Systematic Review and Meta-Analysis

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Adjuvant treatment with Yupingfeng formula for primary nephrotic syndrome in children

A PRISMA systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Yupingfeng formula (YPFF) has been prescribed as adjuvant treatment for pediatric patients with primary nephrotic syndrome (PNS) in China for years. However, the efficacy and adverse effects of these formulations are controversial. A systematic review and meta-analysis of randomized controlled trials (RCTs) were performed to evaluate the benefits and harms of YPFF in treating PNS in children.

Methods: The MEDLINE, EMBASE, Cochrane Library, CNKI, VIP, WanFang, and CBM databases were searched for RCTs comparing therapies with and without YPFF for PNS from inception to May 13, 2017. Relative risk (RR) and 95% confidence intervals (CI) were expressed for dichotomous outcomes, and weighted mean difference (WMD) with 95% CI for continuous outcomes. Cochrane collaboration tool was used to evaluate the risk of bias of methodologies.

Results: Eight studies with 538 participants were identified. Treatment with YPFF significantly increased serum levels of IgA (WMD, 0.48, 95% CI, 0.40–0.56, $P < .001$), IgG (WMD, 3.36, 95% CI, 2.61–4.12, $P < .001$), $CD4^+$ T-lymphocytes (WMD, 3.35, 95% CI, 2.26–4.43, $P < .001$), but decreased the level of $CD8^+$ T-lymphocytes (WMD, –3.38, 95% CI –5.48 to –1.28, $P = .002$). YPFF also increased the rates of complete remission (RR: 1.35, 95% CI, 1.09–1.67, $P = .005$), and decreased the rates of relapse (RR: 0.57, 95% CI, 0.45–0.71, $P < .001$), and infection (RR: 0.72, 95% CI 0.62–0.83, $P < .001$). There was no significant difference in the level of IgM between the groups (WMD, 0.12, 95% CI –0.11–0.35, $P = .322$).

Conclusions: YPFF could improve total remission rate and decrease the frequency of relapse and infection rate. The beneficial influence of YPFF may be associated with its immunomodulatory effects. More high-quality studies with larger sample sizes are needed to further identify its efficacy and safety.

Abbreviations: 95% CI = 95% confidence intervals, CKD = chronic kidney diseases, ESRD = end-stage renal diseases, LMWH = low molecular weight heparin, MeSH = medical subject headings, PNS = primary nephrotic syndrome, RCTs = randomized controlled trials, RR = relative risk, TCM = traditional Chinese medicine, WMD = weighted mean difference, YPFF = Yupingfeng formula.

Keywords: children, meta-analysis, primary nephrotic syndrome, Yupingfeng formula

1. Introduction

Primary nephrotic syndrome (PNS) is a common disease in children, and accounts for about 90% of childhood nephrotic syndrome.[1] The pathological mechanism is still unclear, which is supposed to be associated with immune disorders.[1–4] Pediatric patients mostly need steroids to achieve remission. However, 76% to 93% of them relapse after steroid therapy, 45% to 50% of which are frequent relapse or steroid-dependent.[5,6] In addition, infections are always the "hot potato" because of the application of steroids and the trigger of relapses. It is important to prevent or reduce the infection in children with PNS.

Yupingfeng formula (YPFF) is a traditional Chinese medicine (TCM), the history of which can be traced back to Yuan Dynasty. YPFF consists of *Radix astragali*, *Atractylodes macrocephala*, and *Radix saposhnikoviae* in a proportion of 3:1:1 by weight of dried plants and has been widely used to treat immunocompromised patients.[7,8] Besides, YPFF has been used for infection prevention like recurrent respiratory tract infections.[9,10] Accumulating evidence has proven the immunomodulatory and anti-inflammatory activity of YPFF. YPFF attenuates the inflammatory responses through inhibiting the NLRP3 inflammasome[11] and influencing the levels of inflammatory cytokines.[12] Besides, YPFF exerts immune regulation by impacting the balance of Th17 cells and Treg cells[12] and upregulating the proportion of $CD4^+/CD8^+$ and NK cells' activity.[13] Therefore, YPFF has been used to treat PNS for years in China.[14] However,

Editor: Antonio Palazón-Bru.

This study was supported by the Application of Yupingfeng in Childhood Renal Diseases.

The authors declare no conflicts of interest.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:29(e11598)

Received: 6 November 2017 / Accepted: 26 June 2018

http://dx.doi.org/10.1097/MD.0000000000011598

no previous meta-analysis was carried out to evaluate the effects of YPFF on PNS in children. Therefore, we performed this systematic review and meta-analysis to assess the clinical efficacy and immunomodulatory effects of YPFF in children with PNS using the available randomized controlled trials (RCTs).

2. Methods

This meta-analysis was conducted according to the recommendations of the PRISMA[15] guidelines.

2.1. Protocol and registration

A protocol has been registered for this systematic review and meta-analysis in PROSPERO (CRD42017071260).

2.2. Search strategy

XS and XZ comprehensively searched the MEDLINE, EMBASE, Cochrane Library, CNKI, VIP, WanFang, and CBM databases independently from inception to May 13, 2017. We conducted searches by using medical subject headings (MeSH) terms for MEDLINE, EMTREE terms for EMBASE, and text words without language restrictions. The detailed search strategy is shown in S1 Protocol. In addition, we checked the references of published studies to further identify relevant studies.

2.3. Study selection

The titles and abstracts of all records were screened independently by 2 investigators (XS and XZ) for relevance and the full text of relevant studies was identified for eligibility by the same 2 investigators. Any discrepancy was resolved by discussion with a third reviewer (JD).

Studies were included if they met the following criteria: study design: RCTs; study population: children with diagnosis of PNS; intervention: YPFF plus other drugs versus other drugs (such as prednisone and low molecular weight heparin); outcome measures: the primary outcomes were complete remission, partial remission, urinary protein excretion, plasma albumin, relapse, the serum immunoglobulin levels (IgA, IgG or IgM) or T-lymphocytes subtype ($CD4^+$, $CD8^+$), and complications of PNS. The second outcomes were mortality, total cholesterol, triglycerides, edema remission, the duration of remission, adverse effects, the number, and proportion of patients developing hypertension, chronic kidney diseases (CKD) or end-stage renal diseases (ESRD); and the follow-up duration was no less than 3 months. We excluded studies with insufficient data or irrelevant topics. No experiment on humans or animals was performed, so that the ethical approval was not necessary.

2.4. Data extraction and quality assessment

Detailed information was extracted from all included studies and entered into a standardized extraction form by 2 reviewers (XS and XZ) independently. The extracted data contained: the first author, year of publication, country, sample size, age of children, gender, YPFF interventions and controls, diagnosis, follow-up duration, and outcome measures. We collected incomplete data by contacting with the first or the corresponding author by e-mail. Disagreements were settled by an independent adjudicator (JD).

We assessed the risk of bias according to the Cochrane Risk of Bias tool without masking the trial name.[16,17] Two reviewers (XS and XZ) respectively labeled each trial with "low," "unclear," or "high" risk of bias on following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. If at least 1 key domain was judged to be at high risk for a trial, it would be considered as at high risk of bias overall. If all key domains were judged to be low risk for a trial, it would be considered as at low risk of bias, otherwise it would be considered as at unclear risk of bias.[18]

2.5. Statistical methods

Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and weighted mean differences (WMDs) with 95% CIs for continuous outcomes.

Statistical heterogeneity was evaluated using the I^2 statistic and the Cochrane Q statistic. Data were analyzed with a fixed-effect model if $I^2 < 50\%$ or $P > .10$, otherwise random-effects model was used if $I^2 < 50\%$ or $P > .10$. Pre-defined subgroup analysis was performed when the heterogeneity was high, and sensitivity analysis was conducted to explore potential sources of heterogeneity by omitting each trial in turn. All statistical analyses were performed using Review Manager 5.0 and STATA software, version 12.0 (StataCorp, College Station, TX). If studies were less than 3, then we provided a qualitative description.

3. Results

3.1. Search flow and description of included studies

A total of 1387 studies were yielded in the initial literature search. Eight studies eligible for inclusion criteria were included (Fig. 1). In total, 538 children with PNS were identified in this meta-analysis. All of the studies were conducted in China and published in Chinese. Treatment duration varied from 12 weeks to 1 year. Serum immunoglobulin levels were measured before and after treatment. Patients in the control group were treated with conventional Western medical treatment, while those in experimental group received YPFF in addition to Western medicine. YPFF involved in these studies were all by herbal particle.

3.2. Characteristics of the trials included

The number of patients included in the studies varied from 50 to 86, with a total of 538 patients in the 8 studies. The proportion of males was 67.3%. The age of the patients ranged from 2 to 14.4 years, with a mean age of 5.65 years. Seven studies mentioned the follow-up duration of the disease: from 12 weeks to 2 years.

Among the 8 studies, the inclusion and exclusion criteria were defined in 3 studies, and 7 studies reported the termination and completion. Seven studies reported interventions with YPFF plus prednisone therapy versus prednisone alone. Only 1 study used YPFF plus low molecular weight heparin (LMWH) versus LMWH. The doses of YPFF used ranged from 5 to 10 g 3 times a day according to age. Detailed description of included studies was shown in Table 1. A variety of outcome measures were reported. The evaluation of the outcomes was performed at the end of the treatment.

3.3. Methodological quality

The risk of bias assessment was shown in Figure 2. All studies mentioned randomization, but only 6 studies had a detailed

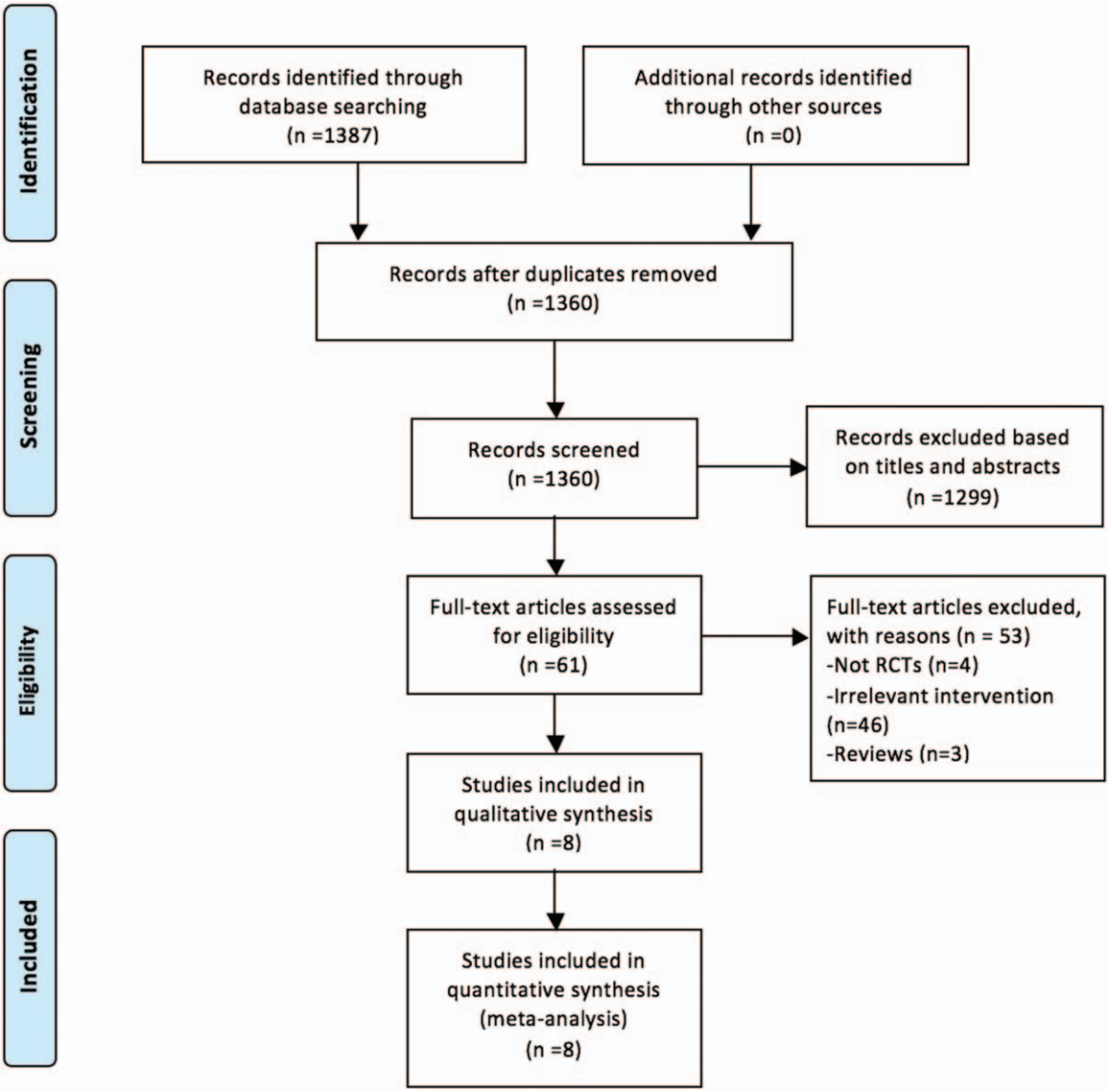

Figure 1. PRISMA flow diagram of study selection.

description of random sequence generation. None of the studies described allocation concealment or blinding of patients. Seven studies mentioned follow-up; and one of these described the drop-out or withdrawal information. Seven of the studies included reported that characteristics of subjects in different groups have similar baseline (age, sex, race, and disease course).

3.4. Remission

Three studies[19–21] evaluated the rate of complete remission. As shown in Figure 3, compared with the conventional therapy, treatment with YPFF significantly improved the complete remission rate (RR: 1.35; 95% CI: 1.09–1.67; $P = .005$; I^2: 0.0%).

3.5. Relapse

Five studies[4,7,21–23] reported the data of relapse. Treatment with YPFF decreased the rate of relapse (RR: 0.57; 95% CI: 0.45–0.71; $P < .001$; I^2: 0.0%) compared with conventional treatment (Fig. 4).

3.6. Infection

Five studies[4,7,19,22,23] assessed the rate of infection. Treatment with YPFF decreased the risk of infection (RR:0.72; 95% CI:0.62 to 0.83; $P < 0.001$; I^2:0.0%) compared with conventional treatment (Fig. 5).

3.7. Changes of immunoglobulin levels

Seven studies[4,7,19,21–24] evaluated the changes of serum IgG and IgA level and 4 studies[7,19,21,24] of IgM level. A total of 267 patients were involved in the YPFF treatment groups, and 271 in the control group. As shown in Figures 6 A and B, treatment with YPFF significantly increased serum IgG level (WMD: 3.36; 95% CI: 2.61–4.12; $P < .001$; $I^2 = 75.4\%$) and IgA level (WMD: 0.48; 95% CI: 0.40–0.56; $P < .001$; $I^2 = 78.8\%$) compared to control

Table 1

Characteristics of the individual trials included in this study.

Author [References]	Published year	Study period	Cases E/C	Age, yrs, range, mean	Sex Male/female
Xiang M[16]	2008	2004–2008	31/31	E:5.87 C:5.63	E:19/12 C:17/14
Chen L[19]	2006	2003–2006	38/40	2.7–12.3,5.2	62/16
Lin N[4]	2010	2002–2009	45/41	3.5–12	58/28
Wei R[7]	2013	2010–2011	32/32	2–14,4.33	45/19
Xu JF[17]	2014	2010–2013	38/44	E:5.6 C:6.1	E:30/14 C:29/9
Zhu XL[20]	2014	2010–2012	25/25	1.4–13.2,6.3	28/22
Yan XH[21]	2015	2010–2015	28/28	2–14,4.32	32/24
Li XY[18]	2016	2013–2014	30/30	E:6.2 C:7.97	E:20/10 C:22/8

Author [References]	YPF group	Control group	Treatment duration	Follow-up duration	Outcome interesting
Xiang M[16]	YPF particle + Prednisone	Prednisone	1 year	1 year	1+2+3+4+9+10+11+12+14+15
Chen L[19]	YPF particle + Prednisone	Prednisone	1 year	1 year	6+7+8+9+10+13+14
Lin N[4]	YPF particle + Prednisone	Prednisone	1 year	1 year	3+4+5+6+7+8+9+10+13+14
Wei R[7]	YPF particle + Prednisone	Prednisone	12 weeks	6 months	9+10+11+12+13+14
Xu JF[17]	YPF + LMWH+ACH	LMWH + ACH	12 weeks	12 weeks	1+12
Zhu XL[20]	YPF particle + Prednisone	Prednisone	NP	NP	9+10+13+14
Yan XH[21]	YPF particle + Prednisone	Prednisone	9 months	9 months	6+7+8+9+10+11
Li XY[18]	YPF particle + Prednisone	Prednisone	16 weeks	4 months	1+5+6+7+8+9+10+11+12+13

ACH = adrenocortical hormone, C = control group, E = experimental group, LMWH = Low Molecular Weight Heparin, NP = Not provided, YPF = Yupingfeng.
1.complete remission; 2.partial remission; 3.urinary protein excretion; 4.plasma albumin; 5.$CD3^+$; 6.$CD4^+$; 7.$CD8^+$; 8.$CD4^+/CD8^+$; 9.IgG; 10.IgA; 11.IgM; 12.no remission; 13.relapse; 14.Infection; 15. cholesterol.

group. A random effect model was used for the heterogeneity is significant. However, there were no significant differences in IgM levels (WMD: 0.12; 95% CI: –0.11 to 0.35; $P = .322$; $I^2 = 69.5\%$) between with and without YPFF treatment group (Fig. 6C).

3.8. Changes of T-lymphocytes subtype

Four studies[4,21,22,24] reported the changes of T-lymphocytes $CD4^+$ counts and $CD8^+$ counts. As shown in Figures 7 A and B, treatment with YPFF increased $CD4^+$ counts (WMD: 3.35; 95% CI: 2.26–4.43; $P < .001$; $I^2 = 0.0\%$) in a fixed effect model but decreased $CD8^+$ counts (WMD: –3.38; 95% CI: –5.48 to –1.28; $P = .002$; $I^2 = 86.7\%$) in a random effect model.

3.9. Changes of urinary protein excretion and plasma albumin

There were 2 studies[4,19] analyzed the data of urinary protein excretion and plasma albumin. Both of the studies showed significant difference between YPFF group and control study.

3.10. Changes of cholesterol

One study[19] reported the changes of cholesterol. There was significant difference between with and without YPFF treatment group.

3.11. Adverse events

Three studies[4,7,22] reported the safety as outcome measures, and no adverse events was mentioned.

3.12. Subgroup analysis and sensitivity analysis on the changes of T-lymphocytes subtype and immunoglobulin level

As summarized in Table 2, subgroup analysis was conducted based on the forms of YPFF (particles vs powder), treatment duration of YPFF (≥6 months vs. < 6 months) and follow-up period (≥6 months vs < 6 months). However, the source of heterogeneity was not identified. Sensitivity analysis showed that pooled result changed little after changing to fixed-effects or random-effects models, or after removing anyone study. The details of subgroup analysis and sensitivity analysis were shown in S1–S4 Fig and S5–S6 Fig of the supplementary materials, http://links.lww.com/MD/C351, respectively.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to evaluate the efficacy of YPFF in treating PNS in children. In this systematic review, 8 studies involving 538 participants were included: 267 versus 271 between experimental and control group. Treatment with YPFF significantly increased serum levels of IgA, IgG, $CD4^+$ T-lymphocytes, but decreased the level of $CD8^+$ T-lymphocytes. YPFF also increased the rates of complete remission and decreased the rates of relapse, no remission, and infection. There was so significant difference in the level of IgM between the groups. Two studies referred urinary protein excretion and plasma albumin, and both reported significant difference between YPFF group and control study. One study mentioned cholesterol and reported no significant difference between experimental and control group. We performed a subgroup and sensitivity analysis but didn't find the source of heterogeneity. However, the result remains stable after excluding any one study.

The pathogenesis of PNS has not been fully clarified, which is supposed to be associated with immunologic dysfunction.[4,25] Children with PNS are susceptible to infection, which in return hinder the pharmacological actions of steroids[26] and lead to relapse. Consequently, immunoregulation and infection prevention is of vital importance in treating children with PNS.

YPFF consist of *Radix astragali, Atractylodes macrocephala,* and *Radix saposhnikoviae* is suitable for Lung and Spleen Qi deficiency. Zhou et al[27] reported that YPFF can enhance the body immunity. Xu et al[28] verified that YPFF could improve the

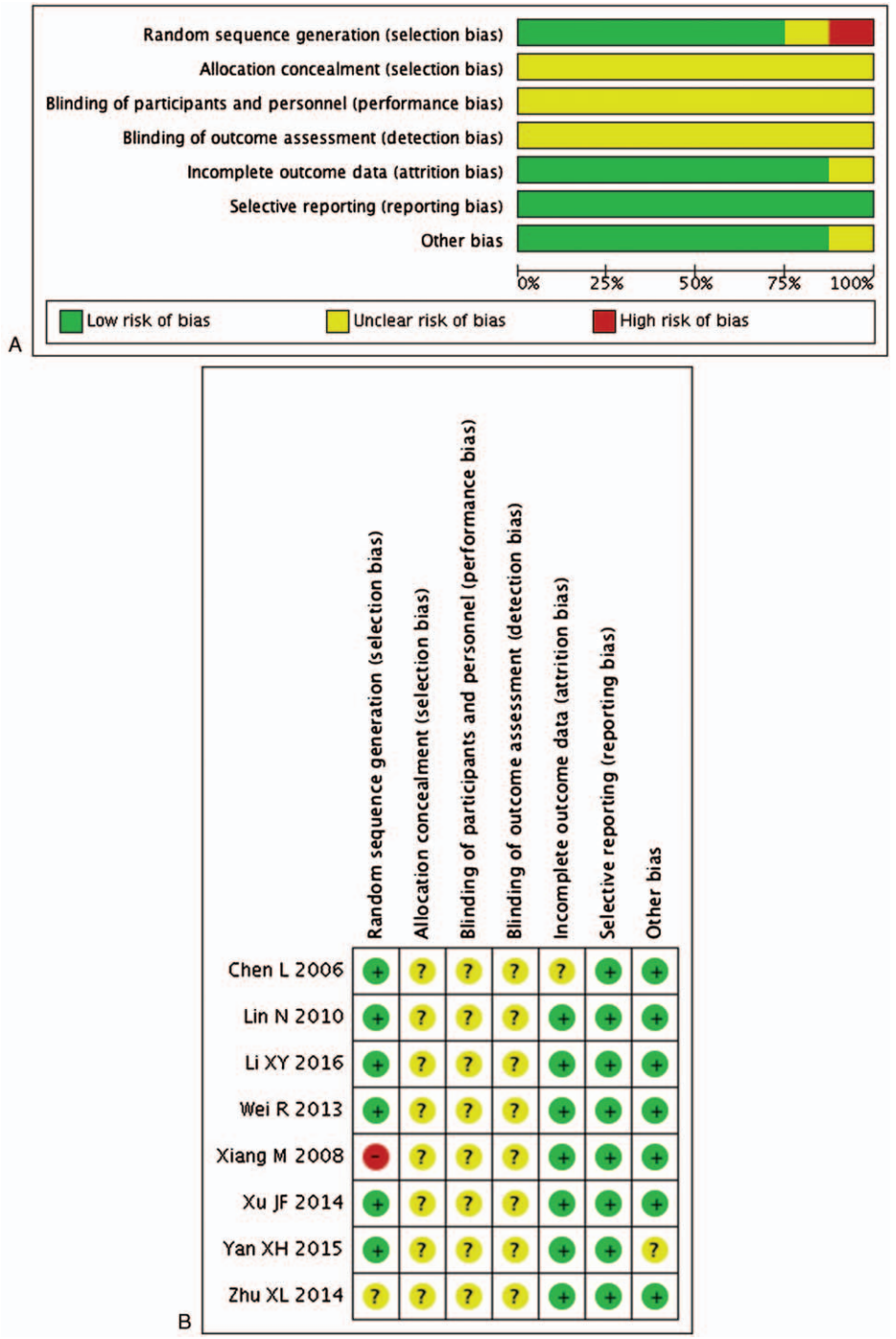

Figure 2. The risk of bias assessment with the Cochrane tool. A, Risk of bias graph. B, Risk of bias summary.

serum level of IgA, IgG, and the intestinal level of sIgA. YPFF acts on the intestinal mucosa and then further influences systemic immune function.[29] T cells of children with recurrent respiratory tract infection increased markedly after treating with YPFF.[30]

Despite benefits of YPFF above, the potential adverse effects of YPFF should be payed attention to. In this systematic review and meta-analysis, none of the included studies reported any adverse events so that YPFF seemed to be safe and well tolerable for children with PNS. However, the adverse effects of YPFF need attention as only three studies[4,7,22] reported safety as outcome. Besides, combined pharmacological activities of medicinal plants may exert adverse effect.[31] Consequently, the safety of YPFF needs to be further investigated.

The methodological quality of included trials was shown in Fig. 2. The baseline characteristics were similar to ensure the reliability of the research. However, there were several flaws in the quality of the included studies. Although most studies provided random sequence generation, none of the trials mentioned allocation concealment so the selection bias could not be excluded. Besides, a few studies mentioned blinding, which may lead to performance and detection bias.

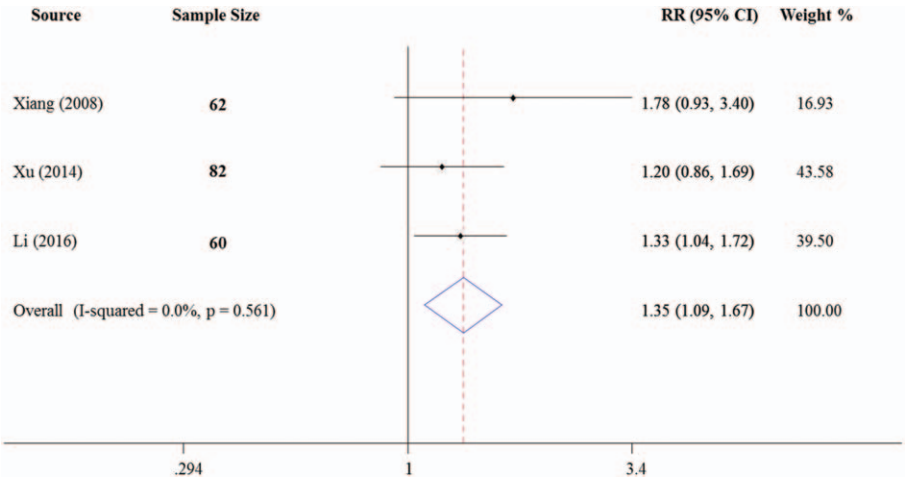

Figure 3. Effect of Yupingfeng on rate of complete remission compared with control group.

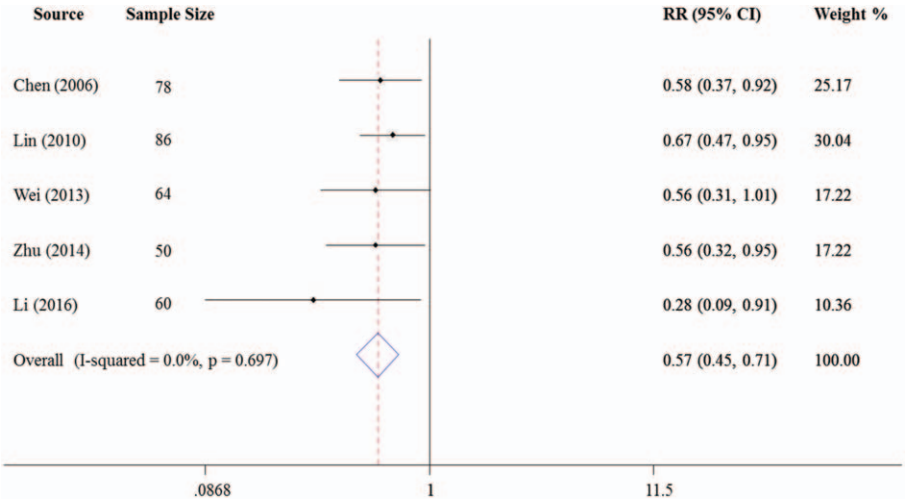

Figure 4. Effect of Yupingfeng on rate of relapse compared with control group.

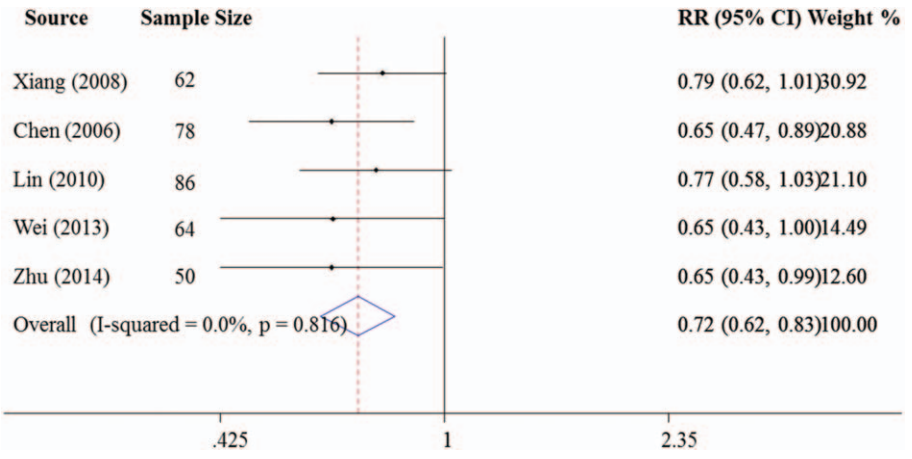

Figure 5. Effect of Yupingfeng on rate of infection compared with control group.

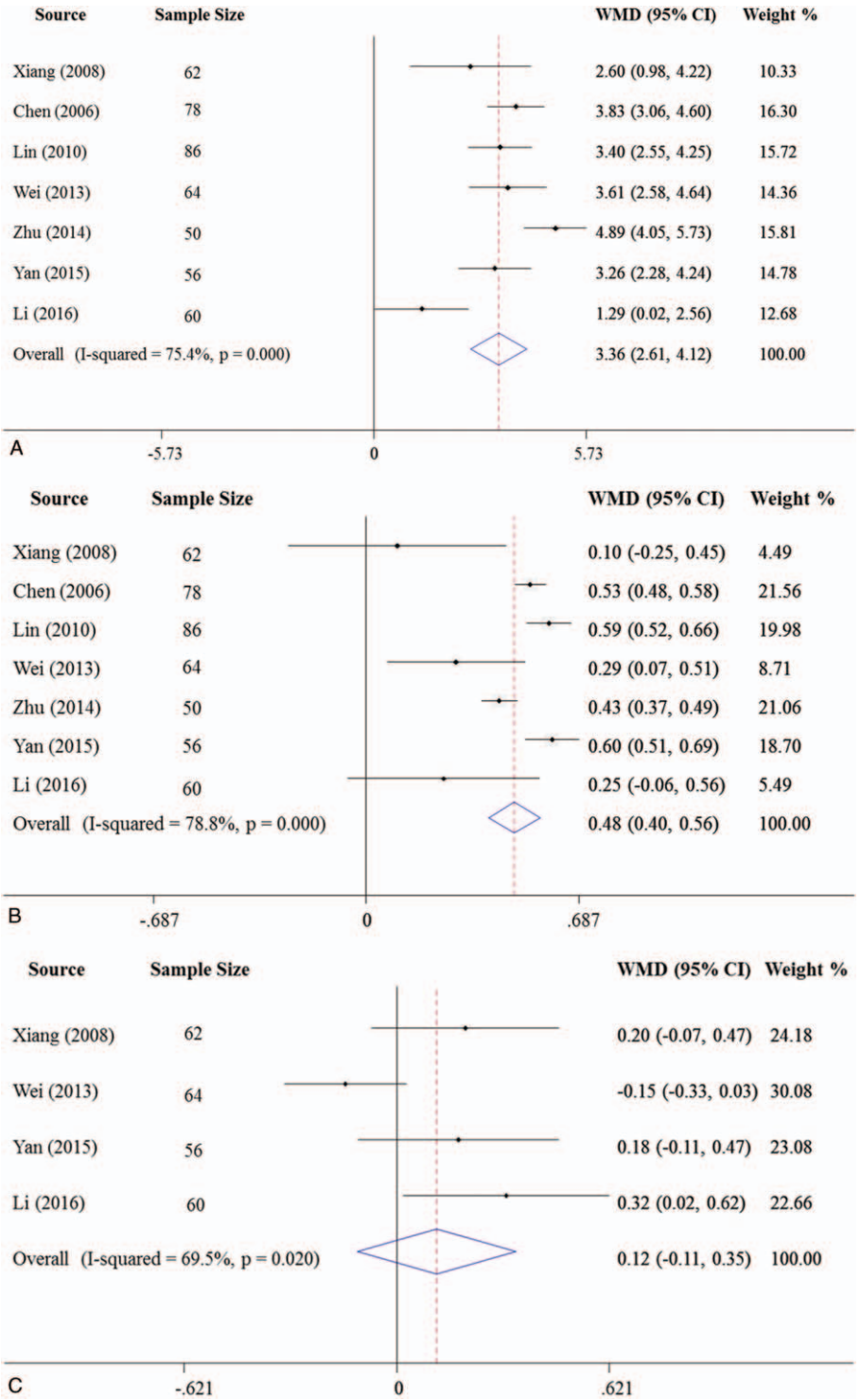

Figure 6. Effect of Yupingfeng on serum level of immunoglobulin compared with control group. A, IgG; B, IgA; C, IgM.

There were several potential limitations in our meta-analysis. First, some linguistic biases may exist due to language limitations, though a systematically search strategies was used to minimize publication bias. Second, the sample size of included studies was relatively small. Further large-scale studies were still needed. Finally, most RCTs involved in the meta-analysis had limitations such as the lack of detailed methodology and suboptimal quality of the study design. Consequently, well-designed, large-scale RCTs were needed to further explore the effects of YPFF for PNS.

5. Conclusions

YPFF could improve total remission rate and decrease the frequency of relapse, no remission and infection rate. The beneficial influence of YPFF may be associated with its

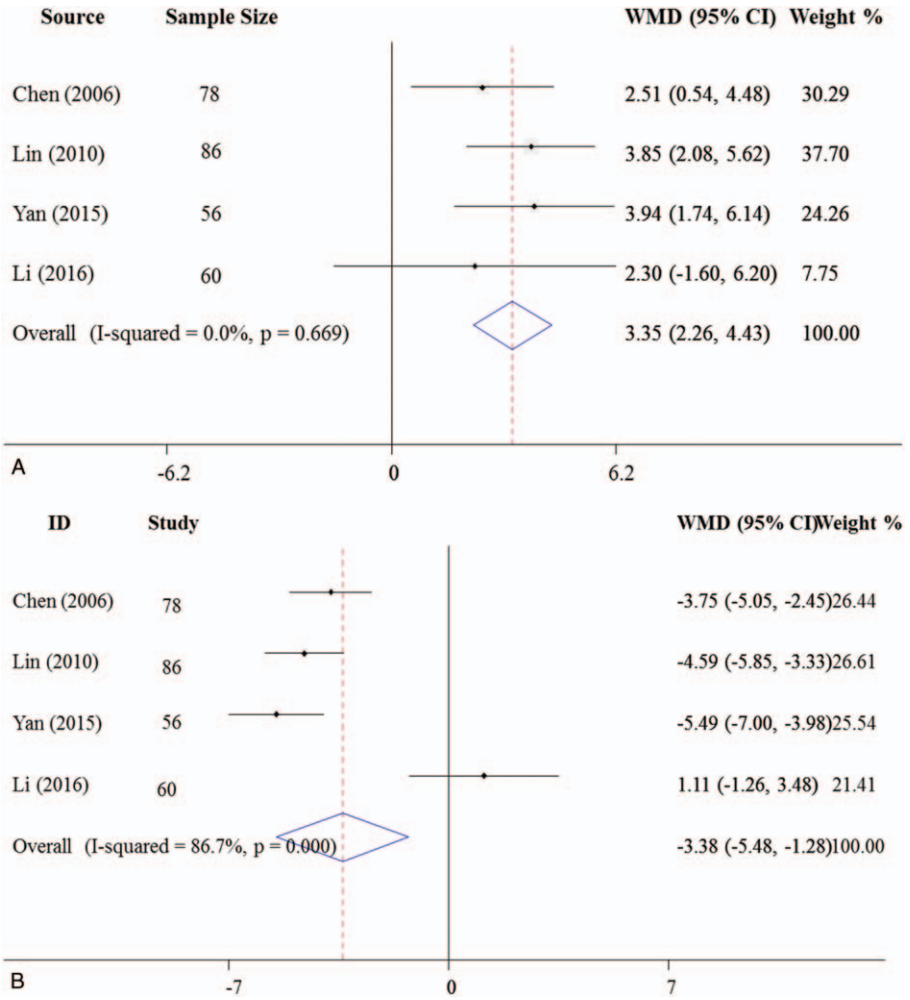

Figure 7. Changes of T-lymphocytes CD4+ counts and CD8+ counts. A, CD4+; B, CD8+.

Table 2

Subgroup analyses on the changes of immunoglobulin level.

Subgroups	Number of trials	Pooled WMD	95% confidence interval	Heterogeneity between trials
1.IgA				
Treatment duration				
≥6 months	4	0.55	0.47 to 0.63	$P<0.001$; $I^2=67.6\%$
<6 months	2	0.28	0.10 to 0.46	$P=0.003$; $I^2=0.0\%$
Follow-up period				
≥6 months	5	0.52	0.43 to 0.60	$P<0.001$; $I^2=72.5\%$
<6 months	1	0.25	-0.06 to 0.56	-
Forms of Yupingfeng				
particles	5	0.44	0.30 to 0.58	$P<0.001$; $I^2=77.2\%$
powder	2	0.48	0.38 to 0.58	$P<0.001$; $I^2=84.3\%$
2.IgG				
Treatment duration				
≥6 months	4	3.46	2.99 to 3.93	$P<0.001$; $I^2=0.0\%$
<6 months	2	2.48	0.21 to 4.75	$P=0.032$; $I^2=87.1\%$
Follow-up period				
≥6 months	5	3.49	3.06 to 3.92	$P<0.001$; $I^2=0.0\%$
<6 months	1	1.29	0.02 to 2.56	-
Forms of Yupingfeng				
particles	5	2.92	2.16 to 3.69	$P<0.001$; $I^2=58.7\%$
powder	2	3.36	2.61 to 4.12	$P<0.001$; $I^2=70.0\%$

immunomodulatory effects. More high-quality studies with larger sample sizes are needed to further identify its efficacy and safety.

Acknowledgments

The authors would like to thank all the participants in the study. This study was funded by Application of Yupingfeng in Childhood Renal Diseases.

Author contributions

Conceptualization: Jie Ding.
Data curation: Xinmiao Shi, Jie Ding.
Formal analysis: Xinmiao Shi.
Funding acquisition: Jie Ding.
Investigation: Xuhui Zhong.
Methodology: Xinmiao Shi, Xuhui Zhong.
Project administration: Xuhui Zhong, Jie Ding.
Resources: Xinmiao Shi, Xuhui Zhong.
Software: Xinmiao Shi.
Supervision: Xuhui Zhong, Jie Ding.
Visualization: Xuhui Zhong.
Writing – original draft: Xinmiao Shi.
Writing – review & editing: Xinmiao Shi.

References

[1] Filler G, Young E, Geier P, et al. Is there really an increase in non-minimal change nephrotic syndrome in children? Am J Kidney Dis 2003;42:1107–13.
[2] Liu YG, Lin N, Qin ZJ. Effect of glucocorticoid on cytokines of children with primary nephrotic syndrome. J App Clin Pediatr 2006;21:1133–4.
[3] Del Rio M, Kaskel F. Evaluation and management of steroid -unresponsive nephrotic syndrome. Curr Opin Pediatr 2008;20:151–6.
[4] Lin N, Liu YG, Guo YX, et al. Yupingfeng powder on immune function in children with primary nephrotic syndrome. Lishizhen Med Mate Medi Res 2012;21:2006–8.
[5] Koskimies O, Vilska J, Rapola J, et al. Long-term outcome of primary nephrotic syndrome. Arch Dis Child 1982;57:544–8.
[6] Tarshish P, Tobin JN, Bernstein J, et al. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the international study of kidney disease in children. J Am Soc Nephrol 1997;8:769–76.
[7] Wei R, Ruan YY, Qiu YF, et al. The effect of Yupingfeng particle on humoral immunity of children with primary nephrotic syndrome. Mod J Integ Trad Chin Western Med 2013;22:1211–2.
[8] Chen TY, Zhang HG, Huang KD. Observation on the clinical effect for *Astragalus* injection and low molecular weight heparin in the treatment of children with idiopathic nephrotic syndrome. Mod Preven Med 2012;39:4670–3.
[9] Yang SM, Deng GP. Progress in the clinical application of Yupingfeng powder. Northwest Pharmaceutical J 2008;23:192–3.
[10] Wang L, Bian HM. Research on immunological effect of Yupingfeng powder. of Gan Coll Trad Chin Med 2008;25:48–51.
[11] Liu X, Shen J, Fan D, et al. Yupingfeng san inhibits NLRP3 inflammasome to attenuate the inflammatory response in asthma mice. Front Pharmacol 2017;8:944.
[12] Wang Z, Cai X, Pang Z, et al. Yupingfeng pulvis regulates the balance of T cell subsets in asthma mice. Evid Based Complement Alternat Med 2016;2016:6916353.
[13] Li Y, Zheng B, Tian H, et al. Yupingfeng Powder relieves the immune suppression induced by dexamethasone in mice. J Ethnopharmacol 2017;200:117–23.
[14] Cui YQ, Song TD. Yupingfeng powder treatment of infantile repeated respiratory infection. J Prac Trad Chin Int Med 2013;27:168–70.
[15] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Medicine 2009;6:e1000100.
[16] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0. Oxford, the Cochrane Collaboration, 2011. Available at: http://www.cochrane.org/handbook. Accessed on 14 January).
[17] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Int Med 2009;151:264–9. W64.
[18] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[19] Xiang M. Yupingfeng particle on analysis of course intervention in children with primary nephrotic syndrome. Journal of Clinical and Experimental Medicine 2008;7:75–6.
[20] Xu JF, Xiao YF, Liu J. The effect of Yupingfeng combined with low molecular weight heparin on tissue-type plasminogen activator and plasminogen activator inhibitor of children with primary nephrotic syndrome. Chin J Basic Med 2014;20:943–4.
[21] Li XY, Wang H. The effect of Yupingfeng granules on immunologic function of childhood primary nephrotic syndrome. Henan Med Res 2016;25:1927–9.
[22] Chen L, Xu JW. Yupingfeng powder in treatment of immune function in children with simple nephrotic syndrome. J AppClin pediatricsV 21 2006;1662–3.
[23] Zhu XL. Clinical observation on Yupingfeng powder in treatment of immune function in children with simple nephrotic syndrome. Liaoning J Tr Chinese Med 2014;41:749–50.
[24] Yan XH, Yan XP. Immunomodulatory effect of Yupingfeng powder on children with primary nephrotic syndrome. Shaanxi J Traditional Chin Med 2015;36:1311–2.
[25] He WB, Liu GL. Approach of immunity pathogenic mechanism in primary nephrotic syndrome. Chin GeneralV 13 2010;3461–3.
[26] Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behavior Immunity 2007;21:9–19.
[27] Zhou W, Yuan JL, Tong XL, et al. Immunological regulation and mechanism research overview of Yupingfeng powder. J Gansu College 2015;32:67–9.
[28] Xu PP, Ding W, Zhao F, et al. Research the relations between the efficacy of Chinese medicine in the prevention influenza and mucosal immune. Chin J Immunol 2012;28:992–8.
[29] Zhang L, Li DX, Wu X. Research on Yupingfengsan total polysaccharide on entero-respiratory tract secretion of sIgA in small intestinal mucosa injury mice. Pharmacol Clini Chin Materia Medica 2007;23:43–5.
[30] Huang JB, Wu Y. Clinical results of Yupingfeng particles on children with asthma and recurrent respiratory tract infections. Med Recapi 2015;21:3451–3.
[31] Khan AU, Gilani AH. Natural products useful in respiratory disorders: focus on side-effect neutralizing combinations. Phytother Res 2015;29: 1265–85.