Int J Clin Exp Med 2016;9(8):15066-15072
www.ijcem.com /ISSN:1940-5901/IJCEM0020524

Review Article

The present and future of diabetes mellitus secondary prevention: the role of traditional Chinese medicine cannot be ignored

Jiaxing Tian[1,2*], Linhua Zhao[1*], Jun Song[1], Xiaotong Yu[2], Yashan Cui[3], Fengmei Lian[1], Xiaolin Tong[1]

[1]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China; [2]Beijing University of Chinese Medicine, Beijing 100029, China; [3]Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China. [*]Co-first authors.

Received July 5, 2015; Accepted May 5, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Diabetes mellitus (DM), one of the most common non-communicable chronic diseases, jeopardizes human health severely. The incidence of DM had increased rapidly in recent years, whereas the situation control is not satisfying. DM secondary prevention (i.e. prevention of diabetes complications) has become the most important part in diabetes management. The main interventions of DM secondary prevention currently were focused on indirect factors (glucose, lipids, blood pressure), lacking of medications targeted on the complications. It was well known that traditional Chinese medicine (TCM) had unique advantages in the prevention and control of complex diseases such as DM. In this study, we reviewed the present situation and future trends of DM secondary prevention, the applications and advantages of TCM in DM secondary prevention would also be commented.

Keywords: Diabetes mellitus, secondary prevention, traditional Chinese medicine, activate blood circulation, evidence-base medicine

Introduction

Currently the overall prevalence of diabetes mellitus (DM) in adults was estimated to be 8.3% in the world according to the International Diabetes Federation (IDF). The population of DM patients has reached 382 million and estimated nearly 592 million by 2035 [1]. Huge medical resources were spent on DM, according to the research released by the American Diabetes Association (ADA), in the United States $245 billion in 2012 was spent on DM and the average annual health care spending on a person with diabetes was 2.3 times than a person without diabetes. The health spending in the United States ranks first in the world, yet it failed to prevent the deterioration of the diabetes epidemic [2]. The latest report of Diabetes UK showed that although diabetes management in the UK costs accounted for 10% of National Health Service (NHS), but the situation is still not optimistic. In view of nearly 300 thousand people are diagnosed with type 2 diabetes in UK each year, the prevention of complications becomes the top priority of diabetes management. Patients with a long duration complications lose their ability to work, which causes a heavy social and economic burden. More and more experts have reached a consensus that preventing and reducing the risk of person with diabetes complications in DM patients is the primary goal [3]. Therefore, it is particularly urgent to develop effective strategies for DM secondary prevention (ie, prevent complications), which could counter the growing threat of DM.

Strategies and considerations of DM secondary prevention

Glucose control

The Diabetes Control and Complications Trial (DCCT) [4], United Kingdom Prospective Diabetes Study (UKPDS) [5] and Japan Kumamoto Study [6] which focused on enhanced glucose control had indicated that enhanced glucose control could significantly reduce the risk of

person with diabetes microvascular disease in the early stage of DM. UKPDS also showed that among the overweight population, the application of metformin could significantly reduce the risk of myocardial infarction and related death [7]. In the long-term follow up of DCCT [8, 9] and UKPDS [10], early stage enhanced glucose control is related to the reduction of person with diabetes microvascular disease and myocardial infarction and related death. These findings indicated the importance of enhanced glucose control in early stage DM.

Yet enhanced glucose control is not absolutely beneficial. The ADVANCE [11] and ACCORD [12] studies showed enhanced glucose control did not decrease the mortality and risk of large vascular disease. And the results from VADT study is disappointing [13], the risk of large vascular and microvascular did not decreased.

Blood pressure and lipid control

UKPDS has shown that among the newly diagnosed DM patients, enhanced blood pressure control could significantly reduce the risk of large vessel and microvascular disease [14]. Hypertension Optimal Treatment (HOT) and other anti-hypertension trials have shown that in the DM subgroup, enhanced blood pressure control could reduce the risk of cardiovascular disease in DM patients without obvious vascular complication [15]. Heart Protection Study (HPS) DM subgroup [16] and Collaborative Atorvastatin Diabetes Study (CARDS) showed that the application of statin lowering low density lipoprotein cholesterol (LDL-C) could also reduce the risk of cardiovascular disease in patients without obvious vascular complication. While in ACCORD [18], on the basis of statin, combination of other lipid lowering drugs might not gain extra cardiovascular benefit.

Application of aspirin

It is controversial to use aspirin in DM. Several systematic reviews showed the protective effect of aspirin in DM patients with cardiovascular risk factors [19-21]. Yet JAPD trial reported that type 2 DM patients with high risk of cardiovascular disease gain no extra benefit from aspirin [22]. JPPP trial showed that the application of aspirin in adults aged over 60 with high risk of cardiovascular disease could not decrease the incidence of end event [23]. Besides, Early Treatment Diabetic Retinopathy Study (ETDRS) indicated that aspirin failed to prevent the development of proliferative retinopathy and visual loss [24].

Other interventions

The China Da Qing Diabetes Prevention Outcome Study applied lifestyle intervention on impaired glucose tolerance (IGT) patients for 6 years, the results of 20-year follow up showed the significant decrease on cardiac death, all cause death and incidence of person with diabetes retinopathy, but no benefit on neuropathy and nephropathy [25]. One research drew our attention that the time to the onset of micro albuminuria in T2DM was increased by 23% with olmesartan, but the higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern [26]. On the other hand, morning blood pressure monitoring, physician telephone guidance, personal structured nursing, gastrectomy and pancreatic islets transplantation could delay and reduce the incidence of diabetes complications to a certain extent [27-29].

The gap between the anticipation and reality in the treatment of DM gives us meditation. The 2015 standards for diabetes care from American Diabetes Association (ADA) points out that individual management, glucose goal and glucose intervention should be given to each patient [30]. The management of DM is continuously improving and modifying, seeking for optimal treating strategy and intervention timing, balancing the safety and benefit are the best interpretation for individualized treatment.

Applications and advantages of TCM in the DM secondary prevention

Traditional Chinese medicine, which is an important scientific and technological resource with original and independent advantage, has been treating diabetes thousands of years. The "whole view" and "multi-targets" of TCM owes unique advantages in controlling complex diseases, such as diabetes [31]. TCM is characterized by individualized treatment based on syndrome differentiation, principles of balance control, treatment of humanity, various routes of administrations, natural medication orienta-

tion, highly fits the development trend of individualized treatment, also contains the advanced ideology of the modern system biology [32, 33]. In recent years, large-scale clinical trials have confirmed that TCM has made breakthrough progress on blood glucose control. The application of modern science and technology had clarified parts of the therapeutic mechanism [34-36]. The study on optimization of the formulation and dosage had improved the efficacy of TCM compared to ancient time [37, 38]. Series of outstanding results have drawn attentions and recognitions. Further developing and modifying TCM treating strategies on DM secondary prevention in the future would improve the comprehensive prevention and control of diabetes significantly.

Current applications of TCM on diabetes

Several large-scaled evidence-based clinical researches have been launched, the subjects cover pre-diabetes to diabetes complications, verifying the preventive and therapeutic effect of TCM on diabetes thoroughly. TCM has achieved exciting results in the DM primary prevention. It is reportedly that Tianqi capsule, a Chinese patent medicine, combined with lifestyle intervention for 12 months could significantly decreased the incidence of T2DM in subjects with IGT. Cox's proportional hazards model analysis showed that Tianqi reduced the risk of diabetes by 32.1% compared with the placebo [35]. In adouble-blinded trial, 187 T2D patients were randomly allocated to receive Chinese herbal formula GegenQinlian Decoction (GQD), structural changes of gut microbiota are induced by GQD, the treatment may enrich the amounts of beneficial bacteria and the changes in the gut microbiota are associated with the antidiabetic effects of GQD [34], which provides new evidence to explain the mechanism of TCM chain and new targets and technical methods. Another Chinese patent medicineTM81 showed that TM81 group could decrease the HbA1c 1.02% versus 0.47% in the placebo group on patients with early-stage type 2 diabetes, and the symptoms related to diabetes were also improved [36]. Moreover, Studies have shown that the combined use of Jinlida, a Chinese patent medicine, is more effective than metformin monotherapy. Jinlida could significantly enhance the hypoglycemic action when the subject was in poor glucose control using metformin alone [39]. TCM also shows its unique advantages in DM tertiary prevention, research showed that the treatment of TCM could improve persons with diabetes extremely severe gastroparesis on symptoms of refractory nausea and vomiting when western medicine was not effective [40]. High dose of aconitum in combination with HuangqiGuizhiWuwu Decoction could improve the symptoms of pain, numbness and cold in patients with diabetes peripheral neuropathy [41]. What's more, danshen-containing Chinese herbal medicine could reduce serum creatinine and urine protein quantitative, significantly delay the renal failure and dialysis on patients with diabetes nephropathy [42]. Treatment of Qi Ming granule could improve the fundus diseases of diabetes retinopathy patients [43]. These researches have provided the possibility and consideration for DM secondary prevention treated by TCM.

"Preventive treatment of disease" reflects the perspective of TCM for disease prevention

TCM has a solid theoretical foundation for the DM secondary prevention. Ancient physicians called premedical intervention before diseases as "preventive treatment of disease". These concepts have been practiced in TCM for thousands of years. The full awareness of that prevention is more important than treatment, is taking various measures not only to prevent before the disease (i.e. prevention before disease), but also prevent the development of the disease in the case of illness (i.e. prevention before worsening). TCM has developed various strategies for tackling health problems early in the long-term medical practice, which gives advantage and specialty to TCM [44, 45]. The combination of TCM health concept and the modern medication system would improve the diabetes management and help form a new system and pattern for the diabetes prevention and treatment.

The concept of "activate blood circulation" has achieved preliminary success in practice

Through the experimental study and clinical practice, it was confirmed that hyperglycemia could induced damage of collaterals. From the perspective of TCM, it is important to seize the notion and connection of "diabetes-blood stasis" and make full use of the theory of promoting blood circulation. It is vital to paying atten-

tion to the intervention of the collateral since the diagnosis of diabetes. Collateral damage existed through the course of the disease even before the diagnosis. The collateral damage in different degrees could be defined as "collateral qi obstruction, collateral qi stagnation, collateral blood stasis, collateral blockage and collateral damage", and therefore, treatment should aim to promote blood circulation and remove obstruction in vessels throughout the whole process [31].

The exploration of the best intervention time for activate blood circulation has experienced the cognition of late stage to early stage [46]. Researchers reported that the application of collateral disease theory is effective in treating diabetic nephropathy [47]. And treating diabetic peripheral neuropathy with activating blood circulation is satisfying. Early intervention could delay or prevent the occurrence of diabetic peripheral neuropathy [48]. Collaterals damage is found in DM and metabolism syndrome when the glucose is increased, with the appearance of sublingual collaterals changes, fundus changes or urine protein. The usage of activating blood circulation could improve but not reverse the sublingual collaterals changes, fundus changes and urine protein, indicating the significance of early intervention. Later research proved it effective to treat early stage DM patients with activating blood circulation drugs [46]. The research group carried out a multicentered, randomized, double-blinded clinical trial, used Compound Danshen Dripping Pill (CDDP) in the treatment of patients with early diabetic retinopathy, showed the efficacy of CDDP in significantly improving fundus fluorescein angiography and fundus change, delaying the progression of diabetic retinal disease. These researches have confirmed the significant clinical effect of activating blood circulation and removing blood stasis throughout the DM course, especially in the early stage.

The clinical practice experience has been further confirmed in the experimental study. Diabetic rat model of 0 month and 6 months were administered to the activating blood circulation drug intervention respectively, the result showed that early intervention could significantly reduce or delay micro vascular disease occurrence and development, compared to late treatment [49]. Other study confirmed the preventive and therapeutic effects of activating blood circulation drugs on rats with retinal lesions, and the therapeutic mechanisms were thought to be related to enhancing diabetes rat fibrinolytic activity, inhibiting the overexpression of fibroblast adhesion protein and laminin protein [50]. By clinic practice and experimental researches, it has been proven that in the whole process of diabetes, persistence of prevention and control in advance, early intervention and active treatment could achieve better effect in DM secondary prevention.

The future trends of DM secondary prevention

Currently DM secondary prevention mainly focuses on indirect factors of diabetes complications (glucose, lipids, blood pressure), the situation is still not satisfying. In the future research, intervention of blood glucose and other indirect factors and controlling risk factors are urgent. In addition, the integration of scientific and technological resources is needed for prevention and treatment of DM. As a potential advantages resource in DM secondary prevention, TCM contains abundant medical experiences, which has accumulated and summarized valuable methods and theories for DM prevention. The application of TCM in DM secondary prevention is promising. To achieve that, TCM theories should be verified by large-scale clinical trials. Different medications should be used in different DM stages and syndromes. Collect the incidence of diabetes complication and other key efficacy indicators, to construct the clinical research database, connecting the diabetes data platform, to provide high quality evidence-based basis. Further, select advanced biomarkers for diabetes and its complications. Establish effective drugs for the secondary prevention, and reveal the biological mechanisms of TCM intervention. By the application of TCM comprehensive system for the prevention and control, the DM secondary prevention would be improved significantly. The tendency of the rising rates of diabetes and its complications would be controlled, or even the inflection point would appear.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (No. 81430097) and Special Program in Tradi-

tional Chinese Medicine Scientific Research (No. 201007004).

Disclosure of conflict of interest

None.

Address correspondence to: Fengmei Lian and Xiaolin Tong, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. E-mail: lfm565@sohu.com (FML); xiaolintong66@sina.com (XLT)

References

[1] World Health Organization. Country and regional data on diabetes. Available from http://www.who.int/diabetes/facts/world_figures/en/. Accessed September 19, 2014.

[2] American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013; 36: 1033-1046.

[3] Chinese Diabetes Society. Chinese guideline for diabetes prevention and treatment. Chinese Journal of the Frontiers of Medical Science 2015; 7: 26-89.

[4] The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342: 381-389.

[5] UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.

[6] Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care 2000; 23 Suppl 2: B21-29.

[7] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-865.

[8] DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014; 2: 793-800.

[9] Lachin JM, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care 2014; 37: 39-43.

[10] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577-1589.

[11] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560-2572.

[12] ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC Jr, Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH Jr, Byington RP, Rosenberg YD, Friedewald WT. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011; 364: 818-828.

[13] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129-139.

[14] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-713.

[15] Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351: 1755-1762.

[16] Ogrin C, Perkelvald A, Winer N. Heart protection study: a focus on diabetic patients. Curr Diab Rep 2004; 4: 185-186.

[17] Charlton-Menys V, Betteridge DJ, Colhoun H, Fuller J, France M, Hitman GA, Livingstone SJ, Neil HA, Newman CB, Szarek M, DeMicco DA, Durrington PN. Apolipoproteins, cardiovascular risk and statin response in type 2 diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia 2009; 52: 218-225.

[18] ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton

DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1563-1574.
[19] Simpson SH, Gamble JM, Mereu L, Chambers T. Effect of aspirin dose on mortality and cardiovascular events in people with diabetes: a meta-analysis. Gen Intern Med 2011; 26: 1336-1344.
[20] Butalia S, Leung AA, Ghali WA, Rabi DM. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. Cardiovasc Diabetol 2011; 10: 25.
[21] De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, Nicolucci A. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009; 339: b4531.
[22] Soejima H, Ogawa H, Morimoto T, Nakayama M, Okada S, Sakuma M, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Waki M, Saito Y; JPAD Trial Investigators. Aspirin possibly reduces cerebrovascular events in type 2 diabetic patients with higher C-reactive protein level: subanalysis from the JPAD trial. J Cardiol 2013; 62: 165-170.
[23] Okada S, Morimoto T, Ogawa H, Sakuma M, Soejima H, Nakayama M, Sugiyama S, Jinnouchi H, Waki M, Doi N, Horii M, Kawata H, Somekawa S, Soeda T, Uemura S, Saito Y; investigators for the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial. Effect of low-dose aspirin on primary prevention of cardiovascular events in Japanese diabetic patients at high risk. Circ J 2013; 77: 3023-3028.
[24] Early Treatment Diabetic Retinopathy Study Research Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. Ophthalmology 1991; 98 Suppl: 757-765.
[25] Gong Q, Gregg EW, Wang J, An Y, Zhang P, Yang W, Li H, Li H, Jiang Y, Shuai Y, Zhang B, Zhang J, Gerzoff RB, Roglic G, Hu Y, Li G, Bennett PH. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. Diabetologia 2011; 54: 300-307.
[26] Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011; 364: 907-917.
[27] Kamoi K, Ito T, Miyakoshi M, Minagawa S. Usefulness of home blood pressure measurement in the morning in patients with type 2 diabetes: long-term results of a prospective longitudinal study. Clin Exp Hypertens 2010; 32: 184-192.
[28] Krämer HU, Raum E, Rüter G, Schöttker B, Rothenbacher D, Rosemann T, Szecsenyi J, Brenner H. Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes: results from the DIANA study. Cardiovasc Diabetol 2012; 11: 88.
[29] Hansen LJ, Siersma V, Beck-Nielsen H, de Fine Olivarius N. Structured personal care of type 2 diabetes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). Diabetologia 2013; 56: 1243-1253.
[30] Romeo GR, Abrahamson MJ. The 2015 standards for diabetes care: maintaining a patient-centered approach. Ann Intern Med 2015; 162: 785-786.
[31] Tong XL, Dong L, Chen L, Zhen Z. Treatment of diabetes using traditional Chinese medicine: past, present and future. Am J Chin Med 2012; 40: 877-86.
[32] Luo GA, Liang QL, Wang YM, Liu QF, Li X. Development and Prospect of Traditional Chinese medicine Biological system. Chinese Journal of Natural Medicines 2009; 7: 242-248.
[33] Chen KJ. Some thoughts in the development of Traditional Chinese medicine. Chinese Journal of Integrated Traditional and Western Medicine 2000; 20: 294.
[34] Xu J, Lian F, Zhao L, Chen X, Zhang X, Guo Y, Zhang C, Zhou Q, Xue Z, Pang X, Zhao L, Tong X. Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula. ISME J 2015; 9: 552-562.
[35] Lian F, Li G, Chen X, Wang X, Piao C, Wang J, Hong Y, Ba Z, Wu S, Zhou X, Lang J, Liu Y, Zhang R, Hao J, Zhu Z, Li H, Fang Liu H, Cao A, Yan Z, An Y, Bai Y, Wang Q, Zhen Z, Yu C, Wang CZ, Yuan CS, Tong X. Chinese herbal medicine Tianqi reduces progression from impaired glucose tolerance to diabetes: a double-blind, randomized, placebo-controlled, multicenter trial. J Clin Endocrinol Metab 2014; 99: 648-655.
[36] Tong XL, Wu ST, Lian FM, Zhao M, Zhou SP, Chen XY, Yu B, Zhen Z, Qi LW, Li P, Wang CZ, Sun H, Yuan CS. The safety and effectiveness of TM81, a Chinese herbal medicine, in the treatment of type 2 diabetes: a randomized double-blind placebo-controlled trial. Diabetes Obes Metab 2013; 15: 448-454.
[37] Lian F, Wu L, Tian J, Jin M, Zhou S, Zhao M, Wei L, Zheng Y, Wang Y, Zhang M, Qin W, Wu Z, Yuan CS, Tong X. The effectiveness and safety of a danshen-containing Chinese herbal medi-

cine for diabetic retinopathy: a randomized, double-blind, placebo-controlled multicenter clinical trial. J Ethnopharmacol 2015; 164: 71-77.

[38] Tong XL, Zhao LH, Lian FM, Zhou Q, Xia L, Zhang JC, Chen XY, Ji HY. Clinical observations on the dose-effect relationship of gegenqinlian decoction on 54 out-patients with type 2 diabetes. J Tradit Chin Med 2011; 31: 56-59.

[39] Lian F, Tian J, Chen X, Li Z, Piao C, Guo J, Ma L, Zhao L, Xia C, Wang CZ, Yuan CS, Tong X. The Efficacy and Safety of Chinese Herbal Medicine Jinlida as Add-On Medication in Type 2 Diabetes Patients Ineffectively Managed by Metformin Monotherapy: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial. PLoS One 2015; 10: e0130550.

[40] Li JL, Li M, Pang B, Zhou Q, Tian JX, Liu HX, Zhao XY, Tong XL. Combination of symptoms, syndrome and disease: treatment of refractory diabetic gastroparesis. World J Gastroenterol 2014; 20: 8674-8680.

[41] Feng L, Liu WK, Deng L, Tian JX, Tong XL. Clinical efficacy of aconitum-containing traditional Chinese medicine for diabetic peripheral neuropathic pain. Am J Chin Med 2014; 42: 109-117.

[42] Tian JX, Zhao LH, Zhou Q, Tong XL. Retrospective analysis on modified Didang Decoction for treating microalbuminuria of diabetic nephropathy. Journal of Beijing University of Traditional Chinese Medicine 2012; 19: 7-10.

[43] Luo XX, Duan JG, Liao PZ, Wu L, Yu YG, Qiu B, Wang YL, Li YM, Yin ZQ, Liu XL, Yao K. Effect of qiming granule on retinal blood circulation of diabetic retinopathy: a multicenter clinical trial. Chin J Integr Med 2009; 15: 384-388.

[44] Wang Q, Dong J, Wu HD, Li YS, Ren XJ. Exert the unique advantages of Traditional Chinese medicine in disease prevention to achieve health promotion. Traditional Chinese Medicine Journal 2006; 4: 1-4.

[45] Chang SH, Wang HH. Health promotion in traditional Chinese medicine: preventive treatment of a disease. Hu Li Za Zhi 2004; 51: 23-27.

[46] Tong XL, Zhao Y, Bi GZ, Chen L, Li HJ, Dong L. The application of disease prevention and collaterals in diabetic microvascular complication under the guidance of Traditional Chinese medicine. Journal of Traditional Chinese Medicine 2007; 48: 485-486.

[47] Wu YL, Wei C, Jia ZH, et al. Treatment of diabetic nephropathy from the perspective of collaterals. Acta Universitatis Traditionis Medicalis Sinensis Pharmacologiaeque Shanghai 2007; 21: 5-8.

[48] Lv R, Li RJ, Tian GF, Liu P, Feng HS, Pan L. The mechanism of Mudan granules in the treatment of diabetic peripheral neuropathy. Chinese Journal of New Drugs 2009; 2: 123-126.

[49] Tong XL, Zhou SP, Piao XY, et al. The protective effect and mechanism of Luotong on diabetic rat kidney. Chinese Journal of Basic Medicine in Traditional Chinese Medicine 2001; 7: 35-37.

[50] Zhou SP, Tong XL, Pan L, et al. Effects of hirudo on retinal Micrangium in diabetic rats. China Journal of Chinese Ophthalmology 2002; 12: 79-83.