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Comparative study of safflower yellow adjuvant to conventional treatment regimen and conventional treatment regimen on diabetic nephropathy

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Diabetic nephropathy (DN) is one of the most important comorbidities of diabetic patients, which places large physiological and economic burdens on patients. Safflower yellow, a natural pigment extracted from the petals of safflower, has been put into adjuvant therapy. Databases including Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, MEDLINE and etc. will be searched for relevant articles. A meta-analysis was carried out to assess the efficacy and safety of safflower yellow adjuvant to conventional treatment regimen using mean differences (MD) and rate ratios (RR). A cost-effectiveness analysis was also conducted based on the result of meta-analysis. Finally, 28 articles involving 2251 patients were included in meta-analysis. The results showed that compared with conventional treatment, the fasting blood-glucose (FBG) [MD = 0.40], urinary albumin ejection rate (UAER) within 24 h [MD = 48.16], serum creatinine (Scr) [MD = 9.63], blood urea nitrogen (BUN) [MD = 1.73] were significantly lower and the clinical efficacy [RR = 1.28] was more remarkable in safflower yellow adjuvant to conventional treatment group. Our analysis suggested that safflower yellow adjuvant to conventional treatment regimen not only had better clinical efficacy but more cost-effective than conventional treatment regimen.

Diabetic nephropathy (DN), one of the important complications of diabetics, is the second leading cause of end-stage renal disease (ESRD) behind glomerulonephritis with the main clinical features of chronic hyperglycemia and proteinuria. Foreign data display that the prevalence rate of DN is 20% to 40%[1]. In China, the prevalence of DN also significantly increased. The prevalence rate of DN in type II diabetic patients was about 30% to 50% in community patients and 40% in inpatients between 2009 and 2012[2,3]. The domestic and foreign statistical data in patient with secondary DN showed that about 95% percent of patients with insulin-dependent diabetes mellitus (IDDM) with nephropathy die of uremia and coronary heart disease after 15 to 20 years[4]. The morbidity and mortality rates of DN in China is not optimistic.

DN had negative impacts on patients for the reason that patients with DN often suffer from negative emotions due to the physical pain of disease and longer duration of treatment[5]. What's more, long term hospitalization and treatment not only increased society burden but also increased economic burden of family because patient need to be taken care of by their family or friends. The survey revealed that the economic burden of diabetes mellitus in China was not optimistic. The total burden of type 2 diabetes mellitus and its complications was 41.37 billion yuan in urban China ,including direct medical cost 33.02 billion yuan, accounting for 6.2% of the total medical costs in 2002[6]. And 57.469 billion yuan was attributed to health expenditures of diabetes mellitus which occupy 7.57% of the total medical costs in China in 2004[7]. Up to 2007, the overall cost of treating diabetes mellitus has run into 247.8 billion yuan[8]. DN, the main complications of diabetes mellitus, naturally take up a large proportion. Thus, the economic burden of DN was comparatively heavy.

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The current conventional treatment of DN are angiotensin converting enzyme inhibitors (ACEI), diuretic, hypoglycemic agents, calcium channel blockers and so on, such as valsartan, benazepril, metformin and so on. But everyone of them has disadvantages for the treatment of DN accompanied by varying degrees of adverse events. Safflower yellow, a natural pigment extracted from the petals of safflower, has a variety of pharmacological effects, such as dilating blood vessels, improving myocardial blood supply, inhibiting aggregation of platelet, inhibiting thrombosis, antioxidation and so on, and has now been put into clinical treatment of DN[9]. System evaluations on applications of safflower yellow to the treatment of DN have existed, however, the data included in the study ignored the impact of base case values on the result. In this study, a meta-analysis was conducted according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist for meta-analyses of observational studies to assess the efficacy and safety of safflower yellow in the treatment of DN from the perspective of evidence-based medicine[10]. A decision tree model was also conducted to perform the cost-effectiveness analysis based on consolidated health economic evaluation reporting standards to compare the economics of different therapies so as to find the optimal therapeutic strategy with both efficacy, safety and economy, providing guidance for clinical rational drug use, resources rational allocation and medical costs savings[11].

Methods

Methods of *meta*-analysis

Search strategy

We carried out a comprehensive medical literature search on Chinese database, such as VIP database, *Chinese National Knowledge Infrastructure (*CNKI), Wan-fang database, Si-noMed, and English database, such as MEDLINE, OLDMEDLINE, Cochrane Library, Record in process, Record supplied by publisher and ClinicalTrial.gov, for relevant articles published from January 2005 to December 2023. The search terms was: "Diabetic nephropathy" AND "Early" AND "Type II" AND "Safflower flavin" OR "Safflower injection".

Inclusion and exclusion criteria

Related articles were included if meeting the eligibility criteria as follows: (1) Randomized controlled trials (RCTs); (2) The subjects were patient with early DN and there were no restrictions on the age and sex. All patients met the diagnostic criteria of World Health Organization (WHO) type 2 diabetes diagnosis standard in 1999. Nephropathy was diagnosed as early diabetic nephropathy in accordance with the standarded stages of Mogensen[12]; (3) Patients in intervention group receiving safflower yellow injection, safflower yellow sterile powder for injection, safflower yellow adjuvant to conventional treatment or other drugs, such as benazepril, metformin, valsartan, telmisartan and so on. Conventional treatment was consisted of glucose lowering therapy, (including diet control, adding exercise as well as using hypoglycemic drug) and treating comorbidity, such as hypertension, hyperlipidemia and so on. Antihypertensive drugs give preference to angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitors (ACEI); (4) The control group received conventional treatment or used drugs for the treatment of DN independently, such as metformin, telmisartan and compound danshen injection, etc.; (5) Outcome measures we were interested in were the treatment efficacy of DN. Treatments were considered having obvious effect if urinary albumin excretion rate (UAER), blood urea nitrogen (BUN) and serum creatinine (Scr) dropped by more than half, plasma glucose levels falling by more than a third. Being regarded as effective if UAER dropped by less than half, BUN, Scr and plasma glucose levels also slightly reduced but less than marked level. If had little change, the treatment thought to be not effective[12]. Other outcome measures included renal function indexes, hemorheology indexes (high and low-shear viscosity, plasma viscosity, fibrinogen, hematocrit,etc.), blood biochemistry indexes (improvement of lipid indexes), insulin level (fasting blood glucose, FBG), the change in blood pressure (systolic and diastolic blood pressure) and the level of inflammatory cytokines.

On the contrary, the exclusion criteria of studies were as follow: (1) Full-text could not be obtained; (2) Studies with incomplete data or serious errors; (3) Studies with duplicate publications or data duplication; (4) Retrospective studies; (5) The experimental design and the result of the studies remain unclear or incomplete; (6) Studies about animal trial.

Data extraction

Articles searched based on the retrieval strategy mentioned above were imported into NoteExpress for literature management. Two reviewers independently screened the literature based on inclusion and exclusion criteria and data elements of interest were extracted against Excel spreadsheets. Any discrepancies in the extracted data between the two independent reviewers were resolved by involving the third reviewer. The following data were extracted: (1) The general information of the study: author, publication time, sample size, age, research type, etc.; (2) Intervention: the usage, dosage and course of treatment; (3) Outcomes: the criteria for clinical assessment of therapeutic efficacy of DN, renal function indexes, hemorheology indexes, blood biochemistry and insulin level, etc.

Quality assessment

Two reviewers assessed the risk of bias of including studies based on the criteria of the Cochrane Risk of Bias Tool (Cochrane Handbook for Systematic Reviews of Interventions)[13]. Risk of bias rating for each study was estimate as follow: (1) The correctness of randomization, allocation concealment and blinding (performance bias); (2) Evaluator blinding (measurement bias); (3) The completeness of the results data (follow-up bias); (4) Selective reporting (reporting bias); (5) Other bias. Risk of bias for each domain was divided into three levels: low, high and unclear risk of bias. Any discrepancies in the quality assessment between the two independent researchers were resolved by involving the third researcher.

Statistical analysis
The R Programming Language (R version 4.3.0) was used to do the meta-analysis of all eligible studies. Dichotomous data and numerical data were used relative risk (RR), mean difference (MD) as outcome indexes respectively, and the 95% confidence intervals (CI) were also calculated[13]. The presence of heterogeneity among studies was evaluated. If there was no significant statistical heterogeneity ($P > 0.1$, $I^2 < 50\%$), a fixed-effect model was used to analyze the data. If the heterogeneity was obvious ($P < 0.1$, $I^2 > 50\%$), the random-effects model was used to combine the data.

Methods for the cost-effectiveness analysis
For the high incidence rate, heavy disease burden and long disease duration of DN, in this section, we developed a decision tree model to assess the cost-effectiveness of safflower yellow adjuvant to conventional treatment versus conventional treatment over a course of treatment (14 days) from the patient perspective applying the efficacy and safety indexes obtained from meta-analysis completed previously[14,15]. According to per capita gross domestic product (GDP) in China in 2023 (89,358 yuan), the willingness-to-pay (WTP) thresholds for being very cost-effective and cost-effective were 89,358 yuan and 268,074 yuan, respectively. Decision tree model was performed in TreeAge pro software (https://www.treeage.com).

Cost data
This was a retrospective study, therefore indirect cost and implicit cost were not included in our analysis. We adopted patients' perspective to calculate the direct cost. Because the price varied in different areas and time, the latest prices of medicine at the provincial level were chosen. Cost of medicine was the average cost of each disease status which was not related with the disease severity. What's more, we assumed that the cost of routine treatment remained the same at different groups. All costs were discounted to their present values at an annual discount rate of 5%.

The direct medical costs were covered, including drug cost and inpatient cost. The costs were derived from drug price inquiry website (https://www.315jiage.cn). [6] The drug price from the manufacturer which was common used in the randomized controlled trial included in our meta-analysis was selected for base-case analysis. Finally, safflower yellow injection from Yongning pharma was chosen. Drug from other manufacturers were sequenced by price per milligram of active ingredient. The highest and lowest prices were used for sensitivity analysis. The total drug cost was calculated by drug price, as shown in Table 1, multiplied by the dosage weighted according to weight from meta-analysis. For conventional treatment, glucovance, valsartan, benazepril, atorvastatin calcium capsules and salvia miltiorrhiza injection were used for lowering blood glucose, reducing blood pressure, regulating blood lipid and conventional Chinese medicine treatment, respectively. One course of conventional treatment regimen (14 days) and safflower yellow injection (14 days) cost 459.75 (308.87–518.01) and 1140.8 (572.6–2237.2) yuan, respectively. Inpatient cost per day including inspection cost (152.66 yuan), nursing cost (13.04 yuan), operation cost (111.91 yuan) and bed charges (61.12 yuan)[17]. The final inpatient cost within the course of treatment was 9,859.04 yuan on the basis of the treatment cycle and discount rate.

Effectiveness
The effectiveness indicator was the efficacy rate of treating DN, taking the criterion for curative effect judgment of DN as the standard of diagnosis. We scored "1" if the treatment is effective, otherwise we scored "0". The efficacy rate of treating DN used in finial cost-effectiveness analysis was weighted according to the weight of each study in meta-analysis as shown in the forest plot. The result displayed that the efficacy rates were 71.06% and 91.24% for conventional treatment regime and safflower yellow adjuvant to conventional therapy regimen, separately.

Cost-effectiveness analysis and sensitivity analysis
We conducted a cost-effectiveness analysis and report incremental cost-effectiveness ratios (ICERs) in baseline analysis. Both one-way sensitivity analysis and probability sensitivity analysis were conducted to assess the robustness of the results. For one-way sensitivity analysis, the efficacy rate would increase or decrease by 5% and the upper and lower limits of the drug prices were derived from drug price inquiry website as mentioned above (Table 1). Probabilistic sensitivity analysis (PSA) was performed with 1000 Monte Carlo simulations. The beta distribution and triangular distribution were applied for efficacy rate and cost, respectively. Finally, we used a cost-effectiveness acceptability curve to present the results of PSA[18].

Drug names	Baseline/yuan	Minimum/yuan	Maximum/yuan	Daily dose
Glyburide and metformin HCI tablets (60 tablets)	16.37	10.6	32.59	2 tablets
Safflower yellow injection (50 mg*10 tubes)	407.43	204.5	799	100 mg
Valsartan (80 mg*7 pills)	37.53	24	45	80 mg
Benazepril (10 mg*14 tablets)	26	17.5	31.2	10 mg
Salvia miltiorrhiza injection (10 ml*6 tubes)	43.88	30.52	34.2	20 ml
Atorvastatin calcium capsules (20 mg*7 pills)	36.57	24	55.5	40 mg

Table 1. Drug cost. HCI, Hydrochloride; mg, milligram; ml, milliliter.

Results
Results of *meta*-analysis
Search results and study characteristics
A total of 30,224 relevant articles were identified in initial literature search and 540 of them were excluded on duplicate checking and abstract review. Finally, 28 articles, all were in Chinese, were enrolled in our studies according to the inclusion and exclusion criteria. Figure 1 shows the study selection process. There were a total of 2251 patients across the 28 articles, among which, 1134 were experimental group and 1117 were control group. The outcomes including FBG, UAER, Scr, BUN and clinical efficacy. The characteristics of the studies were list in Table 2.

Quality assessment of included literature
The quality assessment was conducted in the included studies. Among the 28 studies, 10 studies mentioned the method of generating the random sequence with most of them using random number method. All studies did not describe their allocation concealment and blinding methods. All studies had complete outcome data. Other sources of bias cannot be judged. The results of quality assessment of included studies were shown in Fig. 2, indicating that the quality of these studies were credible and can be used to further study.

Meta-regression analysis
14 studies reported comparisons in FBG between patients who did and did not undertake safflower yellow for adjuvant treatment. Heterogeneity test showed statistical significance ($P < 0.0001$, $I^2 = 87.17\%$), so random effect model was selected for weighting and pooling data. The result showed that the level of FBG was significantly decreased in safflower yellow adjuvant to conventional treatment group compared with conventional treatment group (MD = 0.40, 95%CI 0.05 to 0.75; Fig. 3A).

16 studies were used in the meta-analysis of UAER by using random effect model ($P < 0.0001$, $I^2 = 99.98\%$). UAER was lower in safflower yellow adjuvant to conventional treatment group than in conventional treatment group (MD = 48.16, 95%CI 28.66 to 67.66; Fig. 3B).

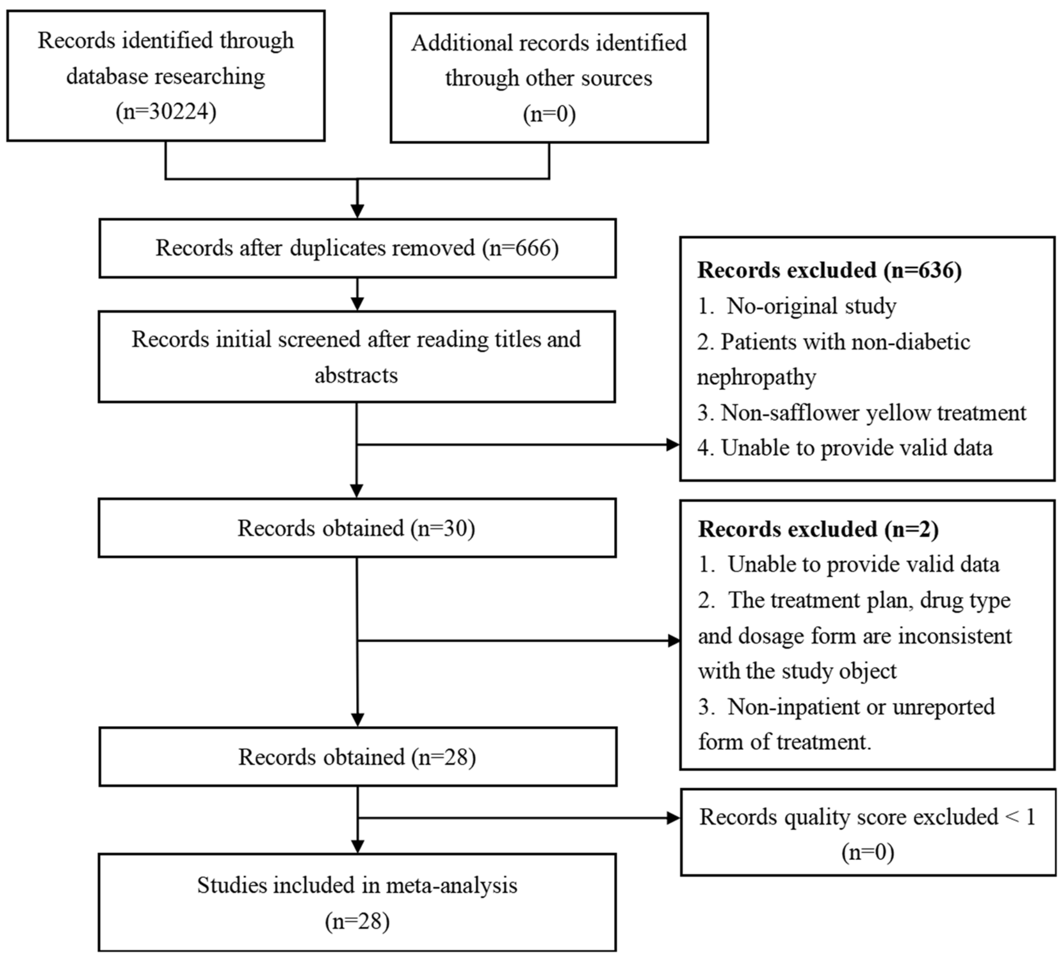

Figure 1. Flow diagram of studies considered for inclusion.

Study ID	Age		Sample size		The dosage regimen		Course	Evaluation indicator
	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group		
Xuemei Bai 2012[19]	55.8 ± 7.6	56.0 ± 7.9	30	30	CT + SY 200 mg	CT	30d	①②
Xijing Bao 2017[20]	49.74 ± 7.03	50.45 ± 7.12	40	40	CT + Metformin hydrochloride 2 g + SY 100 mg	CT + Metformin hydrochloride 2 g	14d	①⑤
Yan Gao 2015[21]	65.0 ± 5.8	64.6 ± 5.7	60	60	CT + Benazepril 10 mg + SY 100 mg	CT + Benazepril 10 mg	28d	①③④⑤
Zhi Li 2012[22]	61.3	61.3	30	30	CT + Losartan potassium 50 mg + SY100mg	CT + Losartan potassium 50 mg	15d	⑤
Jingjing Liu 2019[23]	56.72 ± 6.03	57.36 ± 5.87	55	55	CT + Metformin 5 mg + SY100mg	CT + Metformin 5 mg	21d	①③④
Xiang Fang 2017[24]	65.3 ± 12.8	66.4 ± 11.5	52	50	CT + SY 150 mg	CT	14d	②③④⑤
Tianlin Qiu 2013[25]	52.7 ± 7.1	51.6 ± 6.6	44	42	CT + Valsartan 80 mg + SY 100 mg	CT + Valsartan 80 mg	30d	⑤
Yiming Wang 2017[26]	51.18 ± 12.67	50.66 ± 11.27	60	60	CT + Metformin 4.0 g + SY 100 mg	CT + Metformin 4.0 g	14d	①⑤
Lijun Duan 2017[27]	55.21 ± 4.35	55.21 ± 4.35	60	60	Alprostadil injection 10 μg + SY 100 mg	Alprostadil injection 10 μg	14d	⑤
Yongli Feng 2016[28]	53.7 ± 7.1	50.6 ± 6.6	30	30	CT + SY and sodium chloride injection100 ml + Xylitol injection 150 ml + Shenmai injection 50 ml	CT + SY and sodium chloride injection100 ml	14d	⑤
Yuxia Xiao 2016[29]	59.5 ± 12.4	58.9 ± 13.2	40	40	CT + SY injection 100 ml	CT	28d	②⑤
Yan Gao 2015[30]	51.13 ± 7.42	51.13 ± 7.42	44	44	CT + Telmisartan tablets 80 mg + SY 100 mg	CT + Telmisartan tablets 80 mg	28d	③④
Hailiang Yu 2014[31]	40 ~ 76	40 ~ 76	36	32	CT + SY 100 mg	CT + Compound salvia miltiorrhiza 20 ml	14d	②③
Zhenfu Fang 2015[32]	55.8 ± 7.6	56.0 ± 7.9	45	45	CT + Valsartan 80 mg + SY injection 100 ml	CT + Valsartan 80 mg	56d	②⑤
Shengkai Wu 2019[33]	54.24 ± 2.91	54.24 ± 2.91	50	50	CT + SY injection 20 ml	CT	28d	①
Rui Xie 2018[34]	56.1 ± 8.4	55.1 ± 8.0	34	34	CT + Sulodexide 3 pills + SY 100 mg	CT + Sulodexide 3 pills	21d	①③④
Tongdao Xu 2014[35]	36.8 ± 14.2	36.8 ± 14.2	18	18	CT + Pancreatic kininogenase + SY injection 100 ml	CT + Pancreatic kininogenase	21d	①②⑤
Shufeng Yan 2015[36]	45.6 ± 4.6	45.3 ± 4.5	36	36	CT + Valsartan 80 mg + SY 100 mg	CT + Valsartan 80 mg	30d	①②③④
Bikui Yang 2011[37]	59 ± 7.7	59 ± 7.7	38	34	CT + SY 100 mg	CT + Compound salvia miltiorrhiza 20 ml	14d	②③
Xingshun Yang 2007[38]	53.4 ± 5.4	53.5 ± 5.6	24	24	CT + Safflower yellow 80 mg	CT + Salvia miltiorrhiza 20 ml	28d	①
Xiaoping Yang 2012[39]	66	66	34	33	SY 100 mg + alpha-lipoic acid 600 mg	Conventional western medicine treatment	15d	①②
Siyu Jiao 2012[40]	58	56	30	30	CT + SY injection (Acupoint injection therapy, 2 ml per acupuncture point)	CT	30d	⑤
Meilan Yin 2018[41]	55.89 ± 5.20	56.44 ± 5.20	52	53	CT + SY 100 mg	CT	14d	①②③④
Yong Guo 2010[42]	48 ± 11.6	48 ± 11.6	42	39	CT + SY 100 mg	CT + Danhong injection 20 ml	14d	②③
Lihua Yang 2010[43]	58.6	58.3	30	30	CT + SY 100 mg	CT	14d	①②⑤
Dengzhou Guo 2008[44]	47.3 ± 12.6	46.9 ± 13.2	39	37	CT + Benazepril 10 mg + SY 150 mg	CT + Benazepril 10 mg	30d	②⑤
Xiangying Zhang 2010[45]	48 ~ 80	46 ~ 78	36	36	CT + Irbesartan150mg + SY 100 mg	CT + Irbesartan150mg	28d	①②③④
Zhaoming Shi 2015[46]	48	48	45	45	CT + Valsartan 80 mg/d + SY 150 mg	CT + Valsartan 80 mg/d	84d	②

Table 2. Characteristics of included studies. SY, Safflower yellow; CT, Conventional treatment; d, day; ① = FBG, Fasting blood-glucose; ② = UAER, Urinary albumin excretion rate; ③ = Scr, Serum creatinine; ④ = BUN, Blood urea nitrogen; ⑤ = Clinical efficacy.

The heterogeneity was observed among 11 studies evaluating the change of Scr ($P < 0.0001$, $I^2 = 92.58\%$). The result showed that safflower yellow could also lower the Scr level within the random effect model (MD = 9.63, 95%CI -1.50 to 20.76; Fig. 3C).

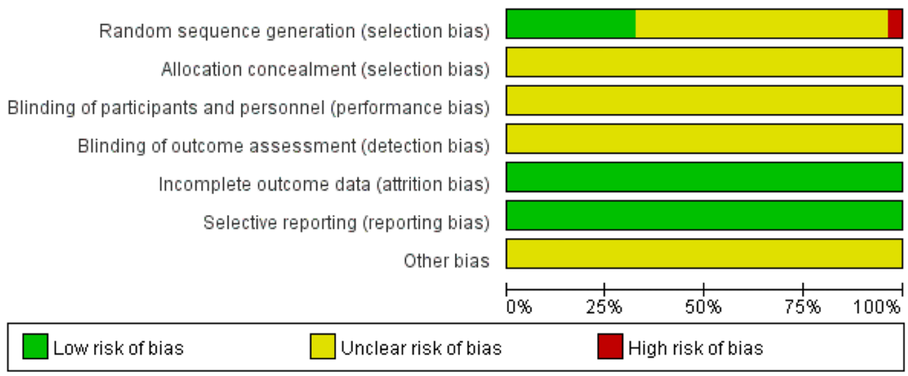

Figure 2. Risk of bias summary.

8 studies were included for the assessment of BUN. The heterogeneity was observed ($P < 0.0001$, $I^2 = 88.06\%$), so the random effects model was used in the meta-analysis. The results indicated that safflower yellow adjuvant to conventional treatment could remarkably reduce the levels of BUN (MD = 1.73, 95%CI 1.03 to 2.43; Fig. 3D).

What's more, a total of 15 studies reported the clinical efficacy were screened out. The fixed-effect model was used to combine the data for the reason that there was no significant heterogeneity ($P = 0.10$, $I^2 = 33.00\%$). The results suggested that the total efficacy rate in safflower yellow adjuvant to conventional treatment group was higher than that in conventional treatment group (RR = 1.28, 95%CI 1.21 to 1.36; Fig. 3E).

Among the 28 studies, 15 studies did not report adverse events, 10 of them claimed that no adverse events were noted, only 3 of them reported the adverse events. In two studies, one patient felt headache and sickness during the course of medicine application in safflower yellow adjuvant to conventional treatment group, respectively, but symptoms relieved after slowing down infusion rate. In another study, one patient had abnormal liver function and one patient had an allergic reaction in conventional treatment group. One patient had an allergic reaction in safflower yellow adjuvant to conventional treatment group. These findings suggested that safflower yellow had good efficacy and safety for treatment of DN with less adverse events.

Results of cost-effectiveness analysis

Table 3 show the expected total costs and effectiveness for each treatment group. Compared with CT group, the ICER of safflower yellow adjuvant to conventional treatment group (5,653.12 yuan) was lower than per capita GDP in 2023 in China, indicating that safflower yellow adjuvant to conventional treatment was very cost-effective. The results of one-way sensitivity analysis were presented in the tornado diagram (Fig. 4). The cost of safflower yellow per course was the most influential parameter, and the ICER varied from 2837.46 to 11,086.22 yuan.

The scatter plot and cost-effectiveness acceptability curve show the results of probability sensitivity analysis over the range of WTP threshold (Fig. 5). When WTP threshold was higher than 5,600 yuan, the probability that safflower yellow adjuvant to conventional treatment being cost-effective would greater than 50%. The results of sensitivity analysis were consistent with base-case analysis, indicating that the result were relatively stable.

Discussion

In this study, we conducted a meta-analysis to compare the efficacy and safety of safflower yellow adjuvant to conventional treatment versus conventional treatment regimen for diabetic nephropathy patients. A cost-effectiveness analysis was also taken by using Bayesian method. The study included 28 studies, although the basic feature of including studies such as sex and age were consistent, most of indexes were inconsistent. Therefore, meta-analysis was derived based on random effects model. The result reflected that there was a significant difference between conventional treatment group and safflower yellow adjuvant to conventional treatment group in each index (FBG, UAER, Scr, BUN and efficacy rate). Compared with conventional treatment, safflower yellow adjuvant to conventional treatment was a better choice because more beneficial effect was found. In terms of safety, only three studies reported adverse effects and all were mild after receiving safflower yellow during 13 studies, suggesting that the safety of safflower yellow adjuvant to conventional treatment was quite well.

Although the efficacy rates used in cost-effectiveness analysis was weighted from several studies, it was consistent with the result of meta-analysis indicating that the weighted result was reasonable. From the perspective of pharmacoeconomics, safflower yellow adjuvant to conventional treatment was more cost-effective in China because the ICER was 5653.5 yuan, lower than per capita GDP in 2023. Furthermore, our research also indicates that Chinese patent drug combined with western medicine treatments would improve health outcomes and being economical at the same time. This field worth more research and attention.

Nevertheless, there were some limitations in our study. First, the sample size included in our study was less which lower the credibility to a certain extent. Second, the implement of randomization, allocation concealment and blinding were not described in the included studies, suffering from risk of bias to a certain degree according to the Cochrane Collaboration's tool. Third, the dose of safflower yellow and drugs for conventional treatment were different from various studies which may lead to selective bias. What's more, risk of bias was also existed in pharmacoeconomics evaluation, because the dose of safflower yellow and drugs for conventional treatment, most

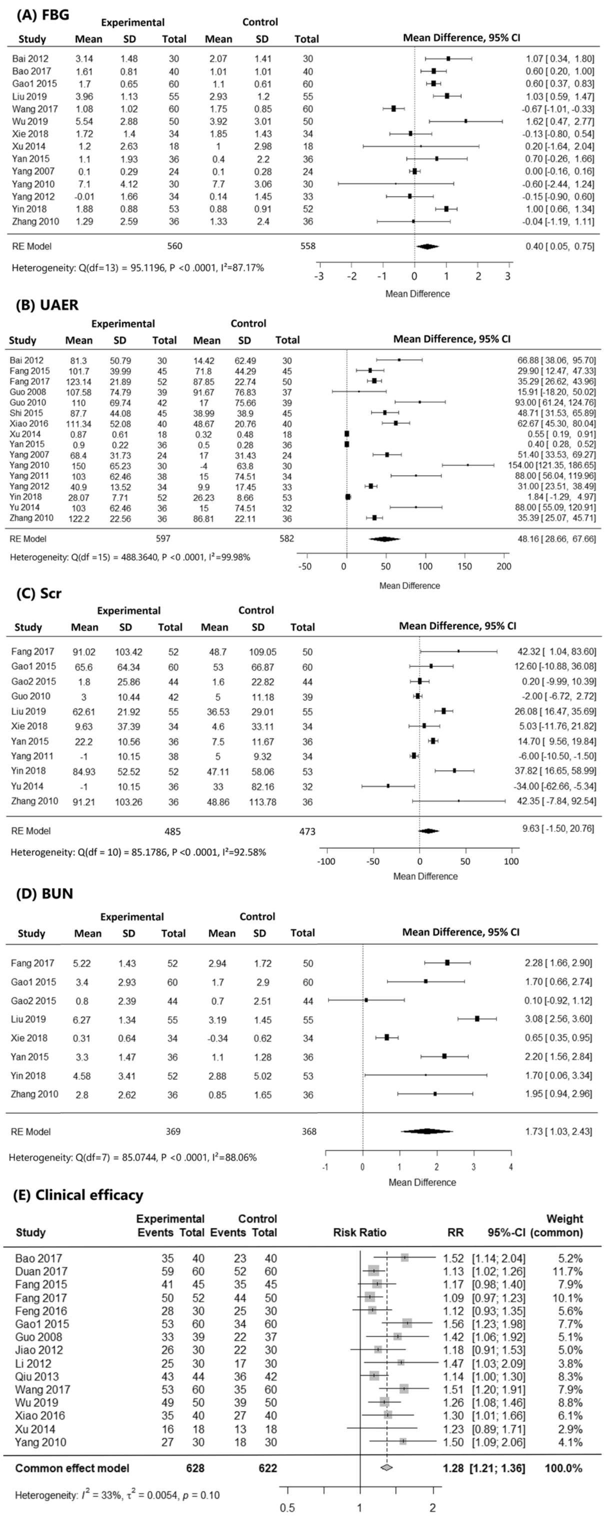

Figure 3. Forest plots from meta-analysis. FBG, fasting blood-glucose; UAER, urinary albumin excretion rate; Scr, serum creatinine; BUN, blood urea nitrogen.

frequently used during the studies, were also applied for cost-effectiveness analysis. Fourth, gray literature, such as special coverage, unpublished materials and so on, was not considered in our study. In addition, long term follow-up studies for safety evaluation was lacking, so the long-term risk of applying safflower yellow remained unknown. Finally, because the costs used in our analysis was the older data, there may be deviation when doing discount calculation which may influence the final result.

Treatment	Cost (yuan)	Effectiveness	Incremental cost (yuan)	Incremental effectiveness	ICER
CT	10,318.79	0.7106	–	–	–
SY adjuvant to CT	11,459.59	0.9124	1140.80	0.2018	5653.12

Table 3. Result of base-case analysis. CT, conventional treatment; SY, safflower yellow; ICER, incremental cost-effectiveness ratio.

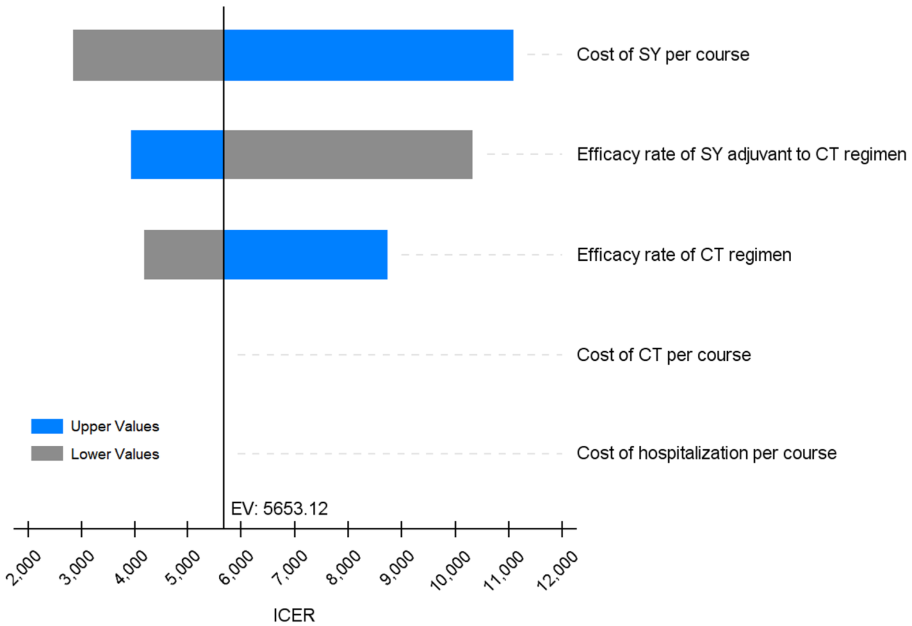

Figure 4. Tornado diagram. CT, conventional treatment; SY, safflower yellow; EV, expected value.

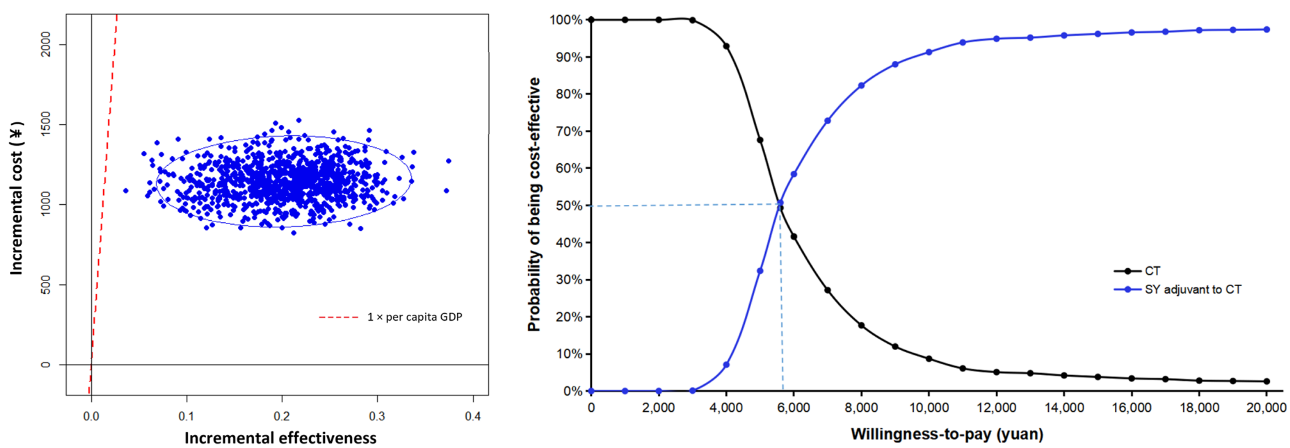

Figure 5. Scatter plot and cost-effectiveness acceptability curve. GDP, gross domestic product; CT, conventional treatment; SY, safflower yellow.

Conclusion

In summary, compared with conventional treatment regimen, safflower yellow adjuvant to conventional treatment regimen could improve the total efficacy rate with less adverse reactions which could be safe to use. Meanwhile, safflower yellow adjuvant to conventional treatment regimen was very cost-effective according to the WTP in China (per capita GDP in 2023). Therefore, safflower yellow was recommended as an adjunct to conventional treatment including hypoglycemic, antihypertensive and lipid-lowering therapy in patients with DN. Given the limited data sets now, additional clinical trials and health economic evidence are needed to support the conclusion of this study.

Data availability

The data used are included in the manuscript.

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Author contributions

L.Y. (Yang Li) conceived the study; L.Y. (Yun Liang) and C.X.D. designed and performed the study; L.Y. (Yun Liang), C.X.D. and L.S.N. drafted and wrote the paper. All authors finally revised and approved the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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