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Add-on tonifying-kidney herbal therapy to conventional Western treatment for adult chronic primary immune thrombocytopenia: a systematic review and meta-analysis protocol

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026100099

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 October 2026 and was last updated on 23 October 2026.

INTRODUCTION

Review question / Objective P: adults with chronic primary ITP. I: Chinese herbal formulae in which tonifying the kidney (bushen) is the principal or a co-principal treatment principle, added to conventional Western treatment. C: identical Western treatment alone. O: primary, overall response (complete response plus response); secondary, complete response, platelet count, bleeding, adverse events, relapse and sustained response. S: randomised controlled trials, including quasi-randomised trials that are removed in sensitivity analysis. Objective: to estimate the benefit and harm of add-on bushen therapy in this population.

Rationale ITP is an acquired autoimmune bleeding disorder. Glucocorticoids produce initial responses in 60-80% of adults, but relapse after tapering is common and prolonged use causes hyperglycaemia, hypertension, osteoporosis and cushingoid features. Tonifying-kidney formulae are widely used as adjuncts in China, yet previous systematic reviews pooled all Chinese medicine together, did not distinguish whether bushen was the principal principle, did not restrict trials to add-on designs, and mixed adults with children and chronic with newly diagnosed disease. A review focused on add-on bushen therapy in adult chronic ITP is therefore needed.

Condition being studied Primary immune thrombocytopenia (ITP) is an acquired autoimmune

disorder characterised by isolated thrombocytopenia (platelet count below $100 \times 10^9/L$) without another identifiable cause. Autoantibodies against platelet glycoproteins increase platelet clearance and impair platelet production. Adults frequently follow a chronic course lasting more than 12 months, with bleeding of variable severity, fatigue and reduced quality of life. Diagnosis is one of exclusion. Treatment aims to raise the platelet count, prevent bleeding and limit treatment toxicity; glucocorticoids are first-line, intravenous immunoglobulin is used for severe bleeding, and second-line options include thrombopoietin receptor agonists, rituximab and splenectomy.

METHODS

Search strategy Eight electronic databases will be searched from inception to 21 October 2026 without language restriction: PubMed, Embase, Cochrane CENTRAL, Web of Science, CNKI, Wanfang Data, VIP and SinoMed. Two registries (ChiCTR and ClinicalTrials.gov) will be searched for ongoing studies, and the reference lists of previous systematic reviews will be hand-searched. The search combines three concept blocks: (1) immune thrombocytopenia (immune thrombocytopenia, idiopathic thrombocytopenic purpura, ITP, thrombocytopenic purpura); (2) tonifying the kidney (bushen, tonifying kidney, warming kidney, nourishing kidney, kidney deficiency, Yougui Wan, Zuogui Wan, Jinkui Shenqi Wan, Zhibai Dihuang Wan, Erzhi Wan); and (3) Chinese herbal medicine (Chinese medicine, Chinese herbal medicine, integrative medicine, decoction). The full strategy for each database is provided in the supplementary material.

Participant or population Adults (18 years or older) with chronic primary immune thrombocytopenia, defined as a disease duration longer than 12 months or explicitly described as chronic by the authors, diagnosed according to the version of the Chinese guideline or consensus cited in each trial (2011 consensus, 2012 consensus, 2020 guideline). Because preliminary screening identified only three eligible adult chronic trials, the population was expanded to all patients with ITP, and trials were stratified as A (adults with chronic ITP), B (populations including minors, lower age limit below 18 years) and C (adults with non-chronic disease or stage not reported). Stratum A remains the primary population; children, mixed populations and newly diagnosed or persistent ITP are not included in stratum A.

Intervention Chinese herbal formulae in which tonifying the kidney (bushen) is the principal treatment principle (class I) or one of the principal principles (class II), given orally in addition to conventional Western treatment. Decoctions, granules and patent medicines are eligible. Classification rests on four sources of evidence: the stated treatment principle, kidney-deficiency syndrome differentiation, the role of kidney-tonifying herbs in the formula (chief or deputy), and the authors' description. Formulae in which tonifying the kidney is only ancillary (class III), formulae containing only one or two kidney-tonifying herbs without a supporting rationale (class IV), and formulae whose effect cannot be separated from concomitant acupuncture are excluded.

Comparator The identical conventional Western treatment given to the intervention group, that is, the same drug, dose and duration in both arms. Eligible backgrounds include glucocorticoids (prednisone or dexamethasone), intravenous immunoglobulin combined with glucocorticoids, and second-line regimens such as cyclosporine A, azathioprine with rituximab, or danazol with prednisone. Trials with head-to-head comparisons between Chinese herbal medicine and Western medicine, unequal background treatment (different drug, dose or duration), or inseparable co-interventions such as acupuncture are excluded.

Study designs to be included Randomised controlled trials are eligible, including trials reporting a verifiable method of sequence generation (random number table, drawing lots, computer-generated sequence) and trials that only state that participants were "randomly divided" without describing the method. The latter are treated as quasi-randomised: they enter the main analysis and are removed in a pre-specified sensitivity analysis. Trials allocating participants by order of attendance or by a "voluntary principle" are handled in the same way. Non-randomised studies, retrospective comparisons, single-arm series, case repo.

Eligibility criteria Trials must report overall response (complete response plus response, or an equivalent composite of complete and partial response) with extractable numbers of events and participants per arm. Excluded are trials in which the herbal formula is given alone, in which the background Western treatment differs between arms in drug, dose or duration, in which acupuncture or another co-intervention cannot be separated from the herbal effect, and duplicate publications of the same cohort (the most

informative report is retained). No restriction is placed on language, year or publication type (journal article, dissertation or conference abstract).

Information sources PubMed, Embase, Cochrane CENTRAL, Web of Science, CNKI, Wanfang Data, VIP and SinoMed, from inception to 21 October 2026. ChiCTR and ClinicalTrials.gov were searched for ongoing or unpublished studies. Reference lists of previous systematic reviews and of all included reports were hand-searched, and authors were contacted when data were missing or inconsistent.

Main outcome(s) Thirty-one trials (1 986 patients) were included. In adults with chronic ITP (15 trials, 941 patients), add-on tonifying-kidney therapy increased overall response at end of treatment (4 weeks to 6 months): RR 1.231 (95% CI 1.164-1.301; $I^2=0\%$). Excluding the quasi-randomised trial gave 1.224; across all 31 trials RR was 1.233 (1.189-1.279).

Additional outcome(s) Secondary outcomes: complete response; platelet count at end of treatment ($\times 10^9/L$); bleeding measured with the scale used in each trial; adverse events (number of patients with at least one event); relapse and sustained response after treatment discontinuation.

Data management Records will be exported to EndNote and de-duplicated by DOI, PMID and standardised title. Two reviewers will screen titles and abstracts independently, then full texts; disagreements will be resolved by a third reviewer. Data will be entered into a piloted Excel template and cross-checked against the source documents by a second reviewer. Discrepancies will be logged and queried with the authors.

Quality assessment / Risk of bias analysis Risk of bias will be assessed with RoB 2 for each outcome (randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result). Trials not reporting the method of sequence generation will be judged at high risk in the randomisation domain and treated as quasi-randomised. Two reviewers will judge independently, citing page numbers; disagreements will be resolved by a third reviewer.

Strategy of data synthesis Dichotomous outcomes will be expressed as risk ratios with 95% confidence intervals, continuous outcomes as mean differences. Random-effects meta-analysis (DerSimonian-Laird τ^2 , Hartung-Knapp-Sidik-

Jonkman intervals) will be used when at least six homogeneous trials are available, with 95% prediction intervals. Heterogeneity will be quantified with I^2 and the Q test; when pooling is inappropriate, results will be synthesised narratively following SWiM. Certainty will be rated with GRADE. Analyses will be run in R 4.5.2 (meta, metafor).

Subgroup analysis Pre-specified subgroups: population stratum (A, adults with chronic ITP; B, populations including minors; C, non-chronic or stage not reported); response criteria version (2020 guideline, 2011/2016 consensus, Zhang Zhinan criteria, 1984 Qingdao criteria); background treatment (glucocorticoid alone versus other regimens); and verifiable versus unverifiable sequence generation. Differences between subgroups will be tested with the Q test.

Sensitivity analysis Four sensitivity analyses of the primary outcome: (1) excluding quasi-randomised trials and those not reporting a method of sequence generation; (2) restricting to trials with a glucocorticoid background, excluding cyclosporine A and azathioprine with rituximab; (3) restricting to trials using the 2011 or 2016 consensus or the 2020 guideline; (4) restricting to trials with verifiable sequence generation. For platelet count, a sensitivity analysis excluding trials with implausibly small standard deviations was planned.

Language restriction No language restriction was applied to the search or to study selection.

Country(ies) involved China. All included trials were conducted in China, and the review was carried out in China.

Other relevant information This protocol was registered after data extraction and analysis had been completed; protocol version 1.0 was drafted before the search. Two amendments were made after preliminary screening, when only three eligible adult chronic trials were identified: the population was expanded to all patients with ITP with mandatory stratification (A/B/C, with A as the primary population), and the pooling threshold was re-defined for the stratified analysis. The primary outcome (overall response) was unchanged. Included trials were published between 1991 and 2026, all in Chinese, and were identified from eight databases, two registries and citation tracking. Ten reports could not be retrieved and are listed in the manuscript appendix. Data are available from the corresponding author on reasonable request.

Keywords immune thrombocytopenia; tonifying kidney; Chinese herbal medicine; glucocorticoid; systematic review; meta-analysis; GRADE.

Dissemination plans Findings will be submitted to a peer-reviewed journal and presented at national haematology or integrative medicine meetings. The dataset and analysis code will be provided as supplementary material.

Contributions of each author

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