The effect and safety of low-dose Tripterygium wilfordii in patients with type 2 diabetic nephropathy: A meta-analysis

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Abstract

Background: This review aims to assess the efficacy and safety of low-dose Tripterygium wilfordii Hook F (TWHF) in treating type 2 diabetic nephropathy (DN) and provide high-level evidence supporting its normalized application.

Methods: Seven electronic databases were queried to locate trials that qualify. Randomized controlled trials (RCTs) about low-dose TWHF long-term treatment of type 2 DN are included. After data extraction and quality evaluation of the clinical studies that met the inclusion criteria, a meta-analysis was performed using RevMan 5.4 and Stata 14.

Results: A total of 23 RCTs were included. For the patients in the trial group, the effective rate [confidence interval (CI), odd ratio] [odd ratio = 1.38, 95% CI (1.22–1.56), P < .001], albumin [standard mean difference (SMD) = 0.58, 95% CI (0.18–0.98), P = .004], 24-hour urine total protein [SMD = −1.329, 95% CI = (−1.647 to −1.012), P < .001], serum creatinine [SMD = −0.64, 95% CI = (−0.86 to −0.31), P < .001], and the untoward effect [RR = 2.43 95% CI = (1.22–4.82), P = .01] were significantly higher than those in the control group. However, in white blood cell [Weighted mean difference = −0.27, 95% CI (−0.54 to 0.01), P = .06] and blood urea nitrogen [Weighted mean difference = −0.11, 95% CI (−0.42 to 0.21), z = 0.67, P = .50], none of the differences were significant compared with the control group.

Conclusion: This suggests that low-dose TWHF positively affects patients with type 2 DN after a long course of treatment. Although there are some side effects, symptoms can improve after medication suspension or symptomatic treatment. Limited by the methodological quality of the included studies, this conclusion needs to be verified by more large-sample RCTs with rigorous design and long-term follow-up.

Abbreviations: 24h UTP = 24-hour urine total protein, ALB = albumin, BUN = blood urea nitrogen, CI = confidence interval, DN = diabetic nephropathy, RCT = randomized controlled trial, Scr = serum creatinine, SMD = standard mean difference, TWHF = Tripterygium wilfordii Hook F.

Keywords: clinical efficacy, diabetes mellitus, diabetic nephropathy, Tripterygium wilfordii Hook F.

1. Introduction

Diabetic nephropathy (DN) estimated to affect nearly 40% of diabetic patients, is the leading cause of chronic kidney disease globally.[1,2] Researchers have discovered that a variety of pathways and/or multiple targets, including aberrant glucose and lipid metabolism, chronic inflammation, oxidative stress, immunological activation, and podocyte dysfunction, are related to the pathogenesis of DN.[3–5] Current treatments are mainly for the comprehensive management of patients suffering from type 2 DN, such as the adjustment of poor lifestyle, control of risk factors (hyperglycemia, hypertension, lipid metabolism disorders, etc), and education of diabetic patients. Renin-angiotensin system inhibitors, which are frequently used in

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as first-line treatments, include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Therefore, to treat DN effectively, further research is required.

Traditional Chinese medicine has recently demonstrated distinct benefits and opportunities in the detection and treatment of diabetes and has been widely used to treat and control diabetes and its complications in many scientific studies and has gradually built a more thorough theoretical framework. Tripterygium wilfordii Hook F (TWHF), a traditional Chinese herb, is the only plant drug with immunosuppressive qualities. It acts as an anti-inflammatory, antiproliferative, antioxidant, and immunosuppressive agent, reducing urine protein excretion in several primary and secondary glomerular disorders. However, research on its efficacy and safety is lacking. A systematic review and meta-analysis was conducted to evaluate the effectiveness and safety of TWHF for the treatment of DN, which may be a potential supplemental therapy for DN.

2. Material and Methods

2.1. Inclusion and exclusion criteria

1.2.1. Inclusion criteria. Randomized controlled trials (RCT) conducted in the study; the subjects of observation are type 2 DN, which was diagnosed according to clear definitions or internationally recognized standards, and there were no requirements for the race, age, geography, etc; the intervention was low-dose TWHF (i.e., <60 mg/d or <1 mg/kg d) for a duration of six months, with consistency between groups of basic therapy.

2.2.1. Exclusion criteria. Studies that were repeated publications; studies that were non-randomized controlled trials and quasi-randomized controlled trials; the dose and duration of the studies did not meet the inclusion criteria; studies that combined treatments with further traditional Chinese medicine treatments including acupuncture, acupoint injections, and herbal extracts.

3.2.1. Outcomes. Effective rate, 24-hour urine total protein (24h UTP), serum creatinine (Scr), albumin (ALB), WBC, blood urea nitrogen (BUN), and safety indicators (including visceral damage, reproductive toxicity and hematological damage, etc).

2.2. Search strategy

Searches were conducted in electronic databases such as Chinese National knowledge infrastructure (CNKI), Wanfang, China Biology Medicine disc (CBM), PubMed, Embase, and Cochrane Library to find studies that would be included in the database after it was established in April 2020. We searched papers using MeSH terms and/or keywords like “randomized controlled trial” and “Tripterygium wilfordii Hook F” or “Tripterygium wilfordii” and “Diabetic nephropathy” or “Diabetic Kidney Diseases” or “DN” or “DKD.”

Only human subjects were used in the investigations. In addition, a comprehensive search for the included literature was done. After many preliminary searches, all search techniques were defined, and retrieval methods were integrated with free-text retrieval. The title and abstracts were independently reviewed by two reviewers. The full text of the articles were reviewed by a third reviewer if there was a disagreement between the two. Inter-investigator reliability was measured utilizing kappa (κ) statistics.

2.3. Data extraction

A data extraction form was developed based on the Cochrane Handbook checklist for data gathering considerations. The author, year, sample size, duration of therapy, outcome measures, and adverse effects were extracted by two independent reviewers. Disagreements were settled by dialogue between the two reviewers and a study of the trial data. When clarifications were required, study authors were contacted. And data was recorded in data in an Excel spreadsheet.

2.4. Quality assessment

Two independent reviewers assessed the methodological quality of randomized controlled trials using the Risk of Bias instrument developed by the Cochrane Collaboration. Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcomes assessment (detection bias), incomplete outcomes data (attrition bias), selective reporting (reporting bias), and other biases were assessed using the Cochrane Handbook. Quality assessment was performed using GRADE Criteria for (Grading of Recommendations Assessment, Development, and Evaluation) designed to assess the overall reliability of a body of information. This method comprises five important domains: risk of bias, inconsistency, indirectness, imprecision of the evidence, and reporting bias. In addition, it takes into account additional optional domains that may be important in certain cases. These included plausible confounding that would decrease the observed effect and strength of association (i.e., magnitude of effect) or factors that would increase the strength of association (i.e., dose-response effect). The risk of bias and quality assessment information were considered in the interpretation of findings.

2.5. Data synthesis

We analyzed the data using Review Manager 5.4 https://en.free-downloadmanager.org/Windows-PC/Review-Manager.html and Stata 14 https://www stata.com stata14/. The binary categorical variable data results are presented as the risk ratios (RR) with 95% CI and standard mean difference (SMD) with the 95% confidence interval (CI) in continuity variable data. I² statistics were used for the heterogeneity assessment. In the absence of significant data heterogeneity (I² > 50%), a model with fixed effects was used. However, considerable heterogeneity was observed (I² > 50%), subgroup analysis, meta-regression, and sensitivity analysis can be performed to eliminate heterogeneity. If heterogeneity persists but clinically suggests homogeneity (patient age, sex, course, underlying condition, etc, baseline conditions are substantially consistent between groups), random-effects model analysis was used. Finally, publication bias was evaluated using funnel charts and Egger tests in Stata 14.

3. Results

3.1. Study selection

Computer and manual searches yielded a total of 1218 papers; after deleting 578 duplicates, 640 articles remained; 120 articles were read in full after reading the title and abstract; 98 pieces were eliminated; and finally, 22 articles were included in the meta-analysis. The entire study selection procedure is presented in the PRISMA flowchart. Inter-rater agreement was excellent at the full-text review (κ = 1) stages.

3.2. Data extraction

Table 1 displays the fundamental content and features of the selected studies. Twenty-two studies have been published between 2012 and 2022. Twenty articles were published in Chinese, while two were published in English. All studies examined the effects of TWHF on DKD and reported at least one clinical measure, such as the efficacy rate, 24h UTP, Scr, ALB, WBC, and BUN levels, as well as safety signs. The duration of the intervention was six months, and the dosage of TWHF was
<60 mg/d or <1 mg/kg/d (see Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/I229, which includes all the data we extracted from the included literature for the meta-analysis).

3.3. Risk of bias and quality assessment

Using the Cochrane risk of the bias assessment instrument, two researchers (Yixuan Chen and Meiqi Lu) independently analyzed all included studies. Figures 1 and 2 provide comprehensive findings of the bias analysis. As a consequence of the variability and publication bias in the majority of research, the GRADE criteria for assessing the quality of evidence revealed that the overall analyses yielded low-quality evidence [12] (see Table S2, Supplemental Digital Content 2, http://links.lww.com/MD/I230, which illustrates the GRADE criteria for assessing the quality of evidence) (see Powerpoint, Supplemental Digital Content 3, http://links.lww.com/MD/I231, which illustrates the risk of bias for all literature included in this meta-analysis).

3.4. Meta-analysis

3.4.1. Effective rate. Five articles reported efficacy outcomes. Because there was no significant heterogeneity in the data ($I^2 < 50\%$), a fixed-effect model was selected for the pooled effect quantity. Figure 3 shows a forest plot for the efficacy comparison. The results show that patients in the TWHF group had significantly higher efficacy than those in the control group (RR = 1.38 (1.22–1.56), $P < .001$).

3.4.2. Effects on the changes of ALB or proteinuria. Effect of TWHF on ALB. Thirteen articles reported ALB outcomes after TWHF therapy. Due to the clinical homogeneity of the trials (the baseline conditions of patients, such as age, sex, course, and underlying condition of patients, were consistent between groups), random effects models were selected. Figure 4 shows a forest plot for ALB comparison. Patients in the TWHF group had markedly higher ALB levels than those in the control group.

### Table 1

Characteristics of included studies.

| Author       | Year | n (E/C) | Experimental group | Control group | Outcomes | Untoward effect (E/C) |
|--------------|------|---------|--------------------|---------------|----------|-----------------------|
| Wang         | 2018 | 20/20   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Xiong        | 2020 | 62/62   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | 1/0                   |
| Diao         | 2010 | 33/33   | Conventional treatment + ACEI/ARB + TWHF | Conventional treatment + ACEI/ARB | ②③④⑦⑩ | -                     |
| Yu           | 2011 | 65/65   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Sun          | 2014 | 74/76   | Conventional treatment + Metformin + TWHF | Conventional treatment + Metformin | ②③④⑦⑩ | -                     |
| Song         | 2014 | 40/40   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Chang        | 2012 | 22/23   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Zhang        | 2012 | 50/50   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Yang         | 2010 | 20/20   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Li           | 2014 | 48/48   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | 1/0                   |
| Wang         | 2013 | 32/32   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Wang         | 2011 | 20/20   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Wang         | 2012 | 52/32   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Shi          | 2006 | 23/23   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Cai          | 2012 | 30/30   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Tan          | 2010 | 25/25   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| He           | 2010 | 31/29   | Conventional treatment + ARB + TWHF | Conventional treatment + ARB | ②③④⑦⑩ | -                     |
| Wu           | 2011 | 52/48   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Zheng        | 2009 | 30/30   | Conventional treatment + ACEI/ARB + TWHF | Conventional treatment + ACEI/ARB | ②③④⑦⑩ | -                     |
| Guo          | 2007 | 24/24   | Conventional treatment + TWHF | Conventional treatment | ②③④⑦⑩ | -                     |
| Gao          | 2014 | 40/40   | Conventional treatment + ACEI/ARB + TWHF | Conventional treatment + ACEI/ARB | ②③④⑦⑩ | -                     |

① Effective rate; ② Urine protein; ③ ALB; ④ Scr; ⑤ ALT; ⑥ WBC; ⑦ BUN; ⑧ FBG; ⑨ HBA1c; ⑩ Ccr. Experimental group: intervention measures in the experimental group; Control group: intervention measures in the control group.

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, TWHF = Tripterygium wilfordii Hook F.

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Figure 1. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
3.4.3. Effects on kidney function changes. Effect of TWHF on Scr. In the included studies, Scr and BUN levels indicated the function of the kidney. Eighteen articles had reported on Scr outcome. Due to the significant heterogeneity of the experiments selected in this study, our sensitivity analysis of the 18 studies found that the two studies by “He, 2010” and “Zhang, 2010” significantly impacted the results. After removing the two studies, the heterogeneity decreased ($I^2 = 68\%$); however, the results did not change significantly. Indicating that although the heterogeneity was significant, the results were stable. Random effects models were selected for effect-size pooling. According to the findings, TWHF group patients had considerably lower Scr than the control group’s patients. $[SMD = -0.64 (-0.86 to -0.31), z = 3.20, P < .001]$ (Fig. 6).

Effect of TWHF on BUN. Seven RCTs$^{[15,23,24,27,29,30,32]}$ reported the BUN outcomes after TWHF therapy. Our findings demonstrated no significant differences between experimental and control groups concerning BUN change from baseline ($P = .50$, $I^2 = 59\%$) (Fig. 7).

3.4.4. Effects on inflammation and immunity. Effect of TWHF on WBC. Four RCTs,$^{[13,20,24,26]}$ including 268 participants, reported WBC outcomes after TWHF therapy. Our results indicated no significant difference in WBC change from baseline between the experimental and control groups ($P = .06$) with no significant heterogeneity ($I^2 = 0\%$) (Fig. 8).

One study showed significantly lower IL-6$^{[33]}$ levels. Whereas two studies showed substantially lower TNF-$\alpha$ levels,$^{[21,33]}$ one study showed that the improvement in CD4/CD8 inversion in the trial group was better than in the control group.$^{[33]}$

3.4.5. Untoward effect. Adverse reactions were reported in seven trials$^{[15,16,19–22,34]}$ including 26 out of 270 cases in the treatment group and 9 out of 247 patients in the control group.$^{[15,16,19–22,34]}$ The meta-analysis results suggested more adverse reactions than conventional therapy ($RR = 2.43 (1.23–4.82), P = .01, I^2=0\%$), including visceral damage, reproductive toxicity, and hematological damage. See Figure 9 for details.

3.4.6. Publication bias. The funnel plot was drawn with the effect of TWHF treatment on Scr, and the funnel plot was roughly symmetrical (Fig. 10). A bias test was performed, and $P = .157 > 0.005$. Therefore, it can be concluded that the literature in the current study had no publication bias, respectively (Fig. 11).

4. Discussion

Microvascular complications of diabetes and diabetic kidney disease (DKD) are the primary cause of the end-stage renal disease (ESRD) worldwide. High glomerular filtration rate (GFR) is followed by microalbuminuria, albuminuria, and end-stage renal failure (ESRD).$^{[35]}$ Uremia can have grave consequences if left untreated. DKD has a complicated pathogenesis characterized by inflammation and invasion of the kidney by an immune cell. Recent techniques for the treatment of DN include anti-inflammatory treatments, cytokine suppression, and the avoidance of podocyte harm. However, no new therapeutics for DKD has been available for nearly 20 years.

In this systematic review, 22 studies were included to analyze the effectiveness of TWHF, an extract of a traditional Chinese herb, in treating DKD. We identified most treatment markers utilized in DKD diagnosis or clinical response assessment, such as albuminuria, proteinuria, Scr, BUN, and other immunoinflammatory signs. Multiple studies have shown that the rate of decline in renal function after the appearance of a large amount of urine protein is greatly accelerated.$^{[16]}$ Therefore, it is recommended that proteinuria should be routinely tested in diabetic

Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

according to the findings $[SMD = 0.58 (0.18–0.98), z = 2.86, P = .004]$.

Effect of TWHF on 24h UTP. Twenty-one$^{[13–32]}$ articles reported on 24h UTP outcome, and significant heterogeneity was present ($I^2 = 86.9\% >50\%$). However, subgroup and sensitivity analyses found that none of the studies substantially impacted the results. Due to the clinical homogeneity of the trials, random effects models were selected for effect-size pooling. Compared with patients in the TWHF group, those in the TWHF group had significantly lower urine protein levels. $[SMD = -1.329(-1.647 to -1.012), z = 8.21, P < .001]$ (Fig. 5).
patients at risk of potential renal impairment. Moreover, to increase the sensitivity of screening tests, Scr and BUN are valuable markers that correlate well with renal function assessment.

The present meta-analysis results showed that the total efficiency of the TWHF group was significantly better than that of the traditional treatment group. It also delayed the decline in renal function (e.g., effectively reducing proteinuria, SCR, and improving ALB level), suggesting that the effect of low-dose TWHF in treating type 2 DN is worthy of affirmation. The mechanism by which TWHF protects the kidneys is as follows: Anti-inflammatory, suppression of humoral immunity, and cellular immunity: In the study performed by Fevziye Burcu Sirin et al, positive correlations were observed between IL-6 and blood glucose, HbA1c, creatinine, urine albumin, and protein excretion, whereas negative correlations were observed with GFR. In patients with high levels of blood glucose maintained for a long time, kidney cells release TNF-α free radicals and accumulate in the body, increase lipid metabolites, cellular intima damage, glomeruli keep a hypertonic state, and promote the production of albuminuria. In this study, we observed a decrease in IL-6 and TNF-α after treatment, which may reduce the local inflammatory response in the kidney and delay renal cell sclerosis and interstitial fibrosis in diabetic patients. CD4 and CD8
are a significant subset of T lymphocytes, which antagonize each other to maintain the balance of immune response in vivo and affect the mechanism of the immune response. Our study suggests that it can correct cellular immune abnormalities to a certain extent. However, owing to the small number of included studies, more in-depth studies are needed. Improvement of podocyte injury: Hyperglycemia induces podocyte transdifferentiation and causes albuminuria. This may be effective in preventing podocyte damage in DKD, which may be mediated at least in part by the downregulation of CTGF, OPN, and TGF expression. Thus delaying the deterioration of renal function and reducing proteinuria. Protection of glomerular endothelial cell function: Hyperglycemic stimulation can increase the production of VEGF in the kidney, leading to endothelial activation followed by macrophage infiltration, which compromises glomerular endothelial cell structure and function, increases glomerular permeability, and causes proteinuria. The primary method of preventing DKD may include preventing VEGF overexpression, which inhibits a cascade of pro-inflammatory proteins and intracellular signaling, thereby relieving kidney injury under diabetic conditions. Inhibition of extracellular matrix and mesangial cell proliferation: Chronic hyperglycemia and excessive development of advanced glycation end products (AGEs) produce anomalies in VEGF synthesis and release in many signaling pathways, including inflammation, excessive ROS production, TGF- and CTGF activation, and foot process effacement, and disrupts VEGF overexpression and inhibits mesangial cell proliferation and extracellular matrix proliferation.

However, this meta-analysis cannot provide reliable evidence on whether it has anti-inflammatory effects, inhibiting humoral immunity and cellular immunity. The meta-analysis also suggested some side effects, mainly visceral damage, reproductive toxicity, and hematological damage. Symptoms can improve after medication suspension or symptomatic treatment. Some investigators stated that the immunosuppressive effect of TWHF is different from that of all other immunosuppressants and that TWHF has an immunosuppressive unique impact. Tripterygium glycosides have powerful immunosuppressive effects without causing significant harm to the normal immune system, malignancies, or infections. Tripterygium glycosides efficiently suppressed T-cells but had little impact on resting cells. Therefore, short delivery of tripterygium glycosides to DKD patients would not have serious side effects.

The above outcome measures were statistically heterogeneous in the different studies, and neither our sensitivity analysis nor our regression analysis was eliminated. The source of heterogeneity may be related to the TWHF dose, the baseline level of patient renal function, the different included populations, or the very low quality of evidence included in the analysis.

The meta-analysis also has some other limitations: most included studies were mainly Chinese and of low quality. The description of random and blind methods is too vague and prone to bias. The majority of indications described in the literature are favorable outcomes; however, there is a possibility that the negative findings were not publicized. Several studies show better double-dose efficacy over smaller doses, but only small doses are discussed in this paper. An agreement has been pre-registered for this review (as in PROSPERO), but because the review time is too long, we have tried our best and failed to register as soon as possible.

![Figure 6](image1.png)

**Figure 6.** Results of meta-analysis for the effect of TWHF on Scr. Scr = Serum creatinine, TWHF = Tripterygium wilfordii Hook F.

![Figure 7](image2.png)

**Figure 7.** Results of meta-analysis for the effect of TWHF on BUN. BUN = Blood urea nitrogen, TWHF = Tripterygium wilfordii Hook F.
as possible. Nevertheless, we believe that this research presents a novel therapeutic intervention technique for patients with DN and a better therapy base to enhance these patients’ prognosis.

5. Conclusion

In conclusion, the efficacy of TWHF in treating DKD is positive, and it can effectively reduce urine protein and blood creatinine levels and improve ALB levels. However, they also have some side effects. It is recommended that future clinical studies consider the following: The literature included in this study are of low quality, so patients with type 2 DN need more high-quality, large-sample, multicenter, randomized, double-blind controlled studies to validate the efficacy and safety of low-dose *Tripterygium wilfordii*. Fixed treatment course and dose to reduce heterogeneity. We also excluded retrospective data from the combined analysis to prevent them from affecting the outcome judgment. While focusing on efficacy, reducing toxicity is one of the key research directions in the future.

**Author contributions**

Yixuan Chen: Data curation; Formal analysis; Investigation; Validation; Visualization; Writing – original draft; Writing – review & editing.

Meiqi Lu: Conceptualization; Data curation; Methodology; Validation; Writing – review & editing.

Yiting Feng: Conceptualization; Methodology; Validation; Writing – review & editing.

Qing Gao: Conceptualization; Funding acquisition; Project administration; Resources; Supervision; Writing – review & editing.

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**Correction**

The corresponding author information has been updated from “Qing Gao, Department of Anesthesiology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen University, Qing Gao.”
NO.201 209 Hubinnan Road, Sining District, Xiamen 361000, China” to “Department of Nephrology, Zhongshan Hospital of Xiamen University, NO.201-209 Hubinnan Road, Sining District, Xiamen 361000, China.”

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