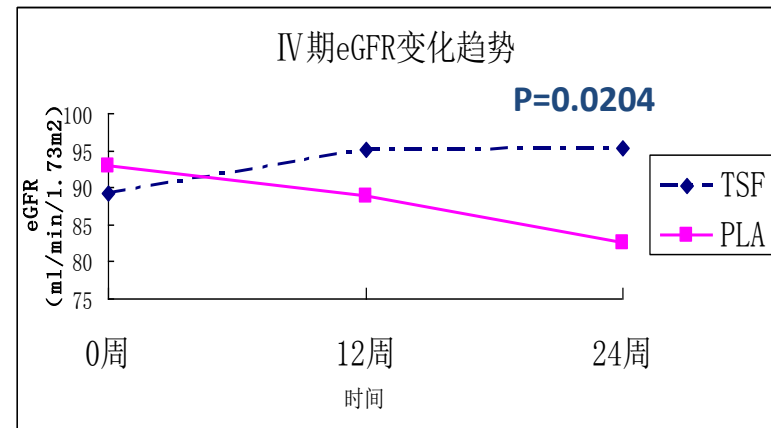
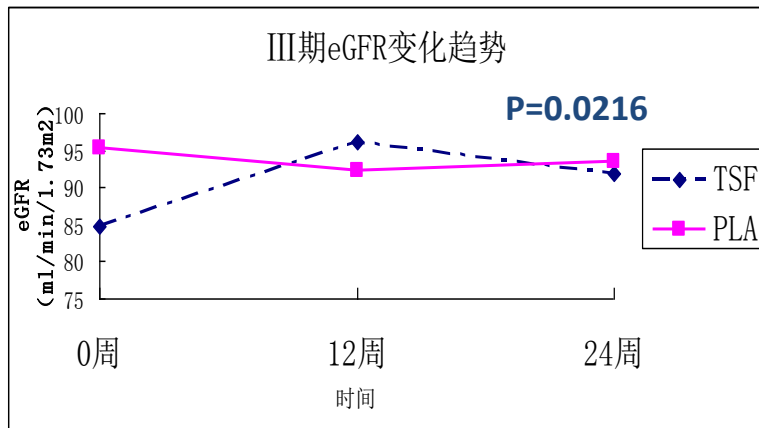
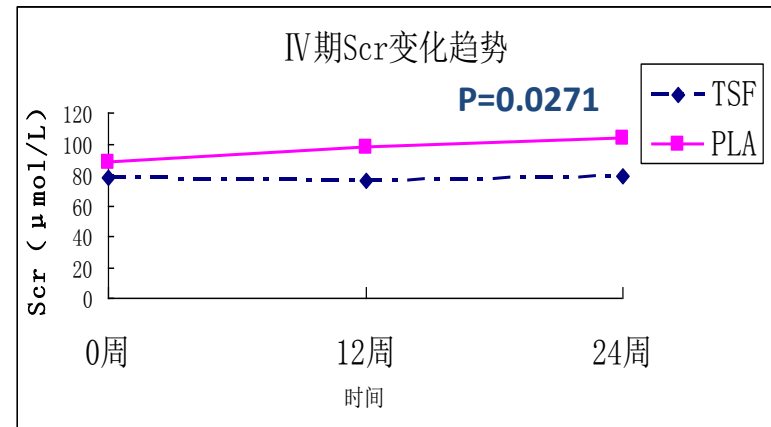
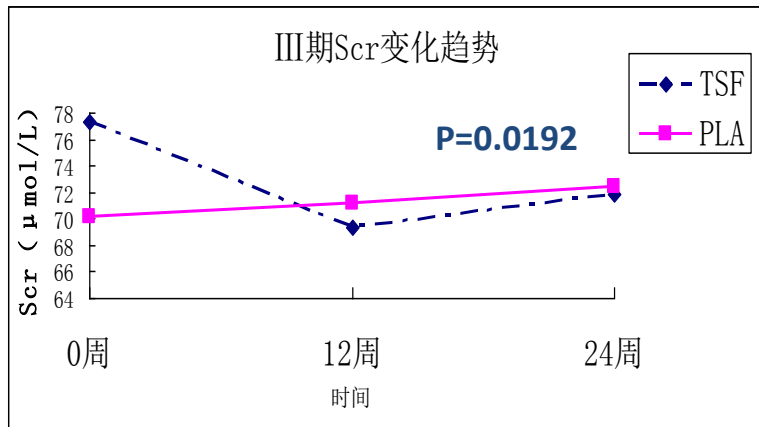
主要评价指标-蛋白尿



■ There were significant reduction of UAER level of stage III DN, however, there was no significant difference between groups.

■ There was significant reduction of 24h-Upro in TFS group, compared with PLA group, $P < 0.05$.

次要评价指标—肾功能



● TSF could reduce Scr level, elevate eGFR level, compared with PLA, $P<0.05$.

结果 (3)

表2 糖肾方组与安慰剂间安全性指标比较

	糖肾方 (n=122)	安慰剂 (n=58)
ALT/ AST大于2	5 (5.1%)	4 (9.09%)
急性心肌梗死	0	1 (1.72%)
死亡	1 (蛛网膜下腔出血 0.82%)	1 (急性心肌梗死 1.72%)
感染	1 (0.82%)	1 (1.72%)
贫血	2 (轻度 1.94%)	1 (中度 1.72%)
合计	9	8

卡方检验： $P=0.169$

结论

- ✓ 糖肾方改善糖尿病肾病患者的eGFR水平，降低24h尿蛋白定量水平。

RESEARCH ARTICLE

Efficacy and Safety of Tangshen Formula on Patients with Type 2 Diabetic Kidney Disease: A Multicenter Double-Blinded Randomized Placebo-Controlled Trial

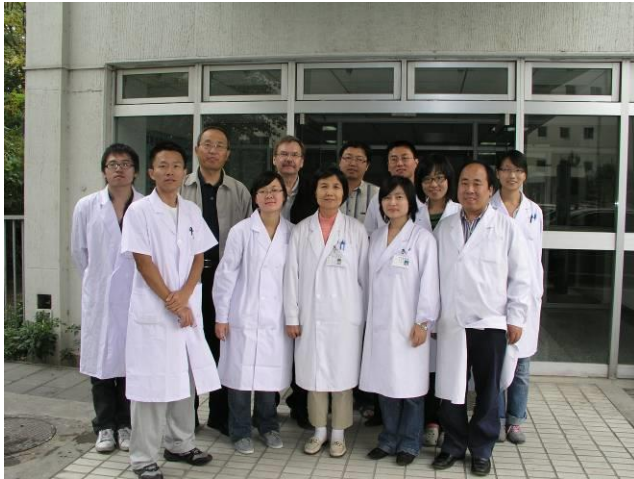
Ping Li^{1*}, Yiping Chen², Jianping Liu³, Jing Hong⁴, Yueyi Deng², Fang Yang⁵, Xiuping Jin⁶, Jing Gao⁷, Jing Li⁷, Hui Fang⁸, Geling Liu⁸, Liping Shi⁹, Jinhang Du¹⁰, Yang Li¹¹, Meihua Yan¹, Yumin Wen¹, Wenying Yang⁴

1 Institute of Clinical Medical Science, China-Japan Friendship Hospital, Beijing, China, 2 Department of Nephrology, Longhua Hospital, Shanghai University of TCM, Shanghai, China, 3 Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, 4 Department of Endocrinology, China-Japan Friendship Hospital, Beijing, China, 5 Research Center of Experimental Medicine, Hebei United University, Tangshan, China, 6 Department of Endocrinology, Hebei United University Affiliated Hospital, Tangshan, China, 7 Department of Nephrology, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing, China, 8 Department of Endocrinology, Tangshan Gongren Hospital, Tangshan, China, 9 Department of Endocrinology, Kailuan General Hospital, Tangshan, China, 10 Department of Nephrology, China-Japan Friendship Hospital, Beijing, China, 11 School of Statistics, Renmin University of China, Beijing, China



China-Japan Friendship Hospital

Institute of Clinical Medical Science



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- Chinese University of Hong Kong
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- Dr. Xiao-ru Huang

Shanghai University of TCM

- Prof. Yiping Chen
- Prof. Yueyi Deng

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患者至上，文明行医

1984-2013