PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chinese Herbal Medicine for Diabetic Kidney Disease: A Systematic Review and Meta-analysis of Randomised Placebo-controlled Trials
AUTHORS	Zhang, La; Yang, Lihong; Shergis, Johannah; Zhang, Lei; Zhang, Anthony; Guo, Xinfeng; Qin, Xindong; Johnson, David; Liu, Xusheng; Lu, Chuan-jian; Xue, Charlie; Mao, Wei

VERSION 1 - REVIEW

REVIEWER	Mayuree Tangkiatkumjai Srinakharinwirot University and Thailand
REVIEW RETURNED	18-Aug-2018

GENERAL COMMENTS	This meta-analysis was well-designed and analysed. The findings were informative. However, there are some minor errors that need to revise as follows. 1. Abstract: it should provide adverse effects of CHM in order to balance between efficacy and safety of CHM as mentioned in the objective of this study. The findings should provide I2. 2. Introduction: From my knowledge, the statement in line 31-43 on page 5 may be exaggerated because numerous evidence and guidelines have reported optimal therapy to control blood sugar and blood pressure, including optimal goals of such parameters. RAS blockers are the first choice of medicine for DM with proteinuria and for advanced chronic kidney disease (CKD) with hypertension to slow progression of CKD. 3. Results: line 40, page 15 Is “microgram” should be “ milligram”? Estimated GFR in this study was calculated by Cockcroft-Gault equation whilst the KDIGO guideline recently suggests to calculate eGFR using CKD-EPI. This is because Cockcroft-Gault equation overestimate eGFR in Asian populations. This issue may affect the findings. Therefore the authors should state this issue as a limitation of this study or the authors re-calculate eGFR using CKD-EPI. 4. Discussion: the first paragraph should be toned down as the fair quality of recruited RCTs and high heterogeneity of the findings. line 50, page 21, “…..the renal protective effect of CHM in younger individuals and in advanced kidney disease is less uncertain.” “less” should be deleted.

REVIEWER	Emily Johnson Providence Medical Research Center, Providence Health Care, Spokane, WA
REVIEW RETURNED	25-Sep-2018

GENERAL COMMENTS	This is a well-constructed meta-analysis evaluating the effect of CHM for DKD. Suggestions for the authors are as follows. - In general, the CHM formulations, chemical constituents, doses, and routes of administration are only briefly mentioned. These are crucial details that should be added, e.g. to Supplementary Table 2, or elsewhere. - Please add information about the duration or follow-up period for each of the studies included in the final analysis. Some of the outcome measures take a very long time (years) to develop or improve, e.g., slowing of DKD progression. A discussion of the duration of these studies and how it may impact the authors' findings is warranted. - The methods need more justification for the search terms. Some of the criteria used in the Mesh search do not meet the formal diagnostic criteria for DKD and may have caused irrelevant conditions to be included in the meta-analysis. - Table 1, please add the criteria for participants' diabetes status (type 1 or 2, duration, etc.) - Figure 1, please sort the exclusion criteria in order of the number of articles (n) - Figure 2, please write a legend to explain the symbols used - Introduction section, SGLT inhibitors should be mentioned in the discussion of potential therapeutic agents under investigation for DKD - Introduction page 6 line 18, please clarify what "some" means (which herbal medicines?) - Introduction page 6 line 50, please clarify this phrase and what study(ies) it refers to "unmasking was associated with exaggeration of intervention effects" - Page 8, eligibility criteria for articles: criterion #2 please exlain the selection of the 2nd eligibility criteria and how it corresponds to established diagnostic criteria for DKD - Page 12 line 18, what does "with exceeded albuminuria" mean? - Page 13 line 23, were conflicts of interest claimed in these articles or are the authors speculating? - Table S5, it is probably not necessary to have the column titled "Statistical Methods" since the values in each row are the same

REVIEWER	FENG WANG Shanghai Jiao Tong University Affiliated Sixth People's Hospital
REVIEW RETURNED	08-Oct-2018

GENERAL COMMENTS	This manuscript mainly focuses on DKD.From 7,255 reports retrieved, 20 eligible studies involving 2,719 DKD patients were included. CHM was associated with greater reduction of albuminuria than placebo, regardless of whether angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) were concurrently administered (SMD -0.56, 95%CI [-1.04, -0.08], P=0.002) or not (SMD -0.92, 95%CI [-1.35, -0.51], P<0.0001). When CHM was used as an adjunct to ACEi/ARB, serum creatinine was lower (MD, -4.02 μmol/L; 95%CI [-7.81, -0.23], P=0.15) and glomerular filtration rate was improved (MD, 5.8 mL/min; 95%CI [2.42, 10.14], P=0.001) in the CHM group than placebo group. The effects of CHM on progression to ESKD

	and mortality were uncertain due to low event rates. CHM appeared to be well-tolerated, with low reported rates of adverse events.With moderate to low quality evidence, CHM may have beneficial effects on renal function and albuminuria beyond that afforded by conventional treatment in adults with DKD. Further well-conducted, adequately powered trials are warranted to confirm the long-term effect of CHM. This manuscript is interesting. However, I have some concerns: 1. The introduction should be more detailed. One citation is recommended: PMID: 28404881 2. The discussion section should be improved. 3. The limitations should be stated clearly.

REVIEWER	Tian, Jinhui Lanzhou University
REVIEW RETURNED	08-Nov-2018

GENERAL COMMENTS	Please consider the following problem: 1.the search term is enough,for example,Chinese Herbal Medicine,please consider the drug name; 2.the author combined the different Chinese herbal medicine,which led to the clinical heterogeneity,how to deal with this.at the same time,how to guide the clicial practice.

REVIEWER	Irene SL Zeng iStatDome registered online datalab and Middlemore Hospital Counties of Manukau District Health Board New Zealand
REVIEW RETURNED	14-Nov-2018

GENERAL COMMENTS	Congratulation for all authors having completed such a significant work. My comments and suggestions are listed as followed: 1)In method, please explain when and why use SMD verse MD. 2)In tables, please include number or event/mortality or event/mortality rate in each study where available. 3)In all results, there are reported I square which is equivalent to 0%. Some of these are due to small number of studies (i.e. 2) , please make comments about this in the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 2.1 Abstract: it should provide adverse effects of CHM in order to balance between efficacy and safety of CHM as mentioned in the objective of this study. The findings should provide I2. 2.2 Introduction: From my knowledge, the statement in line 31-43 on page 5 may be exaggerated because numerous evidence and guidelines have reported optimal therapy to control blood sugar and blood	2.1 As suggested, the adverse effects of CHM were added in the results section in the Abstract, it states “The reported adverse events in CHM groups included digestive disorders, elevated liver enzyme levels, infection, anemia, hypertension and subarachnoid hemorrhage, but the report rates were low, unlikely related to intervention, and similar to control groups.”.

pressure, including optimal goals of such parameters. RAS blockers are the first choice of medicine for DM with proteinuria and for advanced chronic kidney disease (CKD) with hypertension to slow progression of CKD. 2.3 Results: line 40, page 15 Is "microgram" should be "milligram"? Estimated GFR in this study was calculated by Cockcroft-Gault equation whilst the KDIGO guideline recently suggests to alculate eGFR using CKD-EPI. This is because Cockcroft-Gault equation overestimate eGFR in Asian populations. This issue may affect the findings. Therefore the authors should state this issue as a limitation of this study or the authors re-calculate eGFR using CKD-EPI. 2.4 Discussion: the first paragraph should be toned down as the fair quality of recruited RCTs and high heterogeneity of the findings. line 50, page 21, "…..the renal protective effect of CHM in younger individuals and in advanced kidney disease is less uncertain." "less" should be deleted.	The I^2 of each meta-analysis has been added. 2.2 Thank you for your comment. We have revised the 2nd paragraph in the Introduction to better summarise the current knowledge of DKD treatments. 2.3 Thank you for the correction, we have updated the text. As for the impact of Cockcroft-Gault equation, we address this issue in the eGFR results section, it states "It should be noted that Cockcroft-Gault equation may overestimate eGFR, leading to 10-20% higher value in pooled estimation of eGFR than the actual eGFR and these positive results should be interpreted cautiously". We also address this issue in the limitations section of the Discussion, it states "In addition, the positive effect of CHM in eGFR outcomes is dominated by a study using Cockcroft-Gault equation [64.8% weight], leading to possible overestimation of eGFR value." 2.4 The 1st paragraph in the discussion has been revised as suggested, and the "less" in line 50, page 21 has been deleted.
Reviewer 2 3.1 In general, the CHM formulations, chemical constituents, doses, and routes of administration are only briefly mentioned. These are crucial details that should be added, e.g. to Supplementary Table 2, or elsewhere. 3.2 Please add information about the duration or follow-up period for each of the studies included in the final analysis. Some of the outcome measures take a very long time (years) to develop or improve, e.g., slowing of DKD progression. A discussion of the duration of these studies and how it may impact the authors' findings is warranted. 3.3 The methods need more justification for the search terms. Some of the criteria used in the Mesh search do not meet the formal diagnostic criteria for DKD and may have caused irrelevant conditions to be included in the meta-analysis. 3.4 Table 1, please add the criteria for participants' diabetes status (type 1 or 2, duration, etc.) 3.5 Figure 1, please sort the exclusion criteria in order of the number of articles (n)	3.1 In this systematic review, we only included oral CHM studies (mentioned as inclusion criteria in the methods section). We agree that the chemical compositions and doses of CHM are important. Thus, we provide the name of CHM preparations, the form (decoction, granule, tablet etc.), doses of CHM preparations and the herbal ingredients in Table 1 & 2. Unfortunately, the chemical compositions of CHM preparations and doses of each herbal component were not provided in the original studies, noted in the Discussion, "Although the CHM formulae were processed as granules or capsules in order to achieve blinding, quality assurance information for each CHM preparation was not provided in most of the studies. Further studies are strongly encouraged to report following the CONSORT reporting guidelines with sufficient details regarding the manufacture and quality control of investigated CHM". 3.2 As suggested, we added the duration in each meta-analysis in the Results section. In the Discussion section, we discussed the limitation of short follow-up period as follows: "… most of the studies had short follow-up periods (1-3 months) and small sample sizes, leading to

3.6 Figure 2, please write a legend to explain the symbols used 3.7 Introduction section, SGLT inhibitors should be mentioned in the discussion of potential therapeutic agents under investigation for DKD 3.8 Introduction page 6 line 18, please clarify what "some" means (which herbal medicines?) 3.9 Introduction page 6 line 50, please clarify this phrase and what study(ies) it refers to "unmasking was associated with exaggeration of intervention effects" 3.10 Page 8, eligibility criteria for articles: criterion #2 please explain the selection of the 2nd eligibility criteria and how it corresponds to established diagnostic criteria for DKD 3.11 Page 12 line 18, what does "with exceeded albuminuria" mean? 3.12 Page 13 line 23, were conflicts of interest claimed in these articles or are the authors speculating? 3.13 Table S5, it is probably not necessary to have the column titled "Statistical Methods" since the values in each row are the same	imprecision of the estimated effect and low certainty with regard to long-term benefit and effect on renal function and clinical outcomes". 3.3 We used a set of broad search terms (such as albuminuria and proteinuria) rather than DKD synonym alone to avoid missing relevant studies. Then we screened for eligible studies in a double check style based on predefined criteria in case of including non-DKD studies. All participants of included studies in this review fulfilled the clinical diagnosis of DKD. 3.4 As suggested, the type of diabetes is added in Table 1. 3.5 Figure 1 is revised as suggested. 3.6 A legend for Figure 2 is added. 3.7 Details about SGLT2 inhibitors have been added at the end of 2nd paragraph in the Introduction. 3.8 In the 3rd paragraph, line 7 in the Introduction, we clarified that:" Multi-ingredient herbal decoctions and manufactured products of Abelmoschi Corolla and Cordyceps have been recommended for patients with DKD in the practice guidelines of Chinese medicine". 3.9 To clarify, we revised the sentence as "In recent years, there have been a growing number of clinical trials and systematic reviews of CHM for DKD but not of placebo-controlled trials.". 3.10 The 2nd eligibility criteria is designed based on the DKD clinical diagnosis criteria recommended either in the international practice guidelines or those used in China. To clarify, we revised the sentence as below: "…included primary diabetes adults with persistent albuminuria/proteinuria, which was defined as an albumin excretion rate (AER) more than 20 μg/min, an albumin-to-creatinine ratio (ACR) larger than 30 mg/g or 24-hour proteinuria over 0.5 g/d (the overt DKD stage defined by Mogensen and used in DKD diagnostic criteria in China)". 3.11 It refers to albuminuria. We deleted the "exceeded" in text. 3.12 Since the pharmaceutical company employees were listed as co-authors without clarifying their roles in the trial, we judged the risk of conflicts of interest at high. To clarify, we revised the sentence as: "Two studies included pharmaceutical industry employees as co-authors without statements regarding their roles in the study, thereby these two trials were

	judged at high risk of bias in terms of potential conflicts of interest". 3.13 Thank you for the suggestion. The column titled "Statistical Methods" in Table S5 is now removed.
Reviewer 3 4.1 The introduction should be more detailed. One citation is recommended: PMID: 28404881 4.2 The discussion section should be improved. 4.3 The limitations should be stated clearly.	4.1 Thank you for your comments. We have revised the introduction to provide background knowledge of DKD treatment options and challenges, the developmental value of CHM, and the reasons of systematic reviewing the clinical evidence of CHM. 4.2 Thank you for your suggestion. We added the 2nd paragraph in Discussion to provide more details and to discuss the findings from a clinical perspective. 4.3 As suggested, we discussed the limitations of this review from two aspects. The 6th paragraph addresses the issues that may affect the internal validity, such as high heterogeneity, small number of included studies etc. The 7th paragraph discusses the external validity of findings, including different DKD populations and varied CHM ingredients.
Reviewer 4 5.1 the search term is enough, for example, Chinese Herbal Medicine, please consider the drug name; 5.2 the author combined the different Chinese herbal medicine, which led to the clinical heterogeneity, how to deal with this.at the same time, how to guide the clinical practice.	5.1 Thank you for your comments. We agree that it would be more comprehensive if we use the herbs' names and formulae names as search terms. However, since the scope of this systematic review is oral CHM regardless of ingredients, it is impossible to include all herbs/formulae names beforehand. Therefore, we learn from the search strategy in the Cochrane systematic reviews, adopting the terms and synonym represented the concept of "Chinese herbal medicine" to include relevant studies as much as possible. 5.2 Guided by the treatment principles of individualised prescription in Chinese medicine theory, the herbal ingredients of formulae are often diverse in clinical practice. Thus, the aim of this systematic review is to evaluate the overall efficacy and safety of CHM for DKD, regardless the differences of herbal compositions. We incorporate the heterogeneity by using the random effects model in meta-analysis. In addition, subgroup analysis based on formulae was pre-designed and conducted. Unfortunately, due to the small number of included studies used the same CHM interventions, the evidence of efficacy and safety of each herbal formula is inconclusive.

Reviewer 5 6.1 In method, please explain when and why use SMD verse MD. 6.2 In tables, please include number or event/mortality or event/mortality rate in each study where available. 6.3 In all results, there are reported I square which is equivalent to 0%. Some of these are due to small number of studies (i.e. 2), please make comments about this in the discussion.	6.1 Thank you for your suggestion. We explain this in the Data synthesis and analysis sections as "SMD was used in the meta-analysis of albuminuria and proteinuria outcomes due to the different scales used in the included studies such as microgram per minute (μg/min), milligram to gram (mg/g) and milligram per day (mg/24 hours).". 6.2 Only one study (Li et.al 2012) reported mortality and composite renal outcome events, which is listed in Table 1 and Table 3. 6.3 Thank you for your suggestion. We consider it as one of the limitations and we added the following statements in the 6th paragraph, line 5 in Discussion: "Even meta-analyses with low heterogeneity may not be reliable because there were only a very small number of included studies in the subgroup analyses (less than or equal to three studies in each subgroup).".

VERSION 2 – REVIEW

REVIEWER	Emily Cox Providence Health & Services, Spokane, WA, USA
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	The revised manuscript addresses my concerns. I recommend acceptance.

REVIEWER	Irene SL Zeng iSTATDOM online datalab and Counties Manukau Health
REVIEW RETURNED	21-Feb-2019

GENERAL COMMENTS	Thank you, the authors have addressed my comments in the method.