Journal of Ethnopharmacology 133 (2011) 412–419

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Meta-analysis of the clinical value of *Astragalus membranaceus* in diabetic nephropathy

Mingxin Li[1], Weixin Wang[1], Jun Xue*, Yong Gu, Shanyan Lin

Division of Nephrology, Huashan Hospital, Fudan University, Shanghai, China

ARTICLE INFO

Article history:
Received 21 December 2009
Received in revised form 5 October 2010
Accepted 6 October 2010
Available online 13 October 2010

Keywords:
Astragalus
Diabetic nephropathy
Renal function

ABSTRACT

Aim of study: Nowadays diabetic nephropathy (DN) has become a serious problem. *Astragalus membranaceus* is a traditional herb used for thousands of years in China and East Asia for kidney disease. In modern medicine, Astragalus shows significant renal protective effect in DN. We aimed to systematically review the randomized and semi-randomized control trials to ascertain its role in the treatment of DN.
Materials and methods: PUBMED, MEDLINE, Chinese journal full-test database (CJFD), Chinese biological and medical database were searched by computer and manual searching. Two assessors independently reviewed each trial. 25 studies comprising 21 RCTs and 4 CCTs were involved including 1804 patients (945 in treatment group and 859 in control group).
Results and conclusions: Astragalus injection had more therapeutic effect in DN patients including renal protective effect (BUN, SCr, CCr and urine protein) and systemic state improvement (serum albumin level) compared with the control group.
Ethnopharmacological relevance: This study investigates the effect of Astragalus in DN patients. It suggests that although of unknown bioactive ingredients and mechanism of renal protection, the role of Astragalus in the treatment of DN can be disclosed and of profound significance.

1. Introduction

Nowadays diabetic nephropathy (DN) has been a devastating medical, social, and economic problem. According to a recent survey, DN is the most common cause of end-stage renal disease (ESRD) in the United States and accounts for 35% of patients with ESRD (Bethesda, 1996). In Asia, due to the growing number of patients with diabetic mellitus, DN has become an increasingly serious health problem. In China, about 30% of type 1 and 20% type 2 diabetic patients develop into DN, of which 53% will die of renal failure (Jiao, 2004).

Astragalus membranaceus (Fisch.) Bunge of the family Fabaceae (Fabaceae Astragalus L.), also named as syn, Huang-qi, syn: Milk-Vetch Root or syn: Huang Chi's, is a traditional Chinese medicine from Mongolian milkvetch or Membranaceus milkvetch. For thousands of years, Astragalus has been widely used in East Asia as a kind of medicine for different kinds of diseases. Especially in Traditional Chinese Medicine, which laid a lot of emphasis on Qi (vital energy) and Yin–Yang balance (negative and positive equilibrium), Astragalus is considered as benefiting Qi and helping to pass water. Modern analytic techniques have identified more than 100 compounds contained in *Astragalus membranaceus* (Wu and Chen, 2004). The major bioactive constituents are GABA, flavonoid, saponin etc.

With a sweet taste and a warm property, Astragalus is frequently used in many symptoms that in modern western medicine may be considered as kidney disease. First recorded in Shen Nong Ben Cao Jing (Shennong's Herbal Classic), a traditional Chinese medical book written in 500 AD. Astragalus has diuretic effect for kidney disease (Li, 2004).

In modern medicine, Astragalus shows significant renal protective effect in diabetic nephropathy (DN). Astragalus and its active extracts have been integrated in clinical management of diabetes mellitus (Huang and Lu, 2003) and early DN with satisfying safety profiles (Liu et al., 2001), partly for its protective effect against oxidative stress as a free radical scavenger (Toda and Shirataki, 1999). Although widely used for thousands of years, our knowledge is still limited about the mechanism of Astragalus in renal diseases especially in diabetic nephropathy. By now many clinical trials have

Abbreviations: ACEI, angiotension converting enzyme inhibitors; Alb, albumin; ANP, atrial natriuretic peptide; ARB, angiotension receptor blocker; BUN, blood urea nitrogen; CBM, Chinese biological and medical database; CCr, creatinine clearance; CCT, semi-randomized control clinical trial; CJFD, Chinese journal full-test database; CKD, chronic kidney disease; DN, diabetic nephropathy; ESRD, end-stage renal disease; ET, endothelin; GABA, γ-aminobutyric acid; H, hours; Hb, hemoglobin; NO, nitric oxide; RCT, randomized control trial; RT, routine treatment; SCr, serum creatinine; SMD, standard mean difference; TNFα, tumor necrosis factor α; UP, urine protein; WMD, weight mean difference.

* Corresponding author. Tel.: +86 21 52887797; fax: +86 21 62268509.
E-mail address: xuejunxuejun@yahoo.com.cn (J. Xue).
[1] These authors contributed equally to this work.

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doi:10.1016/j.jep.2010.10.012

reported the effect of Astragalus in renal protective and adjustment of serum glucose and lipid metabolism in DN. But uncertainties still exist in the efficacy of Astragalus due to the lack of high-quality, large-sample random clinical trials. Thus, we aimed to systematically review the randomized and semi-randomized control trials to ascertain its role in the treatment of DN.

2. Materials and methods

2.1. Eligible standard

2.1.1. Study design

All the randomized control trials (RCT) and semi-randomized control trials (CCT) searched were involved without limitation of language or publication.

2.1.2. Study object

All the patients studied met the definition of diabetic mellitus (WHO diabetes diagnostic criteria of 1980, 1985 or 1999 or ADA criteria of 1999). Clinic stage III–IV of diabetic nephropathy according to the Mogensen criteria (Mogensen et al., 1983). Patient with chronic diseases (chronic heart disease, chronic liver disease, chronic respiratory disease, tumor, autoimmunity disease, infection disease) were excluded.

2.1.3. Data extraction and methodological quality appraisal

Some important data from primary research were extracted, such as age, gender, duration of DN, basic treatment including diet control, exercise, control of blood glucose with hypoglycemic drugs or insulin, antihypertensive drug, especially for ACEI and ARB. All these mentioned data should be matched in the Astragalus treatment group and control group. The treatment group used intravenous drip of Astragalus injection. Commercial compound Astragalus injection fluid was made of extracted sterilization solution from dried roots of *Astragalus membranaceus* (Fisch.) Bge. Var. Mongholicus (Bge.) Hsiao or *Astragalus membranaceus Astragalus membranaceus* (Fisch.) Bge complied with the quality standard of Chinese State Drug Administration. All the patients in the treatment group received the same type of injection under the same standard, while the dosage ranged from 20 ml to 60 ml every day, and total course of treatment was 2–6 weeks. Therapeutic effect criteria included urine albumin, 24 h urine protein, serum albumin and renal function such as blood urea nitrogen (BUN), serum creatinine (SCr), creatinine clearance (CCr). Studies without quantitative indicators were also excluded.

2.2. Search strategy

We searched PUBMED, MEDLINE, Chinese journal full-test database (CJFD), Chinese biological and medical database (CBM), Chinese sci-tec Periodical full-text database etc by computer and Chinese doctor dissertation full text database, Chinese excellent bachelor dissertation full text database, Chinese important conference papers full text database, Chinese journal of nephrology, Modern journal of integrated traditional Chinese and western medicine, Lishizhen Medicine and Materia Medica Research etc by manual searching.

2.3. Assessment methodology

Two assessors (Mingxin Li and Weixin Wang) independently reviewed each trial, and disagreements were resolved by consensus. Trials were graded for methodological quality according to the Cochrane Collaboration as: randomization, concealment of allocation, blind methods, lost of follow up. Trials that satisfied all the four requirements were ranked as A (adequate) and partly satisfied were B (unclear) and unsatisfied were C (inadequate).

2.4. Statistical methods

Revman 4.2 for meta-analysis was used. All the studies involved were quantitative data and weight mean difference (WMD) was used to value statistics. Standardized mean difference (SMD) was adopted only in 24 h urinary protein because of different measurement units. The confidence interval was 95 percent. Chi-square test was used for heterogeneity. Trials showing clinical heterogeneity were combined according to the random effect model and the rest used fixed effect model.

3. Results

3.1. Description of studies

25 studies comprising 21 RCTs and 4 CCTs were found to be eligible. The included studies are summarized in Tables 1 and 2. A total of 1804 patients were enrolled (945 in treatment group and 859 in control group). All these studies were carried out in People's Republic of China and all the patients involved were Chinese.

3.2. Data analysis

3.2.1. Renal function

3.2.1.1. Blood urea nitrogen (BUN). Eight clinical trials, all RCT, had evaluated the serum urea nitrogen of Astragalus injection group as compared to control group. There were 284 patients in treatment group and 253 in control group. The effects of Astragalus on renal function and the other special intervention methods including ACEI or ARB in studies had been investigated in Table1.

Test for heterogeneity: Because of significant heterogeneity we chose the random effect model. Fig. 1 (also Table 1) showed the forest plots for the outcome measures. WMD = −1.28(−2.00, −0.55), $P = 0.0005$. The results had statistical significance. Thus, compared to the control group, Astragalus could reduce urea nitrogen in CKD patients.

3.2.1.2. Serum creatinine (SCr). Twelve clinical trials, including 11 RCT and 1 CCT, had evaluated the serum creatinine of Astragalus injection group as compared to control group. There were 393 patients in treatment group and 369 in control group. The trials showed clinical heterogeneity and were combined according to the random effect model. Fig. 2 (also Table 1) showed the forest plots for the outcome measures. WMD = −26.39−43.51, −9.27), $P = 0.003$. Thus, compared to the control group, Astragalus could reduce serum creatinine in CKD patients.

3.2.1.3. Creatinine clearance (CCr). Only three clinical trials, including 2 RCT and 1 CCT, had evaluated the CCr of Astragalus injection group as compared to control group. There were 121 patients in treatment group and 98 in control group. The trials showed clinical homogeneity and were combined according to the fixed effect model. Fig. 3 (also Table 1) showed the forest plots for the outcome measures. WMD = 14.02 (12.48, 15.57), $P < 0.00001$. The results showed Astragalus injection could significantly improve CCr in CKD patients. But the funnel plot for the outcome showed no asymmetry.

3.2.2. Urine protein

3.2.2.1. 24 h urine protein. Thirteen clinical trials, including 11 RCT and 2 CCT, had evaluated the 24 h urine protein of Astragalus injection group as compared to control group. There were 506 patients in treatment group and 452 in control group. Standardized mean