Int J Clin Exp Med 2022;15(2):68-73
www.ijcem.com /ISSN:1940-5901/IJCEM0139828

Case Report

Eefooton adjuvant therapy for diabetic nephropathy, heart failure, and pulmonary effusion: a case report and literature review

Chien-An Yao[1], Yin-Chang Chen[2], Chung-Yi Lai[3], Chih-Hui Lin[3]

[1]Department of Family Medicine, National Taiwan University Hospital, No. 1, Changde St., Zhongzheng Dist., Taipei City 100229, Taiwan (R.O.C.); [2]Kompton Clinic, 1F., No. 658, Sec. 1, Xiangshang Rd., Nantun Dist., Taichung City 408, Taiwan (R.O.C.); [3]Gerent Biotech R&D Center, No. 20, Jen Yi St., Taichung City 402, Taiwan (R.O.C.)

Received October 14, 2021; Accepted January 25, 2022; Epub February 15, 2022; Published February 28, 2022

Abstract: Diabetic neuropathy (DN) is a kind of chronic kidney disease (CKD). There are drugs which are conventionally used for the treatment of DN, but there is the risk of polypharmacy, and a more cost-effective therapeutic method for DN still needs to be identified. Herein, we examined the effective role of traditional Chinese medicine in CKD. A 60-year-old male patient with end-stage renal disease from diabetic nephropathy (estimated glomerular filtration rate [eGFR] 19.1 ml/min/1.73 m^2 and urine protein/creatine ratio [UPCR] 4350 mg/g) was being treated with at least 12 medications. The patient was hospitalized with increasing dyspnea and was found to have hydropneumonia and congestive heart failure in addition to renal failure (N-terminal pro-brain natriuretic peptide [NT-pro BNP] >22,000 pg/ml). The patient requested discharge and was treated at home with decreased number of chemical compounds (glimepiride, amlodipine, bisoprolol, and spironolactone) and the traditional Chinese medicine Eefooton, containing 5 herbal extracts. Over 3 months his clinical symptoms and signs resolved, eGFR increased to 59.8 a ml/min/1.73 m^2, and NT-pro BNP fell to 1085 pg/ml. This case report suggested that polypharmacy is a risk in the treatment of CDK, and herbal preparations may be safe and effective in adjunctive treatment of the disease and associated congestive heart failure.

Keywords: Chronic kidney disease, chronic heart failure, traditional Chinese medicines, diabetic nephropathy, brain natriuretic peptide, Astragalus membranaceus

Introduction

Chronic kidney disease (CKD) is defined as kidney damage or estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 for more than 3 months [1]. Kidney damage is defined as abnormal kidney function (eg, proteinuria or albuminuria, or abnormal urinary sediment, such as malformed red blood cells) or structural abnormalities noted with imaging [1]. End-stage renal disease (ESRD) is as an irreversible decline in kidney function that is severe enough to be fatal without dialysis or transplantation. ESRD is included in stage 5 of the National Kidney Foundation Kidney Disease Outcomes and Quality Initiative (NKF-K/DOQI) classification of CKD, where it refers to persons with eGFR <15 mL/min/1.73 m^2, or those requiring dialysis regardless of glomerular filtration rate [2, 3]. Reduced or absent renal function results in a range of maladaptive changes, including fluid retention, dyslipidemia, anemia, disorders of bone and mineral metabolism, and protein-energy malnutrition [2]. Hemodialysis is the most common form of initial replacement therapy, followed by peritoneal dialysis [4].

The management of CKD when it has progressed to ESRD is expensive and complex, often requiring hemodialysis or renal transplantation [5, 6]. Elaborate medical regimens, given with the intent of slowing the decline of residual renal function, often are prescribed [7]. Common contemporary medications used are angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, pentoxifylline, vitamin D, bicarbonate salt, and AST-120. The burden of medications used in the treatment of

CKD can be high, with 20% of patients taking more than 10 different medications per day [8] and increasing CKD stage is associated with an increased number of medications [8, 9]. It is unclear whether this increase is due to progression of the disease or the introduction of new medications added to existing medications. Nonetheless, research is underway to develop less costly and more effective agents.

Traditional Chinese Medicines have been considered alternative agents for treatment of renal diseases. The herbal medicines have been reported to not only improve symptoms but to also block or delay the progress of renal failure [10-13]. Moreover, side effects associated with herbal medications are fewer than those with chemical compound drugs [10, 14]. Some [10, 14] have described using herbal medicines in combination with chemical compound drugs to diminish clinical side effects, improve patients' quality of life, and help complete the course of treatment. We [15] have reported on the efficacy and safety of Eefooton adjuvant treatment in patient with CKD. Eefooton, is a liquid formula of herbal extracts, contained *Astragalus membranaceus, Codonopsis pilosula, Ligustrum lucidum, Panax quinquefolius*, and *Rhodiola sacra*. *Astragalus membranaceus* treatment improved renal function [16], ameliorated renal interstitial fibrosis [17, 18], reduced albuminuria, proteinuria and serum creatinine [19, 20], reduced apoptosis of myocardial cells (Liu et al., 2018). Panax quinquefolius combined with Western medicine standard therapy improved clinical outcomes in patients with acute coronary syndrome [21]. Combination with *Rhodiola* and Western medications has a positive effect on ischemic heart disease [22].

In this report, we describe the case of a 60-year-old man with diabetic nephropathy whose deteriorating kidney function, cardiac function, and pulmonary effusion were palliated by the administration of Eefooton.

Case report

Informed consent was given by the patient. A 60-year-old man had previously been diagnosed with diabetic nephropathy [23]. On February 20th, 2020, he presented to the emergency department with severe hydronephrosis and congenital heart failure leading to severe hydropneumonia [24]. Ultrasonography and chest radiograph revealed left atrial enlargement and left ventricular hypertrophy (**Figure 1**). Urine protein was 114/mg/dL; troponin-T 99.0 ng/L; creatine kinase 490 U/L; estimated glomerular filtration rate (eGFR) 34 mL/min/1.73 m^2; and blood urea nitrogen 326 mg/dL. He had been taking 12 medications: amlodipine (5 mg twice a day), Bokey EM capsules (100 mg once a day), clopidogrel (75 mg once a day), glimepiride (2 mg three times a day), valsartan (80 mg once a day), pioglitazone (30 mg once a day), canagliflozin (100 ng once a day), bisoprolol (1.25 mg once a day), isosorbide mononitrate (20 mg twice a day), spironolactone (25 mg twice a day), hydralazine (10 mg three times a day), and furosemide (40 mg once a day). Management of his complex medication regimen in hospital was difficult; he was dyspneic and edematous; and the eGFR declined to 19.1 on February 28th, 2020. Hemodialysis was being considered. Other laboratory values are given in **Table 1**. His request to be discharged from hospital was granted.

At the same time (on February 28th, 2020), we and the pharmacist discontinued several medications, leaving glimepiride, amlodipine, bisoprolol and spironolactone, and initiated Eefooton (a liquid formula of herbal extracts consisted of *A membranaceus* 3 g, *C pilosula* 3 g, *L lucidum* 3 g, *P quinquefolius* 1.3 g, and *R sacra* 1.3 g in 20 mL water, and it has the ISO22000 and hazard analysis and critical control points certifications approved by United Kingdom Accreditation Service) oral solution 20 ml/bot, 3 times a day, to protect the kidney function. After 3 months of treatment, we decreased the medications to only glimepiride and amlodipine plus Eefooton. After about 4 weeks of treatment, BUN, serum creatinine, and eGFR were in the normal range; UPCR was near normal; and NT-proBNP had decreased dramatically (**Table 1** and **Figure 2**). Markers of diabetes (blood glucose and HbA1c) and amino alanine transferase (ALT) also were normal. No complications were observed during the duration of treatment.

Discussion and conclusions

We believe this is the first report of improved kidney function and heart failure in a patient

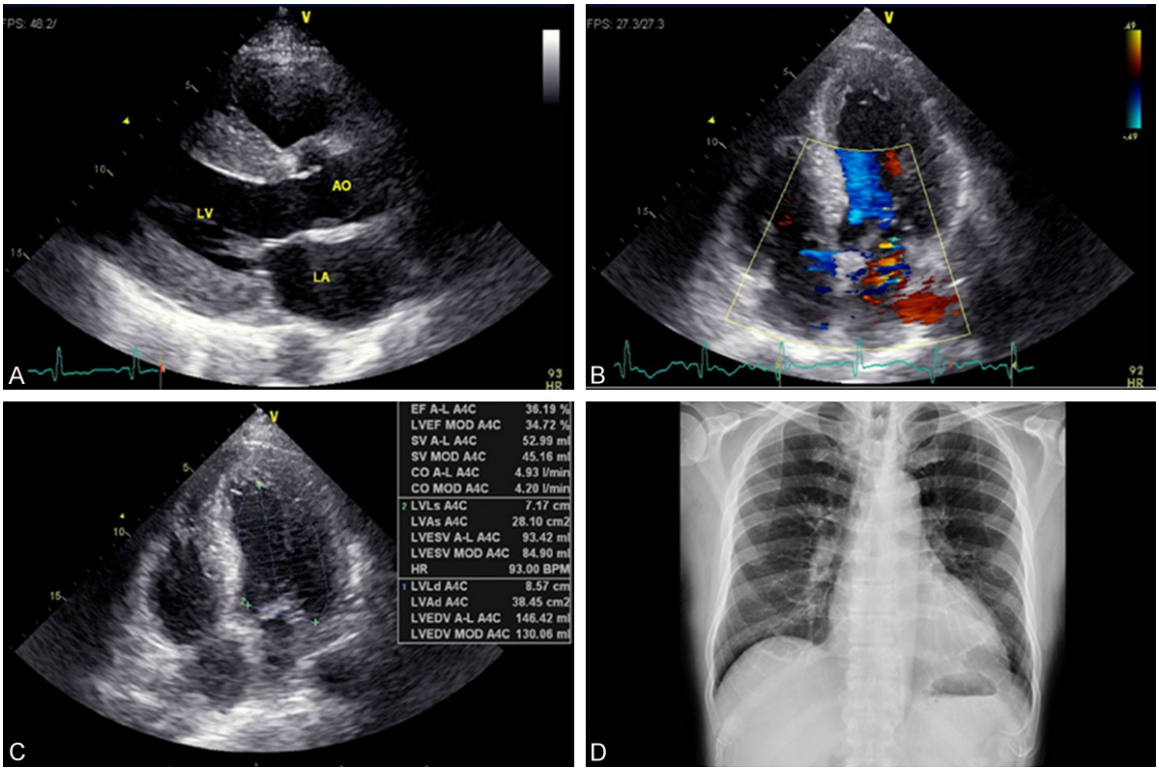

Figure 1. Ultrasonography scanning and X-ray examination at outpatient clinic before Eefooton treatment. The heart ultrasonography exhibited that patient had sinus rhythm, left atrial enlargement (A), and left ventricular hypertrophy (B, C). A left ventricular hypertrophy examined by the X-ray (D).

Table 1. Blood biological parameters of patient before and after the Eefooton treatment

	Normal range	Before treatment	After treatment		
		February 28th 2020	March 23th 2020	May 8th 2020	May 27th 2020
ALT, U/L	<40	260.00	18.00	39.00	-
BUN, mg/dL	7.0-22.0	70.00	21.00	-	22.00
Creatinine, mg/dL	0.5-1.2	3.51	1.40	-	1.10
eGFR, mL/min/1.73 m^2	>60	19.09	54.90	-	72.60
UPCR*, mg/gm	<1000	4350.00	-	1036.83	1092.82
NT-proBNP, pg/mL	<900	22477.00	-	-	1737.00
Sugar, mg/dL	70-110	354.00	107.00	-	-
HbA1c, %	<6.5	9.40	-	-	5.60
P, mg/dL	2.4~4.7	4.20	3.60	-	-

ALT, alanine aminotransferase; Bun, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UPCR, urine protein/creatinine ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; HbA1c, glycated hemoglobin; P, phosphorus. *For diabetic nephropathy.

with diabetic nephropathy treated with Eefooton together with chemical compounds. The patient had severe hydronephrosis and congestive heart failure, leading to severe hydropneumonia. He improved symptomatically and biochemically with discontinuation of several medications that he had been taking, and with the inclusion of Eefooton. Eefooton is a combination of herbal extracts (Astragalus membranaceus, Codonopsis pilosula, Ligustrum lucidum, Panax quinquefolius, and Rhodiola sacra), with reputed individual or combined effects that could have contributed to improved renal, cardiac, and hepatic function in our patient.

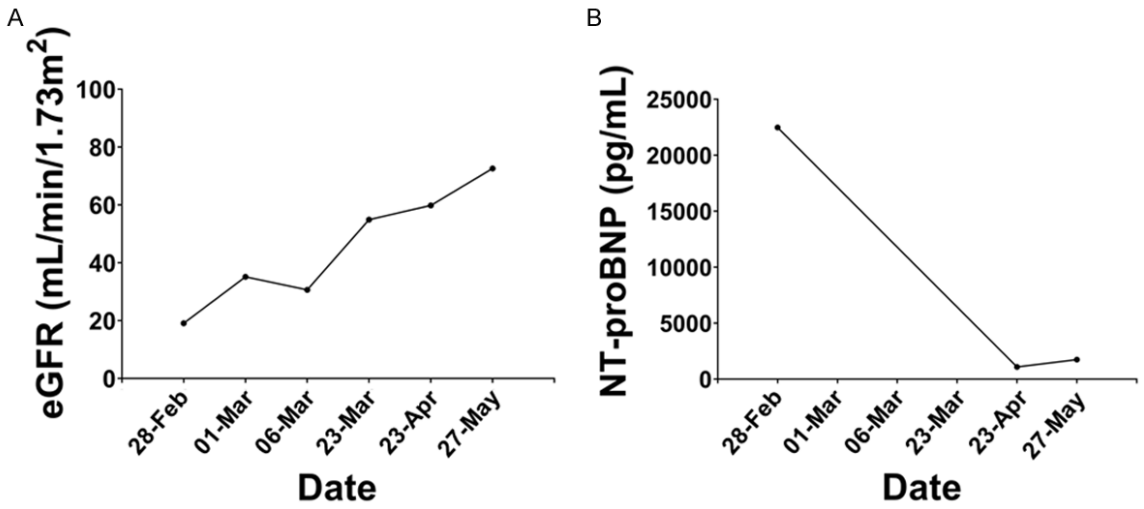

Figure 2. Trends of eGFR and NT-proBNP levels during the Eefooton treatment. The increased level of the eGFR (A) and decreased level of the NT-proBNP (B) at 3 months after the beginning Eefooton treatment on February 28th 2020.

We suspect that polypharmacy caused or at least contributed to the decline in this patient's kidney function. This opinion concurs with the CKD-REIN study of CKD patients in France who had an eGFR <60 mL/min/1.73 m^2, half of whom had been prescribed at least one inappropriate drug [9], and with the German Chronic Kidney Disease study, in which the prevalence of polypharmacy was almost 80% and the median number of medications taken per day was eight (range 0-27) [8]. Thus, our first action was discontinuation of several of the medications the patient had been taking. We also instituted natural plant extracts (Eefooton), which may have fewer side effects. The initial NT-proBNP, the index of heart failure, dropped rapidly from 22477 pq/mL to 1085 pq/mL after two-months' treatment. Although NT-proBNP rose modestly (to 1737 pg/mL) when the patient was taking only amlodipine and glimepiride, the value was considered safe enough to permit trial of other medications for treatment of heart failure.

In the studies of CKD patients, *Astragalus membranaceus* treatment for 3 months was associated with significantly decreased serum creatinine levels, indicating improved kidney function [16]. Astragaloside IV from *Astragalus membranaceus* has been found to ameliorates renal interstitial fibrosis [17, 18]. *Astragalus membranaceus* also was found possibly effective and tolerated for short-term reduction of albuminuria, proteinuria, and serum creatinine as adjunctive therapy for diabetic kidney disease [19, 20]. In our patient, amlodipine combined with Eefooton was associated with a decrease in UPCR, the typical diabetic nephropathy marker [25, 26], from 4350 mg/g to 1037 mg/g after 3 months' treatment, providing that a safe and effective combined treatment option for patients with diabetic nephropathy in the future. Moreover, we speculate that the improvement of UPCR may be due to the effect of *Astragalus membranaceus* extract in Eefooton. The possibility that this improvement resulted from the effect of *Astragalus membranaceus* extract in the Eefooton preparation deserves investigation.

The decrease in NT-proBNP values in our patient with Eefooton treatment is consistent with reports of its herbal extracts having beneficial cardiac effects. *Astragalus* membranaceus extract Astragaloside IV reduced apoptosis of myocardial cells and was effective in the treatment of cardiac hypertrophy [27, 28]. *Panax quinquefolius* plus Western medicine standard therapy improved clinical outcomes in patients with acute coronary syndrome and mild-to-moderate renal insufficiency [21]. *Rhodiola* formulations may have a positive effect on ischemic heart disease alone and in combination with Western medications [22]. Taken together, we speculate that Eefooton has beneficial cardiac effects which may be due to

the *Astragalus membranaceus*, *Panax quinquefolius*, and *Rhodiola sacra* extracts in Eefooton. Further investigation should address the possible synergistic effect of herbal extracts in Eefooton in patients with heart failure and the role of Eefooton in the treatment of patients with acute coronary syndrome.

The kidneys and heart are closely related pathophysiologically, especially through an interrelated circulatory system, including renal control of blood pressure. In traditional Chinese medicine, the heart and kidney are interdependent and mutually restrictive - the "heart-kidney intersection". From the assessment of internal organ workload, heart treatment will be smoother if the kidney function is improved first. Thus, with the use of modern markers in monitoring congestive heart failure, if the eGFR is controlled, abnormal NT-proBNP values will be improved.

ALT improved in our patient from 260 U/L to 18 U/L with treatment of Eefooton. Whether this improvement was due the effects of A. membranaceus or due to the decrease in congestive hepatopathy or other factors is not known, but the herbal medication has been commonly used for its reputed hepatoprotective effects [29].

This study is limited because it is an observational, uncontrolled study of a single patient. Also, correction of the polypharmacy and institution of Eefooton were concurrent events, so it is impossible to assess the effect of Eefooton independently. Nonetheless, the study draws attention to the risk of polypharmacy in the treatment of ESRD and the possible benefit of replacing chemical compounds with potentially less toxic yet effective traditional Chinese medications.

In a patient with diabetic nephropathy, end-stage renal disease, and congestive heart failure, discontinuation of several chemical compounds and initiation of the herbal preparation Eefooton resulted in prompt and sustained resolution of clinical and biochemical manifestations. Polypharmacy is a risk in the treatment of chronic kidney disease, and herbal preparations may be safe and effective in treatment of the disease and associated congestive heart failure.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chih-Hui Lin, Gerent Biotech R&D Center, No. 20, Jen Yi St., Taichung City 402, Taiwan (R.O.C.). Tel: +886-935318221; E-mail: wisdomli@ms2.hinet.net

References

[1] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1-266.

[2] Abbasi M, Chertow G and Hall Y. End-stage renal disease. Am Fam Physician 2010; 82: 1512.

[3] Agarwal R. Defining end-stage renal disease in clinical trials: a framework for adjudication. Nephrol Dial Transplant 2016; 31: 864-867.

[4] Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-1305.

[5] Levey AS and Coresh J. Chronic kidney disease. Lancet 2011; 375: 165-180.

[6] Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M and Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 2014; 63: 713-735.

[7] Vilayur E and Harris DC. Emerging therapies for chronic kidney disease: what is their role? Nat Rev Nephrol 2009; 5: 375-383.

[8] Schmidt IM, Hubner S, Nadal J, Titze S, Schmid M, Barthlein B, Schlieper G, Dienemann T, Schultheiss UT, Meiselbach H, Kottgen A, Floge J, Busch M, Kreutz R, Kielstein JT and Eckardt KU. Patterns of medication use and the burden of polypharmacy in patients with chronic kidney disease: the German Chronic Kidney Disease study. Clin Kidney J 2019; 12: 663-672.

[9] Laville SM, Metzger M, Stengel B, Jacquelinet C, Combe C, Fouque D, Laville M, Frimat L, Ayav C, Speyer E, Robinson BM, Massy ZA and Liabeuf S; Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) Study Collaborators. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. Br J Clin Pharmacol 2018; 84: 2811-2823.

[10] Bahall M. Use of complementary and alternative medicine by patients with end-stage renal disease on haemodialysis in Trinidad: a descriptive study. BMC Complement Altern Med 2017; 17: 250.

[11] Feng Q, Wan Y, Jiang C, Wang C, Wei Q, Zhao Q and Yao J. Mechanisms and effects of chinese herbal medicine delaying progression of chronic renal failure. Zhongguo Zhong Yao Za Zhi 2011; 36: 1122-1128.
[12] Halle MP, Lapsap CT, Barla E, Fouda H, Djantio H, Moudze BK, Akazong CA and Priso EB. Epidemiology and outcomes of children with renal failure in the pediatric ward of a tertiary hospital in Cameroon. BMC Pediatr 2017; 17: 202.
[13] Shen YL, Wang SJ, Rahman K, Zhang LJ and Zhang H. Chinese herbal formulas and renal fibrosis: an overview. Curr Pharm Des 2018; 24: 2774-2781.
[14] Park CH, Lee AY, Kim JH, Seong SH, Jang GY, Cho EJ, Choi JS, Kwon J, Kim YO, Lee SW, Yokozawa T and Shin YS. Protective effect of safflower seed on cisplatin-induced renal damage in mice via oxidative stress and apoptosis-mediated pathways. Am J Chin Med 2018; 46: 157-174.
[15] Yao CA and Lin CH. Treatment with the herbal formulation Eefooton slows the progression of chronic kidney disease: a case report. Medicine (Baltimore) 2019; 98: e17573.
[16] Zhang HW, Lin ZX, Xu C, Leung C and Chan LS. Astragalus (a traditional Chinese medicine) for treating chronic kidney disease. Cochrane Database Syst Rev 2014; CD008369.
[17] Shan G, Zhou XJ, Xia Y and Qian HJ. Astragalus membranaceus ameliorates renal interstitial fibrosis by inhibiting tubular epithelial-mesenchymal transition in vivo and in vitro. Exp Ther Med 2016; 11: 1611-1616.
[18] Zhou X, Sun X, Gong X, Yang Y, Chen C, Shan G and Yao Q. Astragaloside IV from Astragalus membranaceus ameliorates renal interstitial fibrosis by inhibiting inflammation via TLR4/NF-small ka, CyrillicB in vivo and in vitro. Int Immunopharmacol 2017; 42: 18-24.
[19] Zhang, Shergis JL, Yang L, Zhang AL, Guo X, Zhang L, Zhou S, Zeng L, Mao W and Xue CC. Astragalus membranaceus (Huang Qi) as adjunctive therapy for diabetic kidney disease: an updated systematic review and meta-analysis. J Ethnopharmacol 2019; 239: 111921.
[20] Zhang Y, Wu J, Guo S, Lin W, Zhang B, Chen X, Mo H and Zhan T. The clinical efficacy and safety of the Chinese herbal medicine Astragalus (Huangqi) preparation for the treatment of acute myocardial infarction: a systematic review of randomized controlled trials. Medicine (Baltimore) 2019; 98: e15256.
[21] Zhang DW, Wang SL, Wang PL, Du JP, Gao ZY, Wang CL, Xu H and Shi DZ. The efficacy of Chinese herbal medicines on acute coronary syndrome with renal insufficiency after percutaneous coronary intervention. J Ethnopharmacol 2020; 248: 112354.
[22] Yu L, Qin Y, Wang Q, Zhang L, Liu Y, Wang T, Huang L, Wu L and Xiong H. The efficacy and safety of Chinese herbal medicine, Rhodiola formulation in treating ischemic heart disease: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 2014; 22: 814-825.
[23] American Diabetes Association. 11. microvascular complications and foot care: standards of medical care in diabetes-2019. Diabetes Care 2019; 42: S124-S138.
[24] Marantz PR, Tobin JN, Wassertheil-Smoller S, Steingart RM, Wexler JP, Budner N, Lense L and Wachspress J. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. Circulation 1988; 77: 607-612.
[25] Hwang S, Park J, Kim J, Jang HR, Kwon GY, Huh W, Kim YG, Kim DJ, Oh HY and Lee JE. Tissue expression of tubular injury markers is associated with renal function decline in diabetic nephropathy. J Diabetes Complications 2017; 31: 1704-1709.
[26] Krairittichai U, Sarinnapakorn V, Mahannopkul R and Ainwan P. Renal protective effects of combination of diltiazem and ACEI/ARB on the progression of diabetic nephropathy: randomized controlled trial. J Med Assoc Thai 2017; 100 Suppl 1: S40-47.
[27] Liu ZH, Liu HB and Wang J. Astragaloside IV protects against the pathological cardiac hypertrophy in mice. Biomed Pharmacother 2018; 97: 1468-1478.
[28] Zhao Y, Liu Z and Zhang H. Astragaloside protects myocardial cells from apoptosis through suppression of the TLR4/NF-kappaB signaling pathway. Exp Ther Med 2018; 15: 1505-1509.
[29] Ko PH, Huang CW, Chang HH, Chuang EY, Tsai MH and Lai LC. Identifying the functions and biomarkers of Codonopsis pilosula and Astragalus membranaceus aqueous extracts in hepatic cells. Chin Med 2019; 14: 10.