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SYSTEMATIC REVIEW

Effect of Huangshukuihua (*Flos Abelmoschi Manihot*) on diabetic nephropathy: a Meta-analysis

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Abstract

OBJECTIVE: To assess the efficacy of Huangshukuihua (*Flos Abelmoschi Manihot*) on diabetic nephropathy (DN).

METHODS: Articles were retrieved from PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure Database, Chinese Evidence-Based Medicine Database, and Wanfang Database. Two reviewers independently reviewed the article. Only randomized controlled trials were included and 27 were identified involving 2239 patients (1143 in the treatment group and 1096 in the control group).

RESULTS: Huangshukuihua (*Flos Abelmoschi Manihot*) had a significant effect on renal function by improving blood urea nitrogen and serum creatinine, reducing urine protein (24-h urine protein, and urinary albumin excretion rate), and improving serum albumin level, compared with the control group.

CONCLUSION: Our findings suggest that, although the bioactive ingredients and mechanism underlying renal protection are unknown, the role of Huangshukuihua (*Flos Abelmoschi Manihot*) in the treatment of DN deserves further investigation.

Key words: Diabetic nephropathy; Renal insufficiency; *Flos Abelmoschi Manihot*; Meta-analysis

INTRODUCTION

Diabetic nephropathy (DN) is one of the common chronic complications of diabetes. Without active treatment, DN eventually develops into end stage renal diseases (ESRD), which occurs in 20%-40% diabetic patients.[1] In Western countries, DN ranks the first among the primary etiologies leading to ESRD, accounting for about 37%-40%.[2] In China, about 30% of type 1 and 20% of type 2 diabetes develop into DN, and 53% of the patients die from diabetic renal failure.[3] With Centuries of clinical experience with chronic kidney disease (CKD) and DN, Chinese clinicians and practitioners have developed treatments to combat the diseases. The "Noinclude," an ancient book containing records of Traditional Chinese Medicine (TCM), indicates that TCM has been used to treat CKD and DN in China since at least 475 BCE. Today, TCM are still used extensively for the treatment of CKD and DN in China. Huangshukuihua (*Flos Abelmoschi Manihot*) is used to treat kidney disease and infection of skin and mucous membrane. The treatment was first documented in *Jia You Ben Cao*, a Traditional Chinese Medical

book written in 1060 AD.[4] Huangshukuihua (*Flos Abelmoschi Manihot*) is in the same family as okra, Malvaceae, and is found in Vietnam, Laos, Cambodia, Thailand, India, and China. Huangshukuihua (*Flos Abelmoschi Manihot*), it is widely grown in southern China.

The major pharmacologically active constituents of Huangshukuihua (*Flos Abelmoschi Manihot*) are the total flavones of Abelmoschus manihot (L.) Medicus (Hibiscus manihot L.) (TFA).[5,6] The chemical constituents of TFA have been isolated, and their structures have been identified by spectroscopic analysis. TFA contains seven flavone glycosides, including myricetin, hyperin, quercetin, quercetin-3'-β-glucoside, hibiscetin-3-O-glucoside, myricetin-3-O-glucoside, and gossypetin-8-O-β-D-glucuronide. However, it is still not clear which chemical component is responsible for the extract's renoprotective effect. Therefore, researchers commonly use okra capsules [its main component is Huangshukuihua (*Flos Abelmoschi Manihot*)] in pharmacodynamic and pharmacological studies.[7]

Many clinical trials have reported that Huangshukuihua (*Flos Abelmoschi Manihot*) ameliorates DN by mediating serum glucose and lipid metabolism through a caspase-dependent pathway.[7] However, the efficacy of Huangshukuihua (*Flos Abelmoschi Manihot*) is unclear owing to the lack of high-quality, large-sample random clinical trials. Therefore, we systematically reviewed the randomized control trials to evaluate the efficacy of Huangshukuihua (*Flos Abelmoschi Manihot*) in the treatment of DN.

MATERIALS AND METHODS

Search strategy

Databases were searched by electronic and manual methods, including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials , Web of Science, Chinese Biomedical Literarure Database, China National Knowledge Infrastructure Database, Chinese Evidence-Based Medicine Database, Wanfang Database and hand-searching of reference which don't include these electronic databases noted above.

Different search strategies performed are as follows. For English databases, we used free text terms as "Abelmoschus manihot" or "Okra" and "diabetic nephropathy." For Chinese databases, we used free text terms as "Huang Shu Kui" or "Huang Kui" (which is the alternative name of Abelmoschus manihot in Chinese), and "Tang Niao Bing Shen Bing" (which means diabetic nephropathy in Chinese). A filter for clinical trials was applied. We also attempted to identify additional studies by searching the reference lists of included trials.

Selection criteria

All randomized control trials (RCTs) were included regardless of language. Patients met the diagnostic criteria for diabetic mellitus [World Health Organization (WHO)-1999, The American Diabetes Association (ADA)-1997]. Patients in the clinic stage Ⅲ-Ⅳ of DN were included according to the Mogensen DN diagnostic criteria.[8] Patients with other chronic diseases (chronic heart disease, chronic liver disease, chronic respiratory disease, tumor, autoimmunity disease, infection disease) were excluded.

Methodological quality appraisal

The capsule of Huangshukuihua (*Flos Abelmoschi Manihot*) was prepared by Szzy Group pharmaceutical Limited (Jiangsu, China) according to the quality standard of China State Food and Drug Administration. The main components of Huangshukuihua capsule were the total flavonoids extracted from the flowers of Abelmoschus manihot (L.) Medicus (Hibiscus manihot L.). The capsules were administrated orally. The dosage was 2.5 mg/d and the treatment course ranged from 8 to 24 weeks.

Data extraction and criteria of therapeutic effects

Important data from the primary studies were extracted: the number of patients in treatment group and the control group, age, gender, history of DM, intervention, treatment duration, and the use of ACE inhibitor or angiotensin receptor blocker (ARB). Data in the Huangshukuihua capsule treatment group were matched with the data in the control group.

Criteria of therapeutic effects included serum albumin, renal function [blood urea nitrogen (BUN), serum creatinine (SCr)], and urine protein such as 24-h urine protein and urinary albumin excretion rate (UAER).

Assessment method

Two assessors (Sun Qin and Yang Gangyi) independently reviewed each study, and disagreements were resolved by consensus. The following information was extracted: randomization process, allocation concealment, blinding, participant dropout and loss to follow up, intention-to-treat analysis, and explicit diagnostic and outcome criteria. The trials were coded as A: adequate; B: unclear; or C: inadequate, according to the Cochrane Handbook for Systematic Reviews.[9]

Statistical methods

Meta-analysis was conducted using Rev Man 5.2. (Cochrane collaboration, Oxford, UK).[10] Estimated effect of data was calculated by standardized mean difference (*SMD*) or weight mean difference (*WMD*). *Chi*-square test was used for heterogeneity. We tested heterogeneity using the I^2 statistic with significance set at 50%, and the Chi^2 statistic with significance set at $P < 0.10$. If significant heterogeneity was identified, the random-effects model was used. Trials showing clinical heterogeneity were combined according to the random effect model and the remaining studies used the fixed effect model.[11]

RESULTS

Description of studies

Overall, 89 studies including 27 RCTs were eligible (Figure 1).[1,12-37] The included studies are summarized in Table 1 and Table 2. A total of 2239 patients were enrolled for analysis of effectiveness (1143 in the treatment group and 1096 in the control group). All studies were carried out in the People's Republic of China and all patients involved in the trials were Chinese.

Data analysis

BUN: a total of 13 RCTs[16,18,20,22,23,27,28,30,31,33-35,37] (502 patients in treatment group and 492 in the control group) were conducted to analyze serum urea nitrogen. Figure 2 shows the forest plot for BUN comparison. The results show that patients in the Huangshukuihua group had significantly lower BUN levels than those in the control group [*SMD* = - 0.44 (- 0.57, - 0.32), *P* < 0.000 01], which suggests a moderate heterogeneity.

SCr: nineteen trials[12,13,15,16,18-20,22-24,27-32,33,34,37] evaluated the efficacy of Huangshukuihua (*Flos Abelmoschi Manihot*) on SCr in the treatment group compared with the control group. There were 724 patients in the treatment group and 700 in the control group. Because of significant heterogeneity, we chose the random effect model. Figure 3 shows the forest plots for the outcome measures. [*SMD* = - 0.71 (- 1.09, - 0.32), *P* = 0.0004]. Compared with the control group, the Huangshukuihua group had significantly lower SCr.

24-h Urine Protein: eighteen RCTs[12, 14-19, 23-25, 27, 29-32, 34, 35, 37] (803 patients in the treatment group and 773 in the control group) analyzed the 24-h urine protein. Figure 4 shows the forest plot for the 24-h urine protein comparison. The results show that the Huangshukuihua group had significantly lower 24-h urine protein compared with the control group [*SMD* = - 0.87; 95% *CI*: (- 1.14, - 0.61); *P* < 0.000 01].

UAER: eight RCTs[12,21,22,25,26,34-36] evaluated the UAER of the treatment group as compared with the control group. There were 350 patients in the treatment group and 324 in the control group. The trials showed clinical heterogeneity and were combined according to the

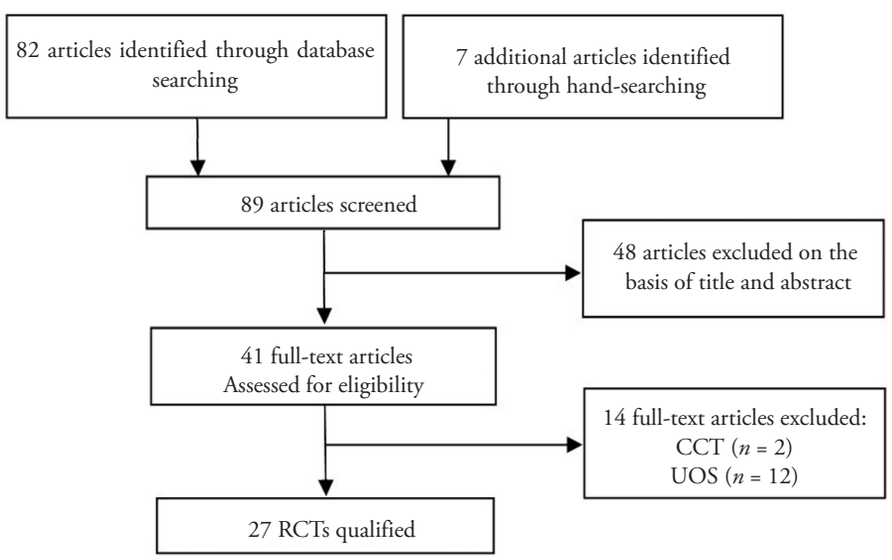

Figure 1 Flow diagram of literature search

CCT: controlled clinical trial; UOS: uncontrolled observational study; RCTs: randomized controlled trials

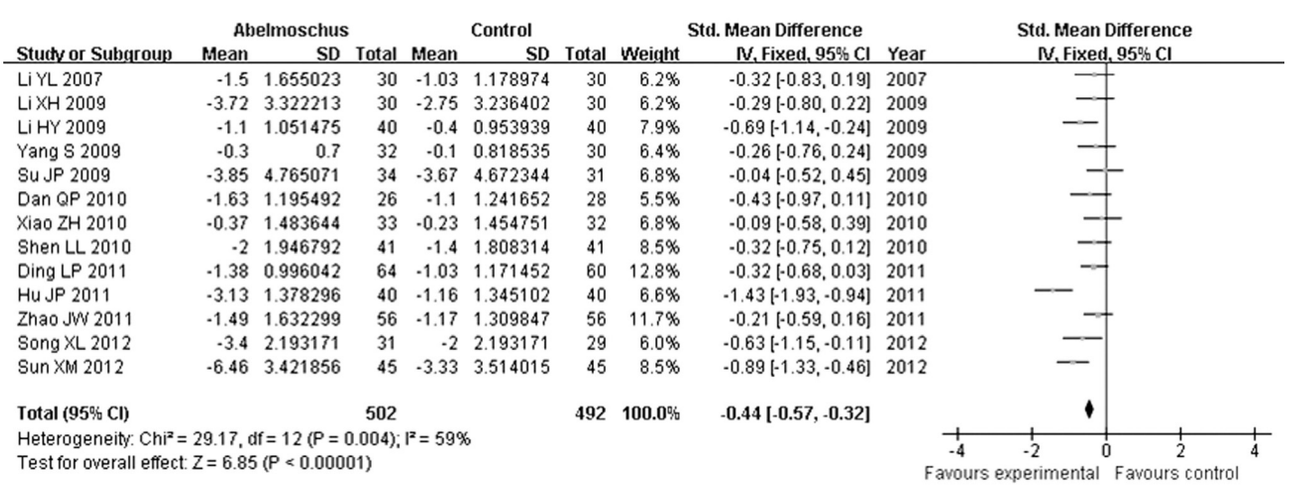

Figure 2 Effect of Abelmoschus manihot on blood urea nitrogen in diabetic nephropathy patients

random effect model. Figure 5 shows the forest plots for the outcome measures. [*SMD* = - 1.04 (- 1.34, - 0.75), *P* < 0.000 01]. Compared with the control group, the Huangshukuihua group had significantly lower UAER.

Serum albumin: four clinical trials[24,28,30,32] evaluated the serum albumin of the treatment group as compared with the control group. There were 128 patients in the treatment group and 126 in the control group. Figure 6 shows the forest plots for the outcome measures. [*SMD* = 0.25 (0.01, 0.50), *P* = 0.04]. Compared with the control group, the Huangshukuihua group had significantly higher serum albumin levels. The effect was homogeneous.

Adverse effects: we did not conduct analysis on adverse effect because of the lack of reports on severe side effects in all the clinical trials involved.

DISCUSSION

This Meta-analysis provides a quantitative evaluation of the clinical effect of Huangshukuihua (*Flos Abelmoschi Manihot*) on DN by integrating outcomes from 27 clinical studies that include 1143 treatment patients and 1096 control patients. Our results show that the levels of BUN and SCr were significantly lower in the treatment group compared with the control group, which suggests a protective effect of Huangshukuihua (*Flos Abelmoschi Manihot*) on renal function in DN patients.

Abdominal distension and other gastrointestinal symptoms might occur after taking the capsule, but the symptoms were mild, and symptoms disappeared when medication was adjusted to the postprandial period. No studies indicated that patients discontinued treat-

Study or Subgroup	Abelmoschus Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Li YL 2007	-14.27	16.38551	30	-12.75	13.18466	30	4.8%	-0.10 [-0.61, 0.41]	2007
Li HY 2009	-18	71.39328	40	-9	62.26556	40	4.9%	-0.13 [-0.57, 0.31]	2009
Li ZF 2009	-48.3	13.65394	30	-35.1	13.81123	31	4.7%	-0.95 [-1.48, -0.42]	2009
Yang S 2009	-2.8	8.190238	32	-2.9	8.265591	30	4.8%	0.01 [-0.49, 0.51]	2009
Li XH 2009	-64.85	39.27282	30	-37.4	38.50176	30	4.7%	-0.70 [-1.22, -0.17]	2009
Su JP 2009	-17.8	31.86973	34	-20.4	28.1725	31	4.8%	0.09 [-0.40, 0.57]	2009
He XL 2010	-1.1	10.95308	40	-0.5	11.01227	40	4.9%	-0.05 [-0.49, 0.38]	2010
Xiong ZZ 2010	-4.1	10.72241	33	-1.6	12.35759	32	4.8%	-0.21 [-0.70, 0.27]	2010
Shen LL 2010	-40.8	12.69606	41	-6.9	11.38464	41	4.6%	-2.78 [-3.40, -2.17]	2010
Su Y 2010	-36.1	48.96846	32	-30.6	43.63164	32	4.8%	-0.12 [-0.61, 0.37]	2010
Chen Y 2010	-56.7	12.05778	52	-29	11.7222	45	4.7%	-2.31 [-2.83, -1.79]	2010
Dan QP 2010	-20.64	14.55789	26	-9.85	13.02695	28	4.7%	-0.77 [-1.33, -0.22]	2010
Cai XY 2010	-4.09	20.071	25	-2.01	19.13807	25	4.7%	-0.10 [-0.66, 0.45]	2010
Ding LP 2011	-28.2	34.57592	64	-15.18	37.18189	60	5.0%	-0.36 [-0.72, -0.01]	2011
Hu JP 2011	-39.16	15.28686	40	-13.37	12.27313	40	4.7%	-1.84 [-2.37, -1.32]	2011
Shen XH 2011	-3.3	13.35178	60	-0.5	14.51241	60	5.0%	-0.20 [-0.56, 0.16]	2011
Liu JF 2011	-26.1	48.96846	24	-28.6	53.36403	24	4.7%	0.05 [-0.52, 0.61]	2011
Zhao JW 2011	-14.26	15.23615	56	-14.88	14.3047	56	5.0%	0.04 [-0.33, 0.41]	2011
Jiang ZJ 2012	-122.24	16.75608	36	-64.68	14.28194	30	4.2%	-3.63 [-4.43, -2.83]	2012
Song XL 2012	-12.1	14.89866	31	-6	14.63591	29	4.8%	-0.41 [-0.92, 0.10]	2012
Bu HX 2012	-75.4	51.02147	38	-54.4	43.38514	37	4.9%	-0.44 [-0.90, 0.02]	2012
Total (95% CI)			**794**			**771**	**100.0%**	**-0.68 [-1.04, -0.33]**	

Heterogeneity: Tau² = 0.63; Chi² = 226.81, df = 20 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.76 (P = 0.0002)

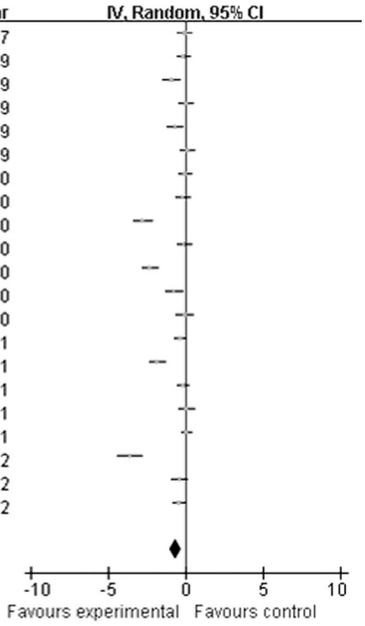

Figure 3 Effect of Abelmoschus manihot on serum creatinine in diabetic nephropathy patients

Study or Subgroup	Abelmoschus Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Liu KH 2005	-0.27	0.17088	111	-0.04	0.185203	105	5.9%	-1.29 [-1.58, -0.99]	2005
Li YL 2007	-0.83	0.597327	30	-0.48	0.62857	30	5.1%	-0.56 [-1.08, -0.05]	2007
Guan ZX 2008	-0.87	0.570877	40	-0.49	0.579396	40	5.4%	-0.65 [-1.10, -0.20]	2008
Chang LL 2009	-3.22	0.664605	64	-2.93	0.3995	64	5.7%	-0.53 [-0.88, -0.17]	2009
Su JP 2009	-0.37	0.167033	34	-0.2	0.165227	31	5.1%	-1.01 [-1.53, -0.49]	2009
Yang S 2009	-0.02	0.06245	32	-0.01	0.072111	30	5.2%	-0.15 [-0.65, 0.35]	2009
Xiao ZZ 2010	-0.15	0.07	33	-0.12	0.055678	32	5.2%	-0.47 [-0.96, 0.03]	2010
Dan QP 2010	-1.169	0.703533	26	-0.748	0.666032	28	5.0%	-0.61 [-1.15, -0.06]	2010
Chen Y 2010	-0.4708	0.121036	52	-0.3789	0.12325	45	5.5%	-0.75 [-1.16, -0.33]	2010
Su Y 2010	-0.7	0.772528	32	-0.36	0.592284	32	5.2%	-0.49 [-0.99, 0.01]	2010
Liu JF 2011	-0.7	0.772528	24	-0.34	0.592284	24	4.9%	-0.51 [-1.09, 0.06]	2011
Hu JP 2011	-0.93	0.557494	40	-0.53	0.516817	40	5.4%	-0.74 [-1.19, -0.28]	2011
Zhao JW 2011	-0.84	0.530283	56	-0.5	0.61	56	5.6%	-0.59 [-0.97, -0.21]	2011
Shen XH 2011	-0.97	0.147309	60	-0.66	0.127671	60	5.4%	-2.23 [-2.69, -1.78]	2011
Ding LP 2011	-0.94	0.494267	64	-0.42	0.641327	60	5.7%	-0.91 [-1.28, -0.54]	2011
Jiang Z 2012	-1.16	0.629524	36	-0.03	0.493254	30	4.8%	-1.95 [-2.55, -1.36]	2012
Song XL 2012	-2.7	0.43589	31	-1.6	0.519615	29	4.6%	-2.27 [-2.93, -1.61]	2012
Bu HX 2012	-0.68	0.827224	38	-0.52	0.68942	37	5.4%	-0.21 [-0.66, 0.25]	2012
Jiang ZJ 2012	-1.16	0.629524	36	-0.03	0.493254	30	4.8%	-1.95 [-2.55, -1.36]	2012
Total (95% CI)			**839**			**803**	**100.0%**	**-0.92 [-1.19, -0.66]**	

Heterogeneity: Tau² = 0.30; Chi² = 116.92, df = 18 (P < 0.00001); I² = 85%
Test for overall effect: Z = 6.76 (P < 0.00001)

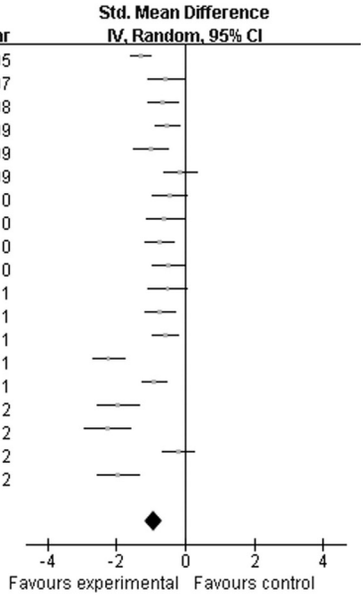

Figure 4 Effect of Abelmoschus manihot on 24-h urine protein in diabetic nephropathy patients

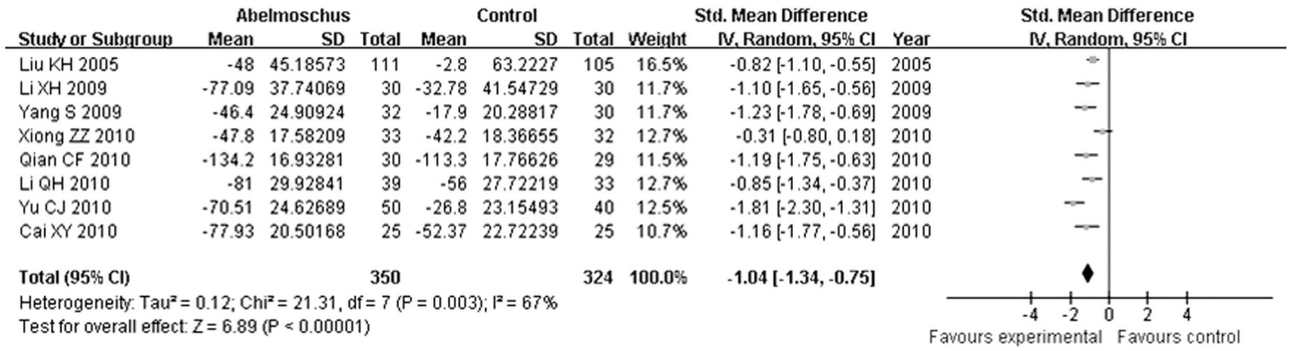

Figure 5 Effect of Abelmoschus manihot on urinary albumin excretion rate in diabetic nephropathy patients

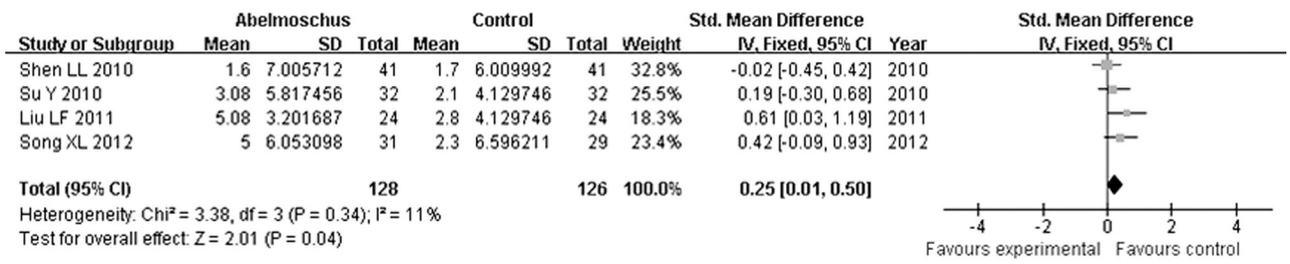

Figure 6 Effect of Abelmoschus manihot on serum albumin in diabetic nephropathy patients

ment because of side effects. This Meta-analysis could not carry out a systematic review on adverse effects because of the lack of reporting on severe side effects in all the clinical trials involved.

The findings of our Meta-analysis demonstrate that Huangshukuihua (*Flos Abelmoschi Manihot*) treats DN patients by improving renal function and reducing urine protein.

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