Effects of Niaoduqing granules on inflammatory response of diabetic kidney disease: A meta-analysis

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Abstract. Diabetic kidney disease (DKD) is one of the most severe chronic microvascular complications of diabetes and the leading cause of end-stage kidney disease worldwide. The mechanism of inflammation underlying DKD has been attracting attention over recent years, but effective therapeutic strategies have remained elusive. Niaoduqing (NDQ) granules are one of the most commonly used drugs for the treatment of DKD in China, and it has therapeutic effects against inflammation in DKD. Therefore, the aim of the present analysis was to evaluate the inflammatory response outcomes and safety of NDQ granules for the treatment of DKD. The following databases were searched from their inception to 31st of May 2023 to obtain published accounts of relevant randomized controlled trials: China National Knowledge Infrastructure, China Science and Technology Journal, Wanfang, The Chinese Biomedicine, PubMed, Web of Science and Cochrane Library. The 'risk of bias' evaluation tool produced by the Cochrane Collaboration Handbook was used for evaluating the quality, whereas Revman software (version 5.3) was used for meta-analysis. In total, 16 studies were included into the present study according to criteria, with a total of 1,526 patients. Compared with those in the control group, the results of the meta-analysis revealed that the combination of conventional treatment and NDQ granules may further decrease C-reactive protein [standardized mean difference (SMD), -1.33; 95% confidence interval (CI), -1.76, -0.91; P<0.00001], TNF-α (SMD, -1.90; 95% CI, -2.35,-1.45; P<0.00001) and IL-6 (SMD, -1.72; 95% CI, -2.52,-0.91; P<0.0001) levels, whilst increasing the clinical effective rate (risk ratio, 1.22; 95% CI, 1.14,1.29; P<0.00001), in patients with DKD. In terms of safety, a total of 34 and 39 patients included in the intervention and in the control group, respectively, developed adverse reactions. Results from the present analysis suggest that NDQ granules may be beneficial in suppressing inflammation caused by DKD when used in combination with conventional treatment, potentially guiding future directions in clinical practice. However, further high-quality studies are needed to confirm the anti-inflammation response in the future.

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Introduction

Diabetic kidney disease (DKD) is one of the most severe chronic complications in patients with diabetes mellitus (DM) and the leading cause of end-stage kidney disease (ESRD) worldwide (1,2). Consequently, DKD-associated ESRD incurs colossal human, social and financial burdens. In 2019, it was estimated that ~463 million individuals were afflicted with DM according to the statement of International Diabetes Federation, the number of which is predicted to increase to 693 million in the next 25 years (3). According to the latest epidemiological survey in China, 34.2% of patients with DM developed DKD (4). Therefore, the early diagnosis and treatment of DKD are of high importance. Since the pathophysiology of progressive microvascular decay caused by DM and its association with inflammatory response was first proposed in 1999 (5), accumulating evidence has supported the notion that the inflammatory response serves a vital role in the occurrence and progression of DKD (6). Such reported inflammatory factors include C-reactive protein (CRP), TNF-α and IL-6. A randomized, double-blind, placebo-controlled 3x3 crossover study previously demonstrated that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARB) were able to induce anti-inflammatory effects (7). In addition, sodium-glucose co-transporter 2 (SGLT2) inhibitors were shown to provide renal protection other than decreasing glucose and reducing the events of composite cardio/kidney endpoints (8). However, SGLT2 inhibitors may also decrease the estimated glomerular filtration rate (eGFR) and increase the risk of genitourinary system infection and ketoacidosis (9). A systematic analysis of a series of chronic kidney disease (CKD) cases from 1990 to 2017 published in The Lancet concluded that the currently existing treatments are not sufficient to prevent the deterioration from CKD into ESRD (10).

Therefore, there are substantial challenges remaining in treating DKD, such that more effective novel treatment methods are urgently in demand.

Emerging advantages of Traditional Chinese Medicine (TCM) have been garnering attention in both academic and clinical research fields. DKD pertains to the category of 'Shenxiao' in TCM (11). On the basis of the theory of TCM, deficiency of kidney and spleen along with dampness, turbid phlegm and blood stasis dominate the pathogenesis of DKD. Correspondingly, the treatment principle is to tonify kidney and spleen, replenish water and tonify qi, supplemented by activation of blood and dissolution of stasis. Niaoduqing (NDQ) granules is a patented TCM formulation that has the reported functions of 'tonifying spleen' (jian-pi), 'free fu' (tong-fu) and 'eliminating pathogens' (jie-du). It has been applied in clinical practice in China for ≥20 years. The NDQ granules received approval by the China State Food and Drug Administration (National Medical Products Administration) to treat CKD (national medicine permit no. Z20073356) in 2000. It is composed of 16 TCM herbs (12), including rhubarb root and rhizome (*Radix et Rhizoma rhei*), white paeony root (*Paeoniae Radix Alba*), milkvetch root (*Astragali Radix*), Pinellia ternata (*Pinelliae Rhizoma*), chrysanthemum flower (*Flos Chrysanthemi*), Danshen root (*Radix Salviae miltiorrhizae et Rhizoma*), Szechuan lovage rhizome (*Chuanxiong Rhizoma*), tuber fleeceflower root (*Polygoni Multiflori Radix*), Medicinal Changium root (*Changii Radix*), Largehead Atractylodes Rh (*Atractylodis macrocephalae rhizoma*), Indian buead (*Poria*), white mulberry root bark (*Mori Cortex*), lightyellow sophora root (*Radix Sophorae Flavescentis*), Asiatic plantain herb (*Plantaginis Herba*), Chinese Thorowax root (*Bupleuri Radix*) and liquorice root (*Glycyrrhizae Radix et Rhizoma*). NDQ granules have been used to treat patients with CKD according to the 'Clinical Application Guide of Chinese Patent Medicine in The Treatment of CKD' (13). Over the past few years, various clinical trials have attempted to assess the effects of treatment with NDQ granules on DKD, and its effectiveness has been initially verified. Evidence from these clinical studies suggested that the NDQ granules are not only able to improve kidney function, but may also reduce the severity of the inflammatory response by adjusting the micro-inflammatory state compared with basic treatment or placebo (14,15). However, the sample size of available clinical trial data on NDQ granules in terms of its anti-inflammatory effects is relatively small, rendering the evidence inconclusive. Therefore, the present systematic review and meta-analysis was performed to assess the effects of NDQ granules on the inflammatory response to provide additional information on the effects of TCM treatment on DKD.

Materials and methods

Database and search strategies. The present systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (16), and has been registered to PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; registration no. CRD42022340017). However, it should be noted that the final search date was extended to 31st of May 2023 to include the most up-to-date clinical studies. In total, seven electronic databases, namely the China National Knowledge Infrastructure database (https://www.cnki.net), China Science and Technology Journal Database (www.cqvip.com), Wanfang Database (https://www.wanfangdata.com.cn), the Chinese Biomedicine Database (http://www.sinomed.ac.cn/), PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science (www.webofscience.com) and Cochrane Library (https://www.cochranelibrary.com) were searched comprehensively for literature from their inception to 31st of May 2023. Only papers published in Chinese and English were selected. The search terms used were as follows: 'NDQ', 'NDQ granules', 'NDQ particle', 'uremic clearance granules', 'diabetic kidney disease', 'diabetic nephropathy', 'nephropathy, diabetic', 'kidney disease, diabetic', 'randomized controlled trial' (RCT), 'RCT' and 'random'. The combination of subject words and free words was adopted. In addition, eligible literature was also obtained by examining the reference lists of relevant reviews and included studies manually.

Inclusion criteria. Studies were selected based on the following conditions: i) Participating patients were ≥18 years old, diagnosed with DKD based on Chinese clinical practice guidelines, expert consensus of DKD or the World Health Organization (WHO) diagnostic criteria of DM (17-19) and the staging criteria based on the internationally recognized Mogensen staging system or those produced by the WHO (5,20), regardless of sex or the presence of primary diseases, such as hypertension, hyperlipidemia or hyperuricemia; ii) intervention was carried out with the NDQ granules combined with the therapeutic regimen in the control group; iii) the control group received basic treatment, including management of hyperglycemia, hypertension, hyperlipidemia, anti-infection, correction of anemia, electrolyte, acid-basic balance and renal replacement therapy; iv) primary outcomes comprised inflammatory factors, such as CRP, TNF-α and IL-6, with or without secondary outcomes, including kidney function, proteinuria, clinical effective rate and adverse reaction rate; and v) the study design was that of an RCT regardless of blinding, protocol or bias.

Exclusion criteria. Studies were excluded based on the following conditions: i) NDQ granules treatment was combined with other Western, Chinese medicine or 'characteristically Chinese' therapies, including acupuncture or Chinese medicine enema in the intervention group; ii) case reports, reviews, observational studies, experiments on animals, experience summaries, theoretical explorations, academic papers and conference literature; iii) incomplete papers; iv) published in a language that is not English or Chinese; v) duplicate publications; vi) non-RCT; and vii) the NDQ granules used without the supplier or doses explicitly stated.

Data extraction. In total, the electronic databases were separately searched and eligible studies were selected in terms of the aforementioned inclusion and exclusion criteria. Duplicated publications were eliminated by Endnote 20 (Clarivate), before the eligible studies were logged into Microsoft Excel 16 (Microsoft Corporation) and checked against each other. Any divergence in opinion would be solved through discussion between two of the authors or by another researcher (PZ,

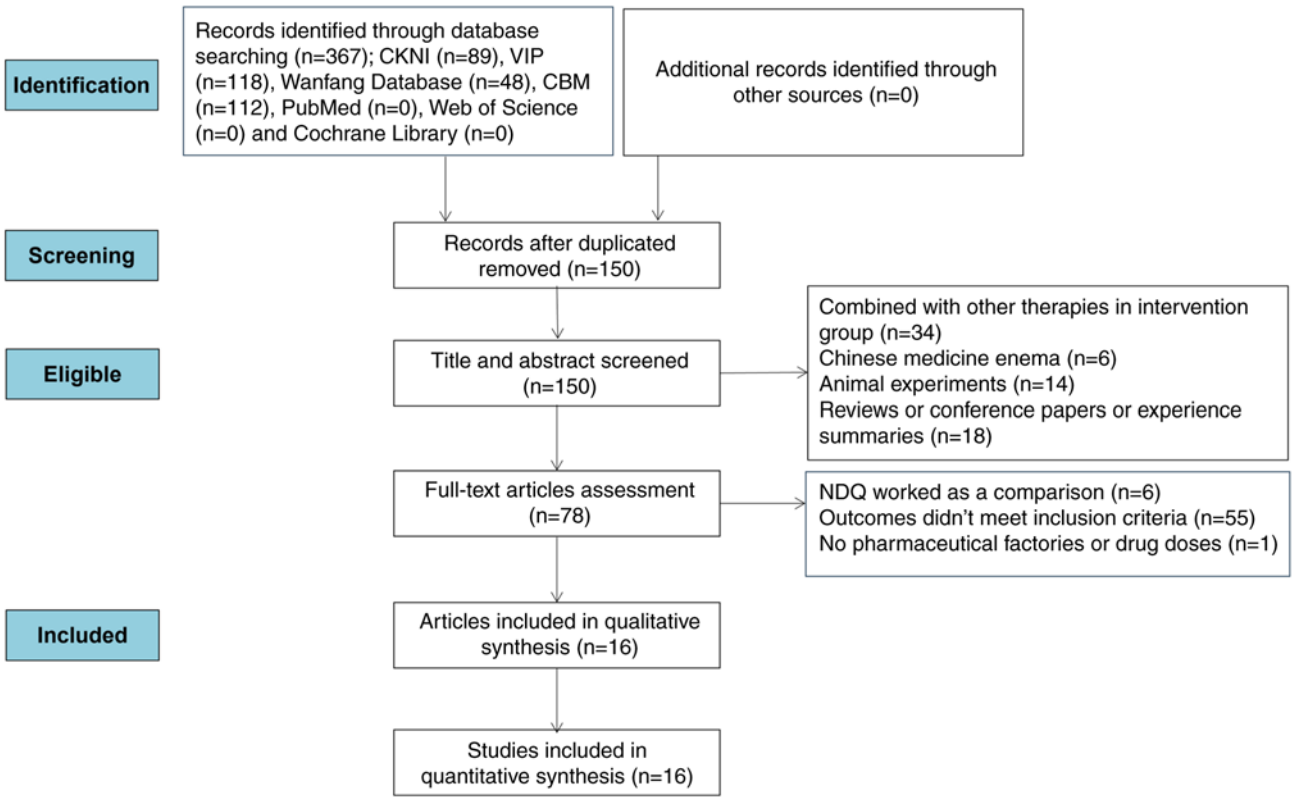

Figure 1. Flow diagram depicting the process of study selection. NDQ, Niaoduqing; CKNI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database; CBM, Chinese Biomedicine.

ZH and WX). The extracted data from each study were the following: Author, publication year, sex, age, course of DM, intervention measures, treatment duration and outcomes of inflammatory factors.

Quality evaluation. The 'risk of bias' evaluation tool provided by the Cochrane Collaboration Handbook for Systematic Reviews of Intervention was applied for the assessment of methodological quality (21). The following seven domains were used for systematic and comprehensive evaluation: i) Methods of generating random sequence; ii) hidden distribution; iii) use of the double blind technique for participants and personnel; iv) blinding of outcome assessors; v) data integrality of outcome; vi) outcome reporting with bias; and vii) other sources of bias. 'High risk', 'low risk' and 'unclear risk' were the three levels of bias designated for evaluating each of the studies included in the present analysis in the aforementioned domains.

Statistical analysis. The Review Manager software (version 5.3; Cochrane) was applied for logging data and conducting data analysis. The diverse effect measures were assigned to different variables, whereas the standardized mean difference (SMD) was used for assessing continuous variables and the risk ratio (RR) was used for dichotomous variables. In addition, the 95% confidence interval (CI) was used for statistical analysis. The tau-squared (Tau^2), inconsistency index (I^2) and chi-squared (χ^2) test were used to measure the heterogeneity of study results. The random-effects model was applied for the analysis of heterogeneity (I^2>50%) and P<0.05 was considered to indicate a statistically significant difference; otherwise, the fixed-effects model would be chosen. Simultaneously, sensitivity analysis was performed by sequentially deleting one study at a time to confirm the robustness of the present findings, whereas subgroup analyses were performed to explore the impact of heterogeneity on the overall findings. If >10 studies were included in the same analysis, the assessment of publication biases was performed using funnel plots.

Results

Search results. A total of 367 potentially relevant entries were retrieved from the aforementioned databases and 217 duplicated articles were eliminated by Endnote. After the titles and abstracts were examined, 72 studies were eliminated due to the combination of treatment with NDQ granules with other therapies in the intervention group, treatment with Chinese medicine enema, animal experiments, conference and academic papers, reviews or experience summaries. In addition, 62 studies were eliminated after the assessment of full-text articles, where NDQ granules was used as a comparison in six studies, 55 studies were rendered illegible according to the inclusion criteria, and one study was removed due to lack of supplier details and drug doses. Ultimately, 16 articles were deemed eligible for the present systematic review and meta-analysis (22-37). A summary of this screening process is depicted in Fig. 1.

Study characteristics. The 16 articles included in the present analysis comprised 1,526 patients, 765 from the intervention

group and 761 from the control group, with a sex ratio of men to women of 1:0.75 (783 males and 587 females). However, one study did not mention the specific sex distribution (30). The sample size range of the individual studies was 40-220. The average age was 57.69±9.74 years and the average course of DM was 7.79 years, while three studies (27,33,36) did not specify the course. The treatment duration range was 1-6 months. The control group received basic treatment and other conventional drugs, such as α-ketoacid, insulin and ARB. The intervention group received treatment with the NDQ granules combined with the treatment of the control group. These detailed characteristics of the studies included are summarized in Table I.

Quality assessment of included studies. All the included studies were RCTs, seven of which (22,25,26,28,29,33,37) specifically used random table methods, and one study (30) used non-standard randomization methods. None of the studies mentioned hidden allocation, triple blinding or other bias. Of note, one study (35) mentioned that incomplete outcome data was the reason for severe adverse reactions. However, a total of eight studies (22,24,26,28,30-32,36,38) briefly stated approval by the Ethics Committee of the subordinate hospital and had obtained informed consent from the patients and their family members, five studies (25,33-35,37) only mentioned informed consent and three studies (23,26,29) mentioned neither. Fig. 2 presents the results of the quality assessment of all included studies in the present review and meta-analysis.

Primary outcomes. For the outcome of CRP, 13 studies (22-25,38-35,37) were included in the analysis, consisting of 1,174 patients. Due to the high heterogeneity noted (P<0.00001; I^2=91%), the random-effects model was used to analyze the data. The combination of NDQ granules with conventional treatment was able to decrease levels of CRP compared with those in the control group (SMD, -1.33; 95% CI, -1.76,-0.91; P<0.00001; Fig. 3). In addition, 11 stu dies (22,24-26,28,30-34,36) reported TNF-α levels as an outcome, comprising 1,154 patients. A random-effects model was chosen due to high heterogeneity (P<0.00001; I^2=90%). The combination of NDQ granules and conventional treatment could decrease the levels of TNF-α compared with those in the control group (SMD, -1.90; 95% CI, -2.35,-1.45; P<0.00001; Fig. 4). A total of 8 studies (24,26,27,30,33,34,36,37) reported IL-6 as an outcome, including 905 patients. The heterogeneity remained high (P<0.00001; I^2=96%), justifying the use of the random-effects model. The data revealed that the combination of NDQ granules and conventional treatment could decrease the levels of IL-6 compared with those in the control group (SMD, -1.72; 95% CI, -2.52,-0.91; P<0.0001; Fig. 5).

Secondary outcomes

Kidney function. In total, 13 studies (22,23,25-32,35-37) contributed to the analysis of blood urea nitrogen (BUN) and these included a total of 1,219 patients. The data were analyzed using a random-effects model because of high heterogeneity (P<0.00001; I^2=82%). The meta-analysis showed that the combination of NDQ granules and conventional treatment decreased the levels of BUN compared with those in the control group (SMD, -0.96; 95% CI, -1.25,-0.66; P<0.00001; Fig. 6). Regarding serum creatinine (SCr) used as an outcome, 13 studies (22,23,25-32,35-37) were included in the analysis, and heterogeneity was found (P<0.00001; I^2=90%). The data revealed that the combination of treatment with NDQ granules and conventional treatment decreased the levels of SCr compared with those in the control group (SMD, -1.05; 95% CI, -1.44,-0.66; P<0.00001; Fig. 7). In total, seven studies (22,23,25,26,29,32,36) reported 24-h urinary protein excretion (24-h UPE), covering a total of 704 patients. Due to the high heterogeneity P<0.00001; I^2=88%), a random-effects model was used to analyze the data. The combination of treatment with NDQ granules and conventional treatment was able to decrease the levels of 24-h UPE compared with those in the control group (SMD, -1.27; 95% CI, -1.75,-0.78; P<0.00001; Fig. 8).

Clinical effective rate. A total of eight studies (22,25, 26,30-32,34,37) reported the clinical effective rate as an outcome, including a total of 744 patients. No significant heterogeneity (P=0.97; I^2=0%) was noted among them, and thus, a fixed-effects model was applied for the analysis. The meta-analysis indicated that the combination of treatment with NDQ granules and conventional treatment could increase the clinical effective rate compared with those in the control group (RR, 1.22; 95% CI, 1.14,1.29; P<0.00001; Fig. 9).

Safety. A total of nine studies (22,26,28,30,35-37) mentioned the adverse reaction rate as an outcome, including a total of 966 patients. Due to the low heterogeneity (P=0.87; I^2=0%), a fixed-effects model was used for the analysis. The data indicated that the combination of treatment with NDQ granules and conventional treatment had an incidence of adverse reactions that was not significantly different compared with that in the control group (RR, 0.87; 95% CI, 0.56,1.34; P=0.52; Fig. 10). A total of 34 patients in the control group developed adverse reaction events and 39 patients in the intervention group. Particularly, nearly half of them had gastrointestinal reactions, accounting for 15 and 14 separately., Statistics regarding the adverse reaction events are summarized in Table II.

Sensitivity analysis. Sensitivity analyses of all the outcomes were conducted to confirm the stability of the meta-analysis results. Each of the studies was removed one by one and the meta-analyses were re-performed with the remaining studies. The obtained results were then compared with the previous ones. However, no significant changes in heterogeneity could be found (data not shown), suggesting that the meta-analysis results were stable.

Subgroup analysis. Due to the persistence of high heterogeneity and a sufficient number of studies, subgroup analyses were performed to explore the sources of heterogeneity based on the dosage of NDQ granules (<30 or ≥30 g). The results revealed that the heterogeneity in the subgroup analysis of the dosage of NDQ granules of ≥30 g regarding CRP, BUN and 24-h UPE was significantly reduced (I^2<50%). However, the rest of the studies remained to be considerably heterogeneous. This finding suggests that the dosage of NDQ granules may be one of the sources of heterogeneity of the CRP, BUN and 24-h UPE data. In addition, none of the included studies regarding TNF-α could be classified because all studies describing

Table I. Details of studies included in the present meta-analysis.

Author, year	Sex, n (M/F)	Age, years, mean ± SD	Course of diabetes mellitus, years, mean ± SD	Intervention measures	Treatment duration	Outcomes	(Refs.)
Liang, 2021					4 weeks	CRP, TNF-α, BUN, Scr, 24-h UPE, CER, ADR	(22)
Intervention group	49 (27/22)	50.05±12.99	4.17±0.82	CON + NDQ 25 g/d			
Control group	48 (26/22)	50.01±13.01	4.14±0.74	Basic treatment + compound α ketoacid			
Zhang, 2011					60 days	CRP, BUN, Scr, 24-h UPE	(23)
Intervention group	40 (49/31)	54.6±7.5	11±2.5	CON + NDQ 30 g/d			
Control group	40 (49/31)	54.6±7.5	11±2.5	Basic treatment			
Zhang, 2014					12 weeks	CRP, TNF-α, IL-6,	(24)
Intervention group	52 (34/18)	68.2±7.6	8.1±3.4	CON + NDQ 20 g/d			
Control group	50 (31/19)	67.3±7.4	7.8±3.7	Basic treatment			
He, 2015					2 months	CRP, TNF-α, BUN, Scr, 24-h UPE, CER	(25)
Intervention group	24 (13/11)	47.15±3.53	6.87±1.61	CON + NDQ 25 g/d			
Control group	24 (14/10)	46.75±3.26	6.97±1.51	Basic treatment			
He, 2021					3 months	TNF-α, IL-6, BUN, Scr, 24-h UPE, CER, ADR	(26)
Intervention group	44 (23/21)	62.2±8.5	6.5±1.4	CON + NDQ 20 g/d			
Control group	43 (24/19)	61.5±8.3	6.4±1.2	Basic treatment + Valsartan			
Yang, 2010					8 weeks	IL-6, BUN, Scr	(27)
Intervention group	20 (13/7)	48.5±12.9	Not mentioned	CON + NDQ 40 g/d			
Control group	20 (13/7)	41.8±11.2	Not mentioned	basic treatment			
Wu, 2021					1 month	CRP, TNF-α, BUN, Scr, ADR	(28)
Intervention group	41 (27/14)	59.87±3.69	8.37±1.58	CON + NDQ 20 g/d			
Control group	41 (26/15)	59.84±3.67	8.36±1.57	Basic treatment + Valsartan			
Li, 2015					60 days	CRP, BUN, Scr, 24-h UPE	(29)
Intervention group	45(22/23)	52.2±6.3	9.4±3.3	CON + NDQ 30 g/d			
Control group	45(22/23)	52.2±6.3	9.4±3.3	basic treatment			
Liu, 2020					6 months	CRP, TNF-α, IL-6, BUN, Scr, CER, ADR	(30)
Intervention group	78	67.20±9.42	10.02±1.49	CON + NDQ 25 g/d			
Control group	78	65.19±7.31	9.85±2.04	Basic treatment + insulin			
Li, 2021					3 months	CRP, TNF-α, BUN, Scr, CER, ADR	(31)
Intervention group	40 (24/16)	63.24±11.36	9.47±3.21	CON + NDQ 25 g/d			
Control group	40 (27/13)	64.55±11.24	10.13±3.75	Basic treatment + Irbesartan			

Table I. Continued.

Author, year	Sex, n (M/F)	Age, years, mean ± SD	Course of diabetes mellitus, years, mean ± SD	Intervention measures	Treatment duration	Outcomes	(Refs.)
Chen, 2021					60 days	CRP, TNF-α, BUN, Scr, 24-h UPE, CER, ADR	(32)
Intervention group	41 (26/15)	51.40±1.38	8.40±1.18	CON + NDQ 20 g/d			
Control group	41 (25/16)	51.38±2.46	8.43±1.20	Basic treatment + insulin			
Zheng, 2019					3 months	CRP, TNF-α, IL-6	(33)
Intervention group	53 (31/22)	55.84±8.33	Not mentioned	CON + NDQ 20 g/d			
Control group	53 (29/24)	56.38±8.42		Basic treatment + artificial kidney			
Wang, 2017					12 weeks	CRP, TNF-α, IL-6, CER	(34)
Intervention group	47 (25/22)	63.54±4.16	4.63±1.82	CON + NDQ 20 g/d			
Control group	47 (24/23)	62.71±5.43	4.13±1.62	Basic treatment + Atorvastatin			
Gong, 2013					3 months	CRP, BUN, Scr, ADR	(35)
Intervention group	31 (15/16)	59.4±7.5	10.3±3.7	CON + NDQ 20 g/d			
Control group	31 (17/14)	60.0±7.3	10.7±3.5	Basic treatment + Irbesatan			
Tong, 2022					4 weeks	TNF-α, IL-6, BUN, Scr, 24-h UPE, ADR	(36)
Intervention group	110 (58/52)	57.1±5.4	Not mentioned	CON + NDQ 25 g/d			
Control group	110 (56/54)	55.8±5.4	Not mentioned	basic treatment + insulin, Dapagliflozin			
Yu, 2022					3 months	CRP, IL-6, BUN, Scr, CER, ADR	(37)
Intervention group	50 (32/18)	52.47±3.17	4.37±1.61	CON + NDQ 15g/d			
Control group	50 (30/20)	51.54±3.68	4.14±1.57	Basic treatment + aspirin			

CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IL-6, interlukin-6; BUN, blood urea nitrogen; Scr, serum creatinine; 24-h UPE, 24-h urinary protein excretion; CER, clinical effective rate; ADR, adverse reaction rate. M, male; F, female; NDQ, Niaoduqing granule; CON, treatment measures of control group; Basic treatment, including the management of hyperglycemia, hypertension and hyperlipidemia, anti-infection, correction of anemia, water, electrolyte, acid-basic balance and renal replacement therapy.

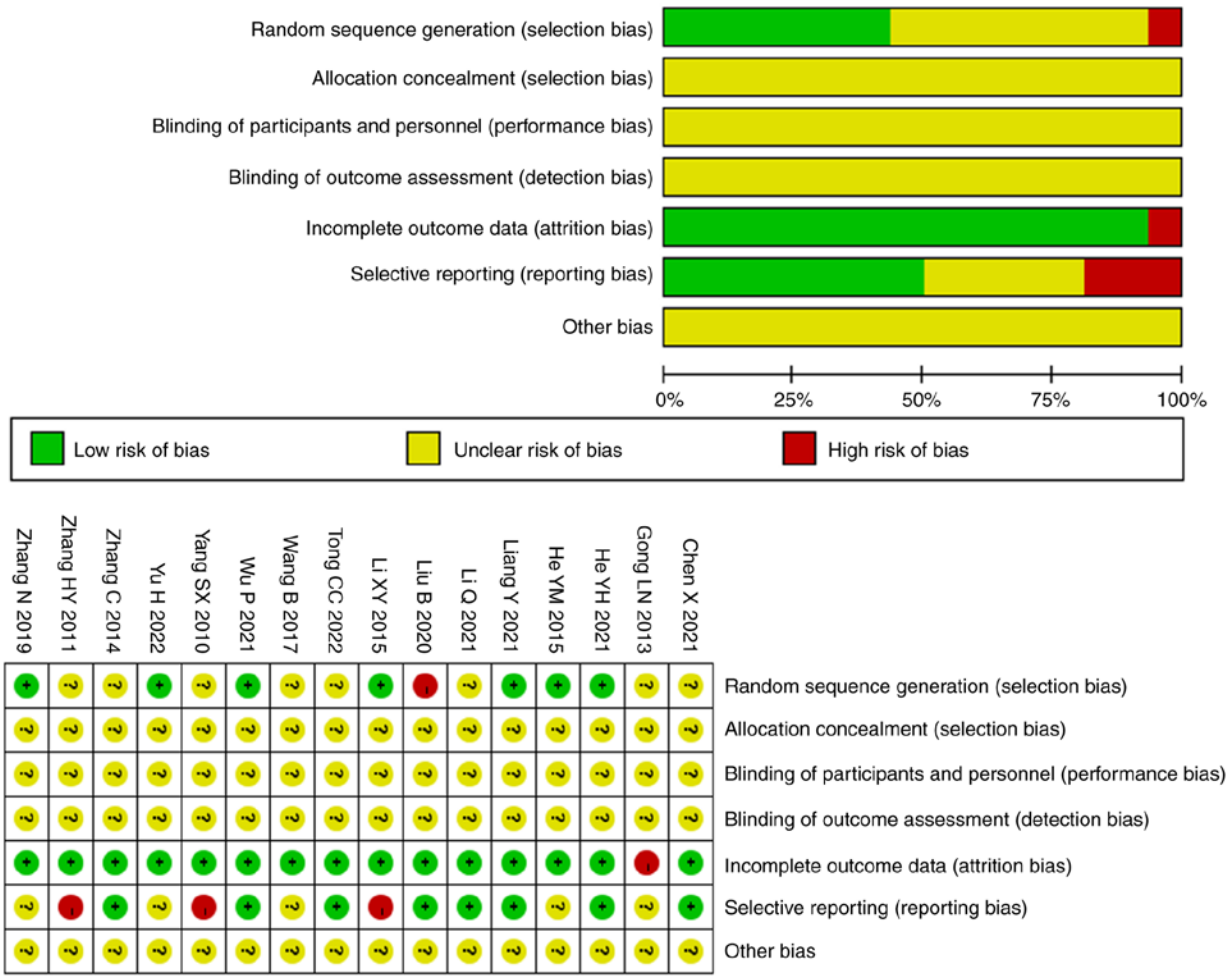

Figure 2. Risk of bias graph and risk of bias summary.

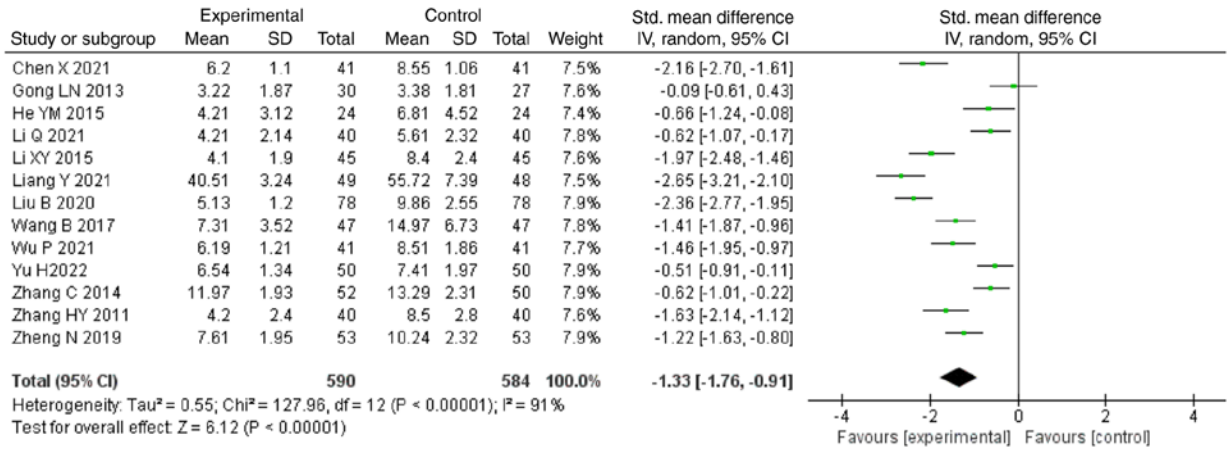

Figure 3. Forest plot of the effect of Niaoduqing granule on C-reactive protein. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standardized.

TNF-α were using NDQ granules <30 g. There was no significance on IL-6 for the dosage of NDQ granules ≥30 g (SMD, -0.10; 95% CI, -0.72,0.52; P=0.74). The results of the subgroup analysis are presented in Table III and Figs. S1-5.

Publication bias. As the numbers of the included studies in the four meta-analyses performed were ~10, a publication bias analysis of the outcomes of CRP, TNF-α, BUN and SCr was performed. Visual inspection of the data in the funnel plots revealed an asymmetrical and sparse distribution, indicating that publication biases likely exist in the included studies. One reason for this may be the small sample size and the other is likely associated with the majority of the studies being of medium or low quality (Fig. 11).

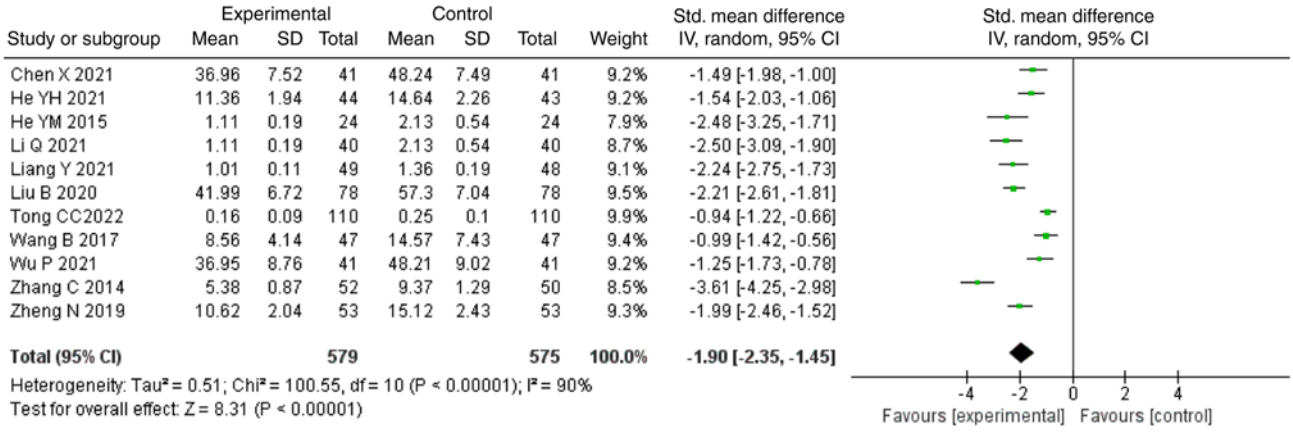

Figure 4. Forest plot of the effect of Niaoduqing granule on TNF-α. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standardized.

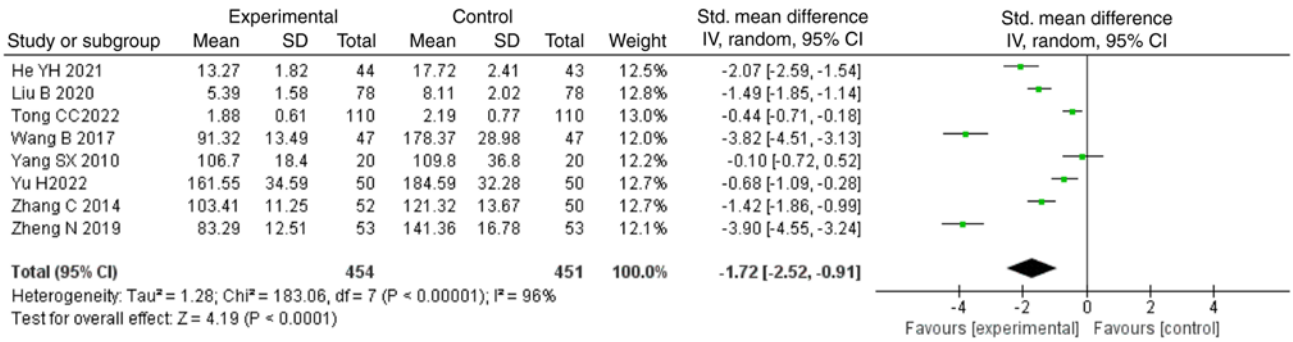

Figure 5. Forest plot of the effect of Niaoduqing granule on IL-6. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standard.

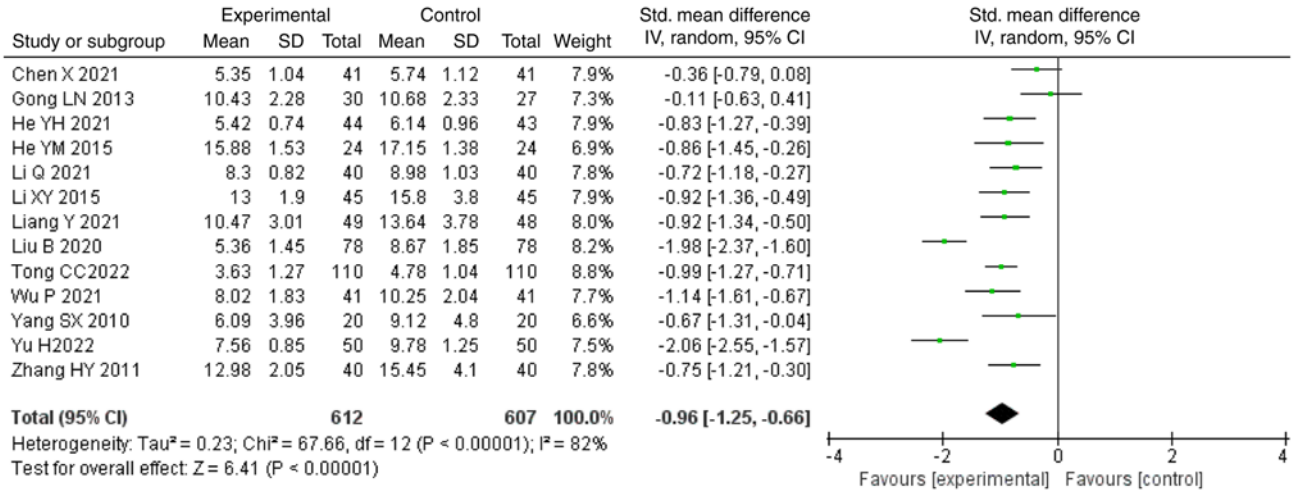

Figure 6. Forest plot of the effect of Niaoduqing granule on blood urea nitrogen. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standardized.

Discussion

The present meta-analysis incorporated 16 studies, comprising a total of 1,526 patients. In comparison to basic treatment, it was discovered that the combination of NDQ with western medicine could further decrease CRP, TNF-α, IL-6, BUN, SCr and 24-h UPE. Although the clinical effective rate in the intervention group was superior compared with that in the control group, the included studies had no consensus criteria. In addition, the results of the present review revealed that the incidence of adverse reactions was not different between the intervention and the control group, suggesting that NDQ granules is likely to be safe for clinical use. Although the sample sizes of all outcomes selected in the present study are relatively small to fully allay the remaining ambiguity, these results provide evidence based on the clinical practice of

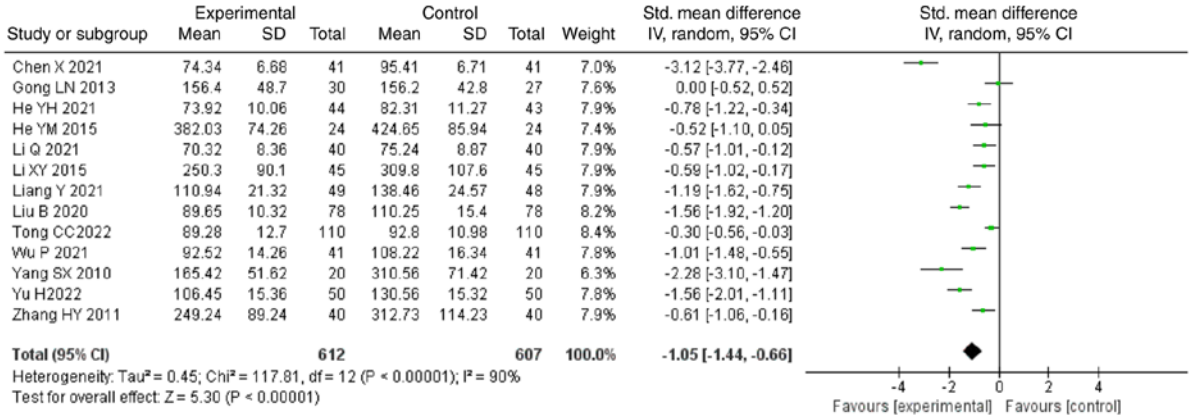

Figure 7. Forest plot of the effect of Niaoduqing granule on serum creatinine. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standardized.

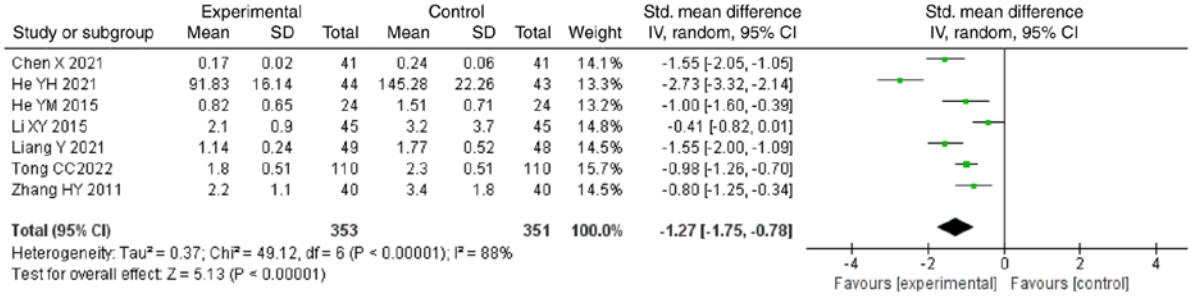

Figure 8. Forest plot of the effect of Niaoduqing granule on 24-hour urinary protein excretion. CI, confidence interval; df, degrees of freedom; IV, inverse variance; Std., standardized.

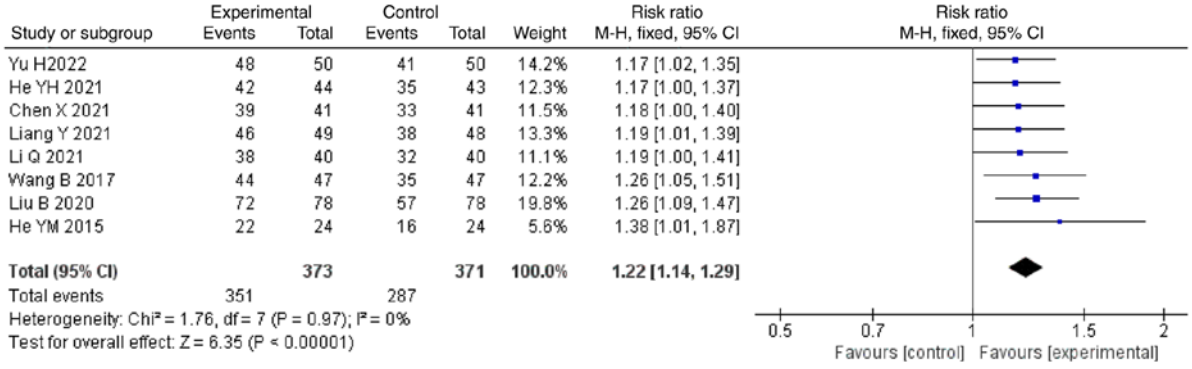

Figure 9. Forest plot of the effect of Niaoduqing granule on the clinical effective rate. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

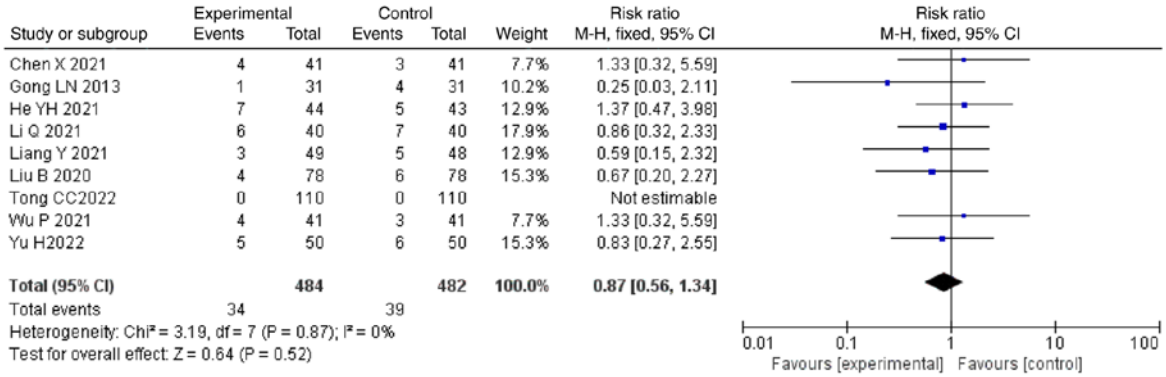

Figure 10. Forest plot of the effect of Niaoduqing granule on the adverse reaction rate. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Table II. Statistics of adverse reaction events in the intervention group (n=484) and in the control group (n=482).

Adverse reaction events	Intervention group, n (%)	Control group, n (%)
Gastrointestinal reactions	15 (3.10)	14 (2.90)
Dizziness	3 (0.62)	5 (1.04)
Hypoglycemia	5 (1.03)	6 (1.24)
Asthenia	6 (1.24)	2 (0.41)
Cough	0 (0.00)	1 (0.21)
Rash	1 (0.21)	1 (0.21)
Allergy	1 (0.21)	1 (0.21)
Hyperkalemia	2 (0.41)	4 (0.83)
High creatinine	0 (0.00)	2 (0.41)
Hypercalcemia	1 (0.21)	3 (0.62)
Total	34 (7.02)	39 (8.09)

NDQ granules for treating the inflammatory response caused by DKD.

Surrogate endpoints rather than clinical endpoints are typically selected in small-scale clinical studies due to the latter requiring larger sample sizes and longer observation periods (38). Furthermore, the effects of treatment with the NDQ granules on the inflammatory response caused by DKD are typically observed at early stages, which provides insufficient evidence. Therefore, the outcomes identified in the included studies in the present systematic analysis were all surrogate endpoints. Although they could not offer direct evidence for clinical prognosis, they potentially lay a foundation for future clinical trials.

CRP is a sensitive and non-specific biomarker and the circulating concentration is solely determined by its synthesis rate (39). At present, CRP is generally recognized as a gold standard for evaluating the degree of inflammation, which is also independently associated with the development of DKD (40). A study discovered that lower concentrations of CRP are associated with endothelial dysfunction in patients with DM (41). A previous animal study reported that CRP can be a therapeutic target for the treatment of DKD by improving the epithelial-mesenchymal transition process through Wnt/β-catenin and ERK1/2 signaling (42).

TNF-α is a potent indicator of inflammation, together with its receptors TNF receptor (TNFR)1 and TNFR2. In DKD, it has been documented to be involved in the synthesis of cytokines and the mediation of a variety of cytotoxic effects on renal cells (43,44). Previous data have suggested that inflammatory biomarkers, including TNF-α and IL-6, rather than CRP, were independently associated with CKD (45). Another study indicated that the concentration of TNF-α in DKD was higher compared with that in DM, suggesting that patients with DKD had more severe inflammation (46). In animal models of DKD, early rises in renal TNF-α levels were found to precede the detection of urinary albumin, suggesting that TNF-α may be used as a predictive factor for early DKD (47).

The IL family of cytokines, including IL-1β, IL-6 and IL-18, is secreted by a variety of cells (such as endocytes, machrophages and fibroblasts) and serves a pivotal role in inflammation, particularly in the progression of DKD (6). IL-6 was found to be elevated in the serum and urine samples of patients with DKD (48). A prospective cohort study previously demonstrated that IL-6 polymorphisms were associated with DKD and the morbidity rate of DKD was increased as the levels of IL-6 also increased (49). Therefore, CRP, TNF-α and IL-6 were selected to be the main outcomes assessed in the present systematic review. The results showed that NDQ granules could decrease the levels of these inflammatory factors, which are consistent with the subgroup analysis of different dosages. Simultaneously, due to the significant reduction of heterogeneity in the subgroup analysis of dosage of NDQ granules ≥30 g on CRP, the dosage was likely to be a source of heterogeneity. This suggests that further in-depth studies are required for future verification. Because the dosage of treatment with NDQ granules in all of the studies reporting on TNF-α was <30 g, a subgroup analysis on TNF-α could not be performed. The effect of IL-6 on the dosage of NDQ granules ≥30 g showed no obvious significance as the sample size was too small, therefore, larger sample sizes are required for future studies.

Parameters such as BUN, SCr and urinary protein excretion are important indicators for assessing the extent of renal damage associated with DKD. A previous study reported that high variability in BUN and SCr levels in patients with CKD can predict the risk of subsequent mortality from non-cardiac causes (50). It was recommended by the Chinese clinical practice guidelines of DKD that the urinary protein levels and eGFR be measured to assist in the early diagnosis of DKD (51). In the present analysis, the effect of the NDQ granules on BUN, SCr and 24-h UPE were explored, where the meta-analysis results showed that the inclusion of NDQ granules decreased BUN, SCr and 24-h UPE. The heterogeneity of BUN and 24-h UPE in the subgroup analysis of dosages of ≥30 g was significantly decreased, suggesting that the dosage of NDQ may be the cause of heterogeneity. However, a high degree of heterogeneity persisted in the subgroup analysis based on dosage, indicating that the heterogeneity may result from other causes. It is possible that publication bias or small sample sizes are the contenders of heterogeneity, which should be investigated further in the future.

The mechanism of DKD is complex and involves alterations in kidney hemodynamics, metabolic changes, oxidative stress and genetic factors. In particular, inflammatory responses may participate in the occurrence and progression of DKD (52). DKD is likely caused by microvascular inflammation in a manner that is independent of pathogenic microorganism infection (53). In addition, it has been reported that, apart from hemodynamic changes, metabolic disorder can also activate proinflammatory pathways and aggravate kidney disease progression by elevating the intraglomerular pressure, mesangial proliferation or damaging podocyte and tubular cells (6,54). A previous study proposed that inflammation-associated indices should be explored as possible biomarkers, therapeutic targets or prognostic factors (55). Various trials of commonly used hypoglycemic agents, including SGLT2 inhibitors, dipeptidyl-peptidase-4 and glucagon-like peptide-1, have also been shown to alleviate inflammatory effects (56,57). However, under the circumstance

Table III. Subgroup analyses of C-reactive protein, IL-6, blood urea nitrogen, serum creatinine and 24 h urinary protein excretion based on the dosage of NDQ granules.

Outcome/dosage of NDQ granule, g	n	MD/SMD (95% confidence interval)	I^2, %	Z	P-value
C-reactive protein					
<30	11	-1.25 (-1.73,-0.77)	92	5.08	<0.00001
≥30	2	-1.80 (-2.16,-1.44)	0	9.83	<0.00001
IL-6					
<30	5	-1.94 (-2.80,-1.08)	96	4.41	<0.0001
≥30	1	-0.10 (-0.72,0.52)	-	0.33	0.74
Blood urea nitrogen					
<30	10	-1.00 (-1.38,-0.63)	86	5.22	<0.00001
≥30	3	-0.81 (-1.09,-0.53)	0	5.63	<0.00001
Serum creatinine					
<30	10	-1.04 (-1.51,-0.58)	91	4.41	<0.0001
≥30	3	-1.08 (-1.91,-0.26)	86	2.58	0.01
24-h urinary protein excretion					
<30	5	-1.54 (-2.11,-0.97)	87	5.31	<0.00001
≥30	2	-0.59 (-0.97,-0.21)	35	3.02	0.003

MD, mean difference; SMD, standardized mean difference; NDQ, Niaoduqing granule.

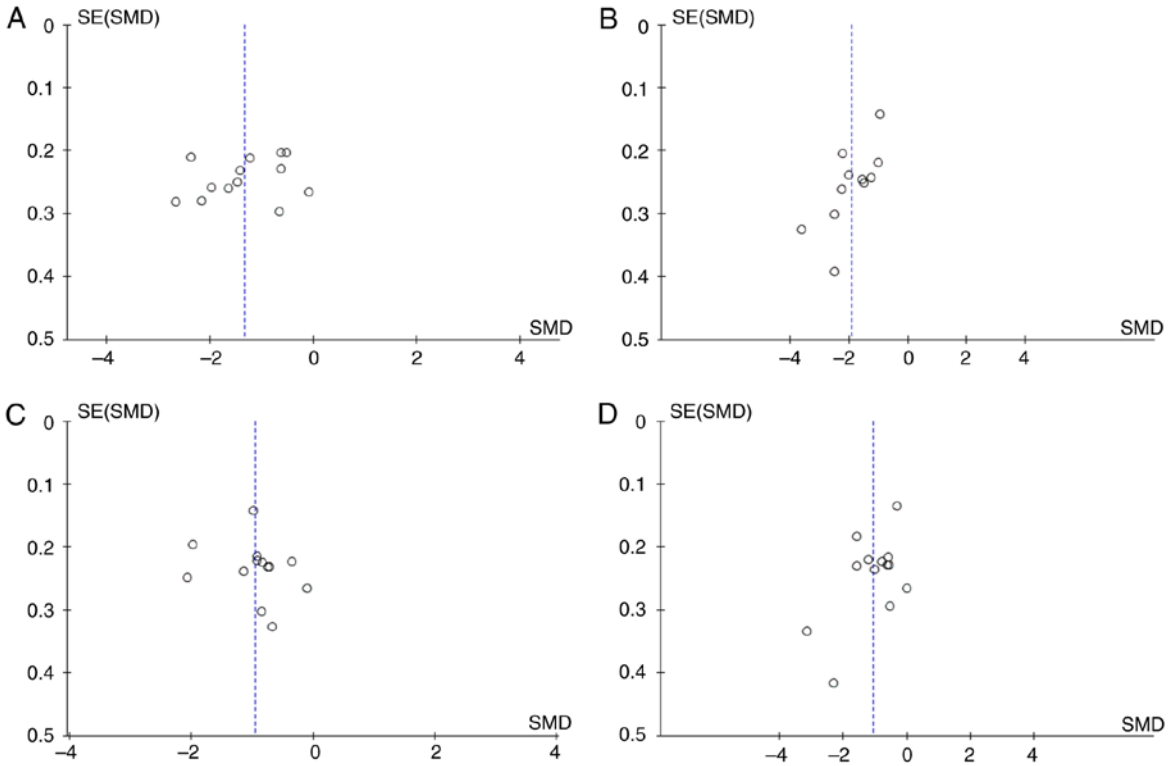

Figure 11. Funnel plots of (A) C-reactive protein, (B) TNF-α, (C) blood urea nitrogen and (D) serum creatinine. SMD, standardized mean difference.

of unsatisfactory curative effects and high rates of morbidity, TCM herbs are under consideration as an alternative choice for treating DKD. Previous pharmacological studies have found that NDQ granules was able to alleviate inflammatory responses and oxidative stress, and improve renal dysfunction and tubular interstitial fibrosis in DKD (12,58). In terms of safety, no significance could be found between the intervention and control group, consistently with a previous review (59). Therefore, it is suggested that NDQ granules has potential in suppressing inflammation and preserving renal function under DKD. However, the underlying mechanism remains poorly understood, which requires further study.

To the best of our knowledge, the present study was the first to evaluate the extent of inflammation after treatment with NDQ granules in patients with DKD. There have been two previous systematic reviews of the effects of NDQ granules on DKD (60,61), but differences exist compared with the present analysis. The key difference is that the outcomes selected in the two previous reviews were mainly the urinary albumin excretion rate, SCr clearance, total cholesterol and fasting blood-glucose, whilst inflammatory factors, such as CRP, TNF-α and IL-6, were lacking. Of note, the present meta-analysis also had limitations. The quality of the included studies was not high, as the allocation concealment, blinding methods and other aspects were not reported in detail and, therefore, selection, performance, detection and other bias affected their credibility. In addition, all of the included studies had small sample sizes and none of them were large-sample, multi-center international RCTs. No placebo groups were included in the control group and conventional therapy was used according to the different conditions, with adjustments of blood pressure and glucose, and acid-base balance used for the treatment of patients with DKD. To a certain extent, it reduced the reliability of the conclusions of the present meta-analysis. Furthermore, a number of included studies did not record adverse reactions, meaning that safety could not be assessed comprehensively. None of the included studies described the follow-up conditions, resulting in the influence of NDQ granules on the prognosis of patients with DKD not being verified.

According to the results of the present analysis, future clinical trials of TCM herbs are required to follow the Consolidated Standards of Reporting Trials guidelines (62), where the evaluation of long-term prognosis should be emphasized. In this regard, more high-quality, large-sample, multi-center and double-blinded RCTs are needed to provide sufficient information on the effects of treatment with NDQ granules on DKD.

In conclusion, current evidence indicates that NDQ granules may be effective for the improvement of inflammation caused by DKD when used in combination with conventional treatment. However, caution should be taken when considering the present meta-analysis results due to the inclusion of low-quality studies, deficient placebo control and large heterogeneity among different studies. In addition, the safety of NDQ granules remains vague, meaning further assessment through high-quality studies is required in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PZ and JY conceived the study and designed the protocol for the systematic review. PZ, ZH and WX conducted the literature screening and data extraction. ZH and WX performed the statistical analysis. PZ and ZH drafted the manuscript. PZ and JY inspected all aspects of this systematic review. PZ and JY confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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