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## Scientific Reports

# Efficacy of Traditional Chinese Herbal Medicine in the Treatment of Immune-Mediated Thrombocytopenia: A Systematic Review and Meta-analysis

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**ABSTRACT**

The objective of this systematic review and meta-analysis was to determine whether there exists sufficient scientific evidence that Chinese herbal medicine (CHM) can be an effective treatment for immune-mediated thrombocytopenia (ITP). Literature was obtained through PubMed, Library & Information Resources Network, Google Scholar, Science Direct, and China National Knowledge Infrastructure, using keywords "purpura, thrombocytopenic, idiopathic", "medicine, Chinese traditional", and "veterinary medicine". The studies that qualified for meta-analysis were controlled trials reporting outcomes with at least one of the following endpoints: effective rate, platelet count (PLT), adverse reactions, immune function indicators. A total of 174 articles were reviewed with 89 qualified studies undergoing meta-analysis. Study results indicated that CHM, either alone or combined with conventional Western medicine (CWM) had significantly better outcomes compared to CWM alone in terms of overall effective rate, post-treatment PLT, and incidence of side effects (all $p<0.0001$). Additionally, studies with classic CHM formulas (*Gui Pi Tang*, *Liang Xue Hua Yu Tang*), used alone or integrated with CWM, demonstrated significantly better outcomes when compared to CWM on overall effective rate and post-treatment PLT (all $p<0.01$). This systematic review and meta-analysis provide evidence that CHM, alone or combined with CWM for treating ITP, has significant advantages over CWM alone, including improved clinical outcomes, enhanced immune regulation, and fewer adverse reactions. These results are noteworthy for veterinarians. Due to limitations in quality of some studies and a scarcity of veterinary clinical trials, this systematic review and meta-analysis highlights the need for more rigorous randomized double-blind controlled trials, especially in veterinary patients.

**Keywords:** Chinese herbal medicine, *Gui Pi Tang*, immune-mediated thrombocytopenia, *Liang Xue Hua Yu Tang*, meta-analysis, platelet count

**ABBREVIATIONS:** APTT: activated partial thromboplastin time; BP: binding protein; CBC: complete blood count; $CD4^+$: T lymphocyte regulatory/helper cell; $CD8^+$: cytotoxic T lymphocyte cell; CHM: Chinese herbal medicine; CWM: conventional Western medicine; CI: confidence interval; CITP: chronic immune-mediated thrombocytopenia; GPT: *Gui Pi Tang*; Hb: hemoglobin; INF-γ: interferon-gamma; IL: interleukins; ITP: immune-mediated thrombocytopenia; LHT: *Liang Xue Hua Yu Tang*; mGPT: modified GPT; MPV: mean platelet volume; PAIg: platelet-associated immunoglobulin; PLT: platelet count; PT: prothrombin time; RCT: randomized controlled trials; SMD: standardized mean difference; SXXBC: *Sheng Xue Xiao Ban* capsule; TCM: traditional Chinese medicine; TCVM: traditional Chinese veterinary medicine; Th: helper T cells; TNF-α: tumor necrosis factor-alpha; TPO: thrombopoietin; Treg: T regulatory cells; WBC: white blood cell count; XCHT: *Xiao Chai Hu Tang*

Immune-mediated thrombocytopenia (ITP) has been recognized for many years with different nomenclature such as idiopathic thrombocytopenic purpura (mostly used in human medicine) and immune thrombocytopenia. The disease, characterized by decreased platelet counts and an increased risk of bleeding, occurs in both humans and animals such as dogs, pigs, cats and horses.[1,2] In companion animals there are more reported cases of ITP in dogs compared to cats.[3] Immune-mediated thrombocytopenia constitutes 30% of bleeding disorders, and primary ITP accounts for approximately 80% of all ITP cases.[4] The clinical symptoms of ITP include skin and mucous membrane petechiae/ecchymoses, gingival bleeding, epistaxis, melena, hematuria, fever, fatigue, and coagulation defects (e.g. prolonged bleeding time, poor thrombus retraction). From the perspective of canine epidemiological

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characteristics, ITP can occur in different age groups, with a significantly higher percentage of female dogs. Breed distribution varies in different regions, which may be influenced by geographical factors and pet ownership practices. Cocker Spaniels and Toy Poodles have a relatively higher incidence than other breeds.[5-8]

The pathogenesis of ITP is still not fully understood. Immune dysregulation characterized by increased platelet destruction by immune-mediated mechanisms has been identified as a primary cause of this syndrome. Thus, immunosuppressive therapy is the cornerstone of treatment for primary ITP in both humans and animals. For secondary ITP, it is important to actively seek the underlying cause and provide appropriate treatment.

The main focus of ITP management is to prevent bleeding and ensure patient safety by increasing the patient's platelet count and improving life quality. The recommended treatment process given by the American College of Veterinary Internal Medicine (ACVIM) starts with first-line drugs such as prednisolone in an immunosuppressive dose.[9] This is followed by observation as to whether the clinical symptoms are controlled within a period of 7 days. If prednisolone is ineffective, then second-line immunosuppressive drugs are added. A typical treatment period of 3-6 months is expected for prednisone or prednisolone in the majority of cases, with an expected duration of 4-8 months for all immunosuppressive treatments. Administration of intravenous immunoglobulin (IVIG) may be considered as a salvage measure in dogs not responding to treatment with two immunosuppressive drugs. Other adjuvant immunosuppressant therapies including cyclosporin, azathioprine, mycophenolate mofetil (MMF), danazol, and human immunoglobulin therapy have been used in veterinary medicine.

The current treatment approaches have the following shortcomings: frequent occurrence of adverse reactions, high cost, long duration of medication, and high recurrence rates.[10,11] Long-term use of immunosuppressive medications for treatment may also have a negative impact on the emotional well-being and quality of life of patients and care providers.[12] New therapeutic approaches that allow a reduction in the utilization and reliance on immuno-suppression for ITP management have been proposed; however, there is currently limited clinical evidence supporting their efficacy in dogs. More clinical data, fundamental scientific research, and follow-up records are needed to ensure the safety and efficacy of these novel medications in both human and animal patients.[13,14]

Traditional Chinese medicine (TCM) has a specific diagnostic system, which is called Syndrome Differentiation and/or TCM Pattern Diagnosis. In TCM, ITP belongs to the category of "Blood Syndrome", "Spotting", "Purpura" or "Epistaxis", depending on the manifestations of different stages of the disease. In addition, the TCM pathogenesis of ITP can be External or Internal, and it mainly includes four patterns: Blood Heat, *Yin* Deficient Heat, Blood Deficiency with Spleen *Qi* Deficiency, and Blood Stasis.[15] Herbal medicine, one of the five branches in TCM or Traditional Chinese Veterinary Medicine (TCVM), has been used for years in internal medicine for treating diseases like ITP with various types of TCM patterns.[15] Numerous scientific studies have found that Chinese herbal medicine (CHM) has effects on immune regulation, increasing the numbers/counts of platelets and white blood cells, as well as the advantages of low-toxicity and multi-targeted. The advantage of using CHM to treat ITP lies in the diversity of treatment individualized to the presenting TCM pattern(s): tonifying *Qi* and Blood, clearing Heat, nourishing *Yin*, stopping bleeding, invigorating the Spleen.

With accurate medication selection based on different TCM patterns, CHM is beneficial for improving tissue metabolism from multiple perspectives. Qin et al. conducted a literature review using a data mining approach to explore TCM treatments for ITP.[16] In 1,248 articles these researchers found that TCM classical herbal medicine formulas for treating ITP had focused on tonifying *Qi* and nourishing Blood, as well as clearing Heat and cooling Blood. Representative formulas included *Gui Pi Tang* (GPT) and *Xi Jiao Di Huang Tang*, which was also effectively modified into *Liang Xue Hua Yu Tang* (LHT) for treating Blood Heat patterns. In terms of treatment effectiveness, most experimental studies demonstrated excellent clinical outcomes with CHM treatment for ITP. There are also reports indicating that the combined approach of integrating Western and Chinese medicine yields significantly better results compared to using CHM or conventional Western medicine (CWM) alone for ITP treatment.[17]

Although the majority of clinical experience and data demonstrate the effectiveness of CHM, even suggesting its potential to reduce the side effects of conventional treatments, there are debates in the field of human medicine regarding its use. For example, a retrospective analysis of ITP treatment with CHM and conventional therapies showed no statistically significant differences in treatment effects.[18] Due to the scattered publication of clinical data and the lack of scientific statistical methods to summarize the clinical reports and trial data, this research was conducted with the aim of scientifically exploring the therapeutic effects of CHM on ITP. The main objective of this systematic review study was to determine whether CHM can be an effective treatment for primary immune-mediated thrombocytopenia through the following comparisons: (1) CHM vs. placebo; (2) CHM vs. CWM; and (3) CHM + CWM vs. CWM alone. The hypothesis was that CHM is more effective in treating patients with ITP with respect to higher effective rate, increased platelet count (PLT), and/or fewer side effects, when compared to the aforementioned control groups. Due to the lack of veterinary clinical studies on this research topic, it was expected that the majority of included data would be from human trials, which could be used to help define areas of interest for future studies in the field of TCVM. It was also expected that results could and should be extrapolated to the veterinary field.

## MATERIALS AND METHODS

### Literature Search Strategy

The literature retrieval period was from the establishment of each database to June 2023. Studies were obtained through the following search engines: Library & Information Resources Network (LIRN), PubMed, Google Scholar, Science Direct, National Library of Medicine (NLM), and China National Knowledge Infrastructure (CNKI). The following keywords were used to find relevant studies: "immune-mediated thrombocytopenia" (ITP, purpura), "herbal formula" [and/or herbal medicine, *tang* (湯), *fang* (方)], "veterinary" and/or "animal". For example, using the CNKI search formula: "immune thrombocytopenia (ITP)" + "ITP" AND "traditional Chinese medicine (TCM) treatment" + "TCM formula granules" + "herbal decoctions" + "pharmacotherapy" + "veterinary medicine" AND "therapeutic efficacy" + "efficacy analysis"; the search yielded 213 results. Using the PubMed search formula: "purpura, thrombocytopenic, idiopathic" AND "medicine, Chinese traditional"; the search yielded 16 articles on PubMed. Titles and abstracts were examined to narrow down the initial search results. Full articles were then reviewed to ensure inclusion and exclusion criteria were met and to assess study quality and bias. All qualified studies were included for the meta-analysis.

### Inclusion Criteria

Study Assessment: All studies involving Chinese herbal medicine and immune-mediated thrombocytopenia that have been published in peer-reviewed journals were considered in initial search results, regardless of species, date of publication, or language, provided translations were available.

Study Design: Both prospective and retrospective studies of controlled clinical trials were included. Whether CHM (including capsules, decoction, pills, other CHM prescription types) was compared to CWM or combined with additional modalities and compared to CWM alone, studies must have demonstrated at least one of 4 required endpoints and provided a statistical analysis of the outcome. The study inclusion criteria required included: 1) effective rate; 2) platelet count (PLT); 3) adverse reactions; and/or 4) immune system indicators.

Study Subject: Patients must have been diagnosed with primary ITP, where the diagnosis criteria conformed to the diagnostic and therapeutic effectiveness standards for TCM and CWM.

### Outcome Measurements

Meta-analysis was conducted on each efficacy-related outcome measurement reported in at least 3 studies. These included overall effective rate [(number of apparently effective cases + number of effective cases + number of improved cases)/total number of cases], post-treatment PLT, and/or immune function indicators (e.g. IL-10, TNF-α, $CD4^+$, $CD8^+$). Side effect rate data, which is related to safety, was also extracted and analyzed.

### Data Collection and Extraction

According to the inclusion criteria, two assessors, the author and Dr. Deng-Shan Shiau, a faculty member at the Chi University, independently screened the eligible literature. For the literature that met the inclusion criteria, the abstracts and full texts were reviewed to determine whether to include them in the study. Additionally, quality assessment and data extraction were performed. In case of any disagreements between the two researchers regarding the inclusion of selected literature, they engaged in joint discussions to reach a consensus. Data extraction included the study title, first author, year of publication, intervention measures, outcome indicators, and important elements of risk evaluation.

### Meta-analysis

For each outcome measurement that warranted meta-analysis, an effect size model was applied on the data collected from the literature. A commercial software[a] was adopted for the effect size meta-analysis and for generating forest plots. When heterogeneity among studies was suggested ($p$-value < 0.1 or $I^2$ > 50%), a random-effects model was used; otherwise, a fixed-effects model was applied. When the outcome measurement was continuous, standardized mean difference (SMD) was used as the effect analysis statistics. For binary outcome data, such as effective rate, the risk ratio was used. A 95% confidence interval (CI) was estimated for each effect size calculation.

### Quality Assessment

For each of the articles included in the meta-analysis, the quality of the study was assessed based on the Jadad Scale.[19,20] The scale, ranging from 0 to 5, is widely used in systematic review studies for assessing the quality of randomized controlled trials. The assessment is based on the following three criteria: (1) randomization, score 1 if mentioned, score 2 if the method described; (2) blinding, score 1 if mentioned, score 2 if the method described; and (3) data outcome, score 1 if the fate of all subjects in the trial is known (e.g. complete the trial, drop-out, excluded due to protocol deviation).

In addition, the risk of bias was evaluated using the Cochrane software risk of bias assessment tool[b]. This software includes 7 aspects: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias.[21] For each of the 7 aspects, the reviewer's judgment is categorized as "low risk," "high risk," or "unclear risk" of bias. If the study provided a detailed description of the method used to generate a random allocation sequence, such as referencing a random number table, the risk of bias for the random sequence generation was assessed as low risk. Conversely, if the sequence was generated using non-random methods, such as odd-even bed numbers, the risk of bias associated with the random sequence generation was assessed as high risk. If the study clearly reported and described dropouts, withdrawals, and

reasons for these occurrences, it was considered low risk. Conversely, if dropout reasons were not reported, it was assessed as high risk. If the reported and described information was consistent with the actual results, it was assessed as low risk. If there was inconsistency, it was assessed as high risk. Any information not mentioned was considered an unclear risk.

## RESULTS

The initial literature search based on the strategy and keywords described resulted in a total of 174 articles with titles and/or abstracts relevant to the topic of this systematic review research. All of these studies were either in human patients or experimental animals. It is worth mentioning that all but one of these articles were published in the Chinese language, but since both assessors can read Chinese, there was no language barrier for accurately assessing and extracting information from these articles. After the full-article reviews and assessments of these 174 articles, it was found that 83 articles did not qualify for study inclusion due to: 65 articles were case (or case series) reports (i.e. observational non-controlled studies), 12 articles reported experimental animal model studies, 5 articles without full text available despite vigorous attempts to contact the articles' authors, and 1 article, though a controlled study, did not have the appropriate treatment groups to test the efficacy of CHM for treating ITP patients.

The remaining 91 articles[17,22-111] reported CHM efficacy controlled studies qualifying for systematic review and 89 articles additionally qualified for meta-analysis (Table 1). Two articles did not qualify for meta-analysis due to the lack of calculable numerical numbers of the outcome data.[88,92] There were 10[(appendix-a)] retrospective studies with the remainder as clinical trials. In terms of the treatment group comparisons, 21 studies[90,91,93-111] compared CHM vs. CWM; 65 studies[(appendix-b)] compared an integrative treatment (CHM + CWM) vs. CWM alone. Additionally, 2 articles[17,44] reported studies of 3-group comparisons: CHM vs. CWM vs. CHM + CWM. The remaining 1 study[62] had two comparisons, one for an integrative treatment (CHM + CWM) vs. CWM alone, and the other for CHM treated group vs. a no-treatment group (observation only without placebo).

**Table 1:** Immune-mediated thrombocytopenia studies that met inclusion criteria for a systematic review and meta-analysis to determine whether there is scientific evidence of treatment benefit associated with the use of Chinese herbal medicine for ITP patients.

| Article | Sample Size (T/C) | Treatment Group | Control Group | Outcome Data^ | Observation Time* |
|---|---|---|---|---|---|
| Chen et al., 2012 [22] | 23/23 | SXXBC + Prednisone | Prednisone | (1)(2) | 12m |
| Chen et al., 2013 [23] | 31/30 | XCHT + Danazol | Danazol | (1)(3) | / |
| Chen, 2019 [24] | 43/42 | SXXBC + Prednisone | Prednisone | (1)(7) | 7m |
| Cui, 2016 [25] | 32/32 | GPT + Prednisone + Immunoglobulin | Prednisone + Immunoglobulin | (1)(2)(3) | 5d |
| Ding et al., 2010 [26] | 57/28 | *Si Jun Zi Tang* + *Si Wu Tang* + Prednisone | Prednisone | (1) | 4w |
| Du, 2014 [27] | 10/10 | SXXBC+ Prednisone | Prednisone | (1)(2) | 3m |
| Guo et al., 2020 [28] | 43/40 | *Jian Pi Zhi Xue Tang* + Prednisone | Prednisone | (1)(2)(3)(7) | 2m |
| Han et al., 2008 [29] | 35/35 | SXXBC+ Prednisone + γ-globulin | γ-globulin | (1)(2) | 5d |
| Hao, 2012 [30] | 43/43 | *Yi Qi She Xue Tang* + Prednisone | Prednisone | (1)(2) | 1m |
| He et al., 2004 [31] | 26/25 | *Bu Qi Yang Xue Tang* + Prednisone | Prednisone | (1)(2) | 4m |
| He et al., 2015 [32] | 33/33 | SXXBC+ Prednisone | Prednisone | (1) | / |
| He et al., 2021 [32] | 21/19 | mGPT + Cyclosporin A + Prednisone | Cyclosporin A + Prednisone | (1)(2)(8)(10) | 12w |
| He, 2015 [34] | 25/25 | *Ning Xue Tang* + Prednisone | Prednisone | (1)(3)(7) | 1m |
| Hou et al., 2022 [35] | 36/35 | *Yi Qi Yang Xue Tang* + Low-dose Rituximab | Low-dose Rituximab | (1)(2)(3)(4)(6)(10) | 4w |
| Hu, 2016 [36] | 15/15 | SXXBC+ Prednisone | Prednisone | (1)(2) | 12m |
| Huang et al., 2016 [37] | 30/30 | *Ning Xue Sheng Ban Tang* + Prednisone | Prednisone | (1)(4)(5) | 8w |
| Jiao et al., 1986 [38] | 29/23 | mGPT + Prednisone | Prednisone | (1)(10) | 10-30d |
| Li et al., 2016 [39] | 40/40 | SXXBC+ Prednisone + Dexamethasone | Prednisone + Dexamethasone | (1)(2) | / |
| Li, 2017 [40] | 35/35 | mGPT + Prednisone | Prednisone | (1)(2)(8) | 21d |
| Li, 2018 [41] | 15/15 | SXXBC+ Prednisone | Prednisone | (1)(9) | 3m |
| Li, 2021 [42] | 56/56 | *Yi Qi Zi Yin She Xue Tang* + Prednisone | Prednisone | (1)(2)(4)(10) | 8w |
| Liang et al., 2007 [43] | 40/30 | SXXBC+ Prednisone | Prednisone | (1)(2)(7) | 1m |

**Table 1:** Cont

| Article | Sample Size (T/C) | Treatment Group | Control Group | Outcome Data^ | Observation Time* |
|---|---|---|---|---|---|
| Liu et al., 2004 [44] | 23/15 | SXXBC+ Prednisone | Prednisone | (1)(3)(9) | 3m |
| Liu et al., 2012 [45] | 24/24 | *Zi Shen Sheng Ban Tang* + Prednisone | Prednisone | (1)(2)(10) | 6m |
| Liu et al., 2018 [46] | 40/40 | SXXBC+ Prednisone + Peanut Clothing Extract | Prednisone | (1)(2)(6) | 4w |
| Liu et al., 2006 [17] | 30/30 | *Hua Yu Xiao Ban Tang* + Prednisone | Prednisone | (1)(2)(10) | 3m |
| Luo et al., 2001 [47] | 21/22 | Recombinant Roasted Licorice Decoction + Low-dose Prednisone | Prednisone | (1)(2) | 20w |
| Lv et al., 2016 [48] | 50/50 | mGPT + Prednisone | Prednisone | (1)(2)(3)(4)(6)(10) | 3m |
| Ma et al., 2004 [49] | 40/40 | SXXBC+ Prednisone | Prednisone | (1)(7)(8) | >3m |
| Mao et al., 2021 [50] | 30/30 | *Ban Xia Xie Xin Tang* + Prednisone | Prednisone | (1)(2)(5)(6)(10) | 8w |
| Peng, 2004 [51] | 30/25 | *Xiao Zi Dian Tang* + Triamcinolone | Triamcinolone | (1) | 3-6m |
| Qiu, 2013 [52] | 36/20 | *Bu Xue Yi Shen Tang* + Prednisone + Cyclophosphamide + Aminopeptide | Cyclophosphamide + Aminopeptide | (1) | 60d |
| Shi, 2022 [53] | 45/45 | SXXBC+ Cyclophosphamide | Cyclophosphamide | (1)(2)(3)(4)(5)(10) | 3m |
| Song et al., 2010 [54] | 24/24 | SXXBC+ Prednisone | Prednisone | (1)(2) | 3m-12m |
| Su, 2020 [55] | 41/41 | *Shen Gui Yi Qi Tang* + Prednisone | Prednisone | (1)(2) | 120d |
| Sun, 2014 [56] | 20/20 | SXXBC+ Prednisone | Prednisone | (1)(9)(10) | >3m |
| Sun, 2022 [57] | 40/40 | *Jian Pi Sheng Xue Tang* + Prednisone | Prednisone | (2)(3) | 6m |
| Wang et al., 2006 [58] | 50/50 | SXXBC+ Prednisone + Dexamethasone +/- γ-globulin | Prednisone + Dexamethasone +/- γ-globulin | (1)(8)(9) | 5d |
| Wang et al., 2009 [59] | 31/31 | SXXBC+ Prednisone | Prednisone | (1)(3) | 3m |
| Wang et al., 2016 [60] | 26/20 | *Bu Shen Yi Qi Liang Xue Tang* + Prednisone | Prednisone | (1)(2) | 1m |
| Wang, 2008 [61] | 30/30 | SXXBC+ Prednisone | Prednisone | (1)(2)(7)(8) | 3-8m |
| Wang, 2012 [62] | 43/42 | SXXBC+ Prednisone | Prednisone | (1)(7) | 3-6m |
| Wang, 2014 [63] | 28/24 | GPT + Cyclosporin | Cyclosporin | (1)(6) | 8w |
| Wen et al., 2015 [64] | 30/30 | *Jia Wei Ba Zhen Tang* + Prednisone | Prednisone | (1)(2) | 18w |
| Wu et al., 2019 [65] | 30/30 | GPT + Prednisone | Prednisone | (1)(2) | 3m |
| Wu, 2015 [66] | 25/25 | *He Ying Ning Xue Tang* + Prednisone | Prednisone | (1)(2) | 3m |
| Xiang et al., 2015 [67] | 50/42 | *Liang Xue Zhu Yu Tang* + Prednisone | Prednisone | (1)(2)(6)(8) | 12w |
| Xiang et al., 2015 [68] | 30/30 | SXXBC+ Prednisone | Prednisone | (1)(2)(4)(10) | 3m |
| Xu, 2018 [69] | 31/31 | *Liang Xue Zhu Yu Tang* + Prednisone | Prednisone | (1)(2) | 3m |
| Xu, 2018 [70] | 40/40 | *Xue Fu Zhu Yu Tang* + Prednisone | Prednisone | (1)(5)(6) | 3m |
| Yang et al., 2012 [71] | 36/34 | *San Di Yi Xue Tang* + Thymic Peptide + Prednisone + Ampeptide Element | Thymic Peptide + Prednisone + Ampeptide Element | (1) | 30d |
| Yang et al., 2013 [72] | 172/134 | Agrimony Decoction+ Prednisone | Prednisone | (1) | 3m |
| Yang et al., 2014 [73] | 30/30 | *Bu Shen Qu Feng Tang* + Prednisone | Prednisone | (1)(2) | 3m |
| Yang et al., 2019 [74] | 34/34 | *Qing Re An Xue Tang* + Prednisone | Prednisone | (1)(2) | 40d |
| Yang, 2016 [75] | 22/26 | SXXBC+ Prednisone | Prednisone | (1)(7) | 12m |
| Yang, 2020 [76] | 43/40 | XCH + Vit C + Prednisone | Prednisone | (1)(3) | 20d |
| Ye, 2016 [77] | 40/40 | *Er Chen Gui Zhi Tang* + Prednisone | Prednisone | (1)(2)(10) | 2m |
| Yu et al., 2015 [78] | 50/42 | *Bu Qi She Xue Tang* + Prednisone | Prednisone | (1)(2)(6)(8) | 14d |

**Table 1:** Cont

| Article | Sample Size (T/C) | Treatment Group | Control Group | Outcome Data^ | Observation Time* |
|---|---|---|---|---|---|
| Yu, 2019 [79] | 35/30 | SXXBC+ Prednisone | Prednisone | (1)(2) | 3m |
| Yuan et al., 2018 [80] | 38/38 | *Yi Qi Sheng Hua Tang* + Prednisone | Prednisone | (1)(2)(4)(5)(10) | 8w |
| Yuan, 2015 [81] | 40/40 | SXXBC+ Dex + γ-globulin + Prednisone | Dex + γ-globulin + Prednisone | (1)(2)(3) | 3-6m |
| Zhang, 2015 [82] | 55/55 | SXXBC+ Prednisone | Prednisone | (1)(9) | >3m |
| Zhang, 2011 [83] | 32/32 | SXXBC+ Prednisone | Prednisone | (1)(2)(3)(7)(8) | 3m |
| Zhao et al., 2012 [84] | 23/21 | *Sheng Jiang Tang* + Prednisone | Prednisone | (1)(2)(6) | 6m |
| Zhao et al., 2021 [85] | 50/50 | *Yi Qi Sheng Hua Tang* + Low-dose Rituximab | Low-dose rituximab | (1)(2)(4)(5)(6)(8) | 4w |
| Zhao, 2018 [86] | 36/36 | GPT + Prednisone | Prednisone | (2)(3) | 4w |
| Zhao, 2020 [87] | 26/25 | *Xue An Ning Tang* + Prednisone | Prednisone | (1)(2) | 3m |
| Zheng et al., 2022 [88] | 32/32 | GPT + Dexamethasone | Dexamethasone | (5) | 4w |
| Zhong, 2015 [89] | 22/21 | *Bu Zhong Yi Qi* Tang + Prednisone | Prednisone | (1)(2) | 4w |
| Chen et al., 2010 [90] | 22/22 | Self-prescription CHM | Prednisone | (1)(2)(6) | 6m |
| Chen, 2014 [91] | 16/16 | Self-prescription CHM | Prednisone | (1)(2)(10) | 3m-2y |
| Guo, 2018 [92] | 15/15 | mGPT | Prednisone | (10) | 2m |
| He, 2006 [93] | 20/20 | GPT | Amino-plypeptide + Prednisone | (1) | 3m |
| Huang et al., 2017 [94] | 40/40 | *Liang Xue Zhu Yu Tang* | Prednisone | (1)(2)(3) | 12w |
| Huang, 2005 [95] | 50/45 | *Jin Jun Ling* Capsule + *Gui Pi Er Cao* Decoction | Prednisone | (1)(2)(3) | 90d |
| Ke et al., 2016 [96] | 21/21 | mGPT | Prednisone | (1)(10) | 2m |
| Li et al., 2014 [97] | 46/43 | modified *Si Jun Zi Tang* | Prednisone | (1)(2) | 3m |
| Li et al., 2014 [98] | 39/30 | *Liang Xue Hua Yu Tang* | Prednisone | (1)(2) | 3m |
| Li, 2017 [99] | 30/30 | *Liang Xue Hua Yu Tang* | Prednisone | (1)(2)(3) | 12w |
| Liu et al., 2004 [44] | 23/15 | SXXBC | Prednisone | (1)(3)(9) | 3m |
| Liu et al., 2012 [100] | 32/32 | *Di Huang Zhi Xue* Capsule + *Sheng Ban Tang* | Prednisone | (1)(2)(3) | 1m |
| Liu et al., 2006 [17] | 30/30 | *Hua Yu Xiao Ban Tang* | Prednisone | (1)(2) | 3m |
| Miao, 2016 [101] | 32/32 | *Liang Xue Jie Du Tang* | Immunoglobulin | (1) | 1m |
| Ning et al., 2019 [102] | 35/35 | *Er Zhi Sheng Ban Tang* | Cyclosporine | (1)(2)(7) | 36w |
| Shao et al., 2007 [103] | 37/32 | *Sheng Xue Ling* | Ampeptide Elemente | (1)(2) | 2m |
| Wang et al., 2021 [104] | 30/30 | GPT | Dexamethasone | (1)(2) | 4d-4w |
| Wang, 2014 [105] | 32/20 | *Bu Yi Qing Ning Tang* | Prednisone | (1) | 2m |
| Yang et al., 1999 [106] | 55/22 | *Yang Xue Qing Dian Tang* | Ethaneperoxoate | (1)(2)(6)(8)(10) | 6m |
| Yu et al., 2013 [107] | 29/29 | GPT | Prednisone | (1)(2) | 4m |
| Zhang, 2016 [108] | 35/35 | GPT | Ethaneperoxoate | (1) | 28d |
| Zhang, 2016 [109] | 39/39 | GPT | Prednisone | (1)(2) | 6w |
| Zhao, 2005 [110] | 45/43 | *Yi Qi Sheng Xue Tang* | Prednisone | (1)(3)(7) | 2m |
| Zhou et al., 2004 [111] | 56/30 | *Sheng Xue Ling* | Prednisone | (1)(2)(6) | 3m |

Articles #17 and #44 occur in both orange color studies and again in blue color studies; articles #88 and #92 did not meet criteria for meta-analysis; * m = months, w = weeks, d = days, / = data unavailable, y = years; SXXBC = *Sheng Xue Xiao Ban* capsule, GPT = *Gui Pi Tang*, mGPT = modified *Gui Pi Tang*, XCHT = *Xiao Chai Hu Tang*; T/C = Test/Control groups; ^ = Numbers in the "Outcome Data Extraction" column: (1) Effective rate, (2) PLT, (3) Side effect, (4) IL-10, (5) TNF-α, (6) T lymphocyte indicators, (7) Recurrent rate, (8) Platelet related IgG, (9) PLT recovery time, (10) Others: IL-17/18, WBC, Hb, MPV, PT, APTT, megakaryocyte; Orange color = studies on CHM + CWM vs. CWM; Blue color = studies on CHM vs. CWM.

Among the 89 controlled studies that investigated CHM's efficacy, there was a relatively large number of studies (14/89 = 15.7%) reporting studies on investigating the efficacy of the Chinese herbal medicine formula, *Gui Pi Tang* (GPT), for treating ITP subjects.(appendix-c) Hence, additional meta-analyses were conducted only including these "GPT" studies. Among the 14 studies, 8(appendix-d) of them compared an integrative treatment (GPT/mGPT + CWM) vs. CWM only, and the other 6 studies(appendix-e) compared GPT/mGPT vs. CWM. Another herbal medicine formula that has been consistently found in Chinese herbal medication prescriptions, *Liang Xue Hua Yu Tang* (LHT), is a commonly used formula for Heat-clearing, Blood-cooling, and Stasis-eliminating. This category had more than two articles per group and was further analyzed through meta-analysis.[37,67,69,74]

Among the 89 articles that qualified for meta-analysis, 79 (randomized controlled clinical trials)(appendix-f) were assessed for quality based on criteria of the Jadad Scale (randomization, blinding, subject's fate description). Among these articles, all of them (100.0%) mentioned that subjects were randomly assigned to treatment groups, but only a little less than half of them (35/79 = 44.3%) described the method of randomization (e.g. based on random number table, simple random strategy).(appendix-g) Only one[23] of the articles indicated that the study was blinded, and only 7 articles(appendix-h) described the fate of the subjects (e.g. number of completions, number of withdrawals and reasons) at the end of the trial; although in most of the studies, it was clear that all enrolled subjects completed the trial, based on the numbers of enrollments and subjects included in the outcome data. In summary, there were 5 articles[23,64,81,100,108] scoring a 3 on the Jadad Scale, 38 articles(appendix-i) scoring a 2, and 36(appendix-j) scoring a 1 on the Jadad Scale. The mean±SD Jadad Scale of these 79 articles was 1.61±0.61, which is considered low quality overall.

The 79 randomized controlled clinical trial articles were also assessed for risk of bias (Figure 1). Among them, 35 studies(appendix-k) described the method of random allocation, 1 study[23] mentioned a single-blind trial, 62 studies(appendix-l) mentioned the outcome data in the outline (all data measured and reported), and 6 studies(appendix-m) mentioned the occurrence of loss to follow-up and dropout conditions (low risk). The presence of repeated similar data, unexplained reasons for dropout, and non-random grouping were classified as high risk. Other domains remained with no information and presented unclear risk.

**Chinese Herbal Medicine Compared to Conventional Western Medicine**

There were a total of 24 studies that reported comparisons between CHM and CWM. Among these studies, 23 reported(appendix-n) effective rate, 15 reported(appendix-o) PLT, 2 reported[92,96] IL-18, IL-18 binding protein (BP), $CD4^{+}$ [106], $CD8^{+}$ [106], $CD4^{+}/CD8^{+}$ [106], and 4 reported [94,99,100,110] side effect rate. Three meta-analyses (with at least 3 studies) were conducted: one based on effective rate, one based on PLT, and the other one based on side effect rate.

For each of the 23 studies reporting effective rate, the risk ratio (with 95% CI) was calculated between the two treatment groups (Figure 2). Testing for heterogeneity showed significant heterogeneity among the studies ($p$=0.0006). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which suggests with strong statistical evidence that ITP patients treated with CHM can have a higher effective rate than those treated with CWM.

For each of the studies reporting PLT, the standardized mean group difference (with 95% CI of the mean) between the two treatment groups was calculated (Figure 3). Testing for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which strongly concluded that ITP patients treated with CHM would have greater PLT than those treated with CWM.

For each of the 4 studies reporting side effect rate, the risk ratio (with 95% CI) was calculated (Figure 4). As shown in the forest plots, all 4 studies had a risk ratio of less than 1 as CHM (Experimental) group had smaller side effect rates than the conventional treatment (Control) group. Test for heterogeneity showed no significant heterogeneity among studies ($p$=0.61). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which suggests with strong statistical evidence that ITP patients treated with CHM would have significantly less chance of having side effects than those treated with conventional medicine.

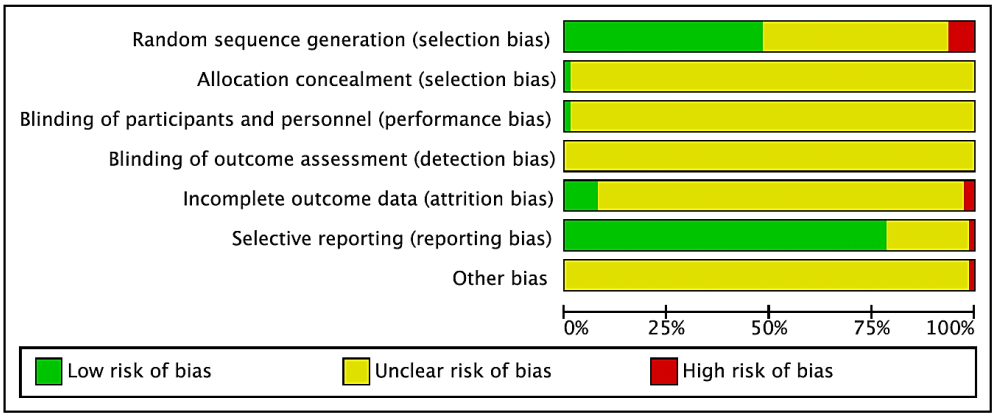


**Figure 1:** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across 79 included RCT studies

**Integrated Chinese Herbal Medicine and Conventional Western Medicine Compared to Conventional Western Medicine**

There was a total of 69 studies that reported comparisons between CHM-integrated treatment and conventional treatment. Among these studies, the outcome measurements that were reported in at least 3 studies were effective rate (66), platelet counts (44), IL-10 (9), TNF-α (5), $CD4^+$ and $CD8^+$ (8), $CD4^+/CD8^+$ (6), and side effect rate (13). Therefore, 8 meta-analyses were conducted for this category of studies.

The risk ratio (with 95% CI) of CHM+CWM vs. CWM from each of the 66 studies(appendix-p) reporting effective rate was calculated (Figure 5). Testing for heterogeneity showed no significant heterogeneity among the studies ($p$=0.15). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which again suggests with strong statistical evidence that ITP patients treated with CHM plus CWM can have a higher effective rate than those treated with only CWM.

For each of the 44 studies(appendix-q) reporting PLT, the standardized mean group difference (with 95% CI of the mean) was calculated (Figure 6). Testing for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which was sufficient to conclude statistical significance, suggesting that ITP patients treated with CHM-integrated treatments have greater platelet counts than those treated with CWM alone.

The standardized mean group difference (with 95% CI of the mean) was calculated for each of the 9(appendix-r) studies reporting IL-10 (Figure 7). Testing for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which concluded with strong statistical significance and suggested that ITP patients treated with CHM-integrated treatments have greater IL-10 values than those treated with CWM alone.

There were 6 studies(appendix-s) that reported TNF-α while only 5 of them[37,53,70,80,85] reported the TNF-α levels used in this meta-analysis ($p$=0.0008; Figure 8), test for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.0008), which concluded with strong statistical significance that ITP patients treated with CHM-integrated treatments have smaller post-treatment TNF-α values than those treated with conventional medicine alone.

There were 8 studies(appendix-t) that reported $CD4^+$ values ($p$<0.0001; Figure 9). The test for heterogeneity showed significant heterogeneity among studies ($p$=0.0005). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), that ITP patients treated with CHM-integrated treatments resulted in greater $CD4^+$ values than those treated with conventional medicine alone.

There were 8 studies(appendix-u) that reported $CD8^+$ values ($p$<0.00001; Figure 10). The test for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), that ITP patients treated with CHM-integrated treatments resulted in lower $CD8^+$ values than those treated with conventional medicine alone.

There were 6 studies(appendix-v) that reported $CD4^+/CD8^+$ ratios ($p$=0.008; Figure 11). The test for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.008), that ITP patients treated with CHM-integrated treatments resulted in greater $CD4^+/CD8^+$ ratio than those treated with conventional medicine alone.

There were 13 studies(appendix-w) which compared side effect rate for CHM + CWM compared to CWN alone. For each study the risk ratio (with 95% CI) between groups was calculated (Figure 12). As shown in the forest plot, there were 10 studies(appendix-x) that had risk ratios of less than 1, demonstrating CHM + CWM (Experimental) group had a smaller side effect rate than the CWM alone (Control) group. Testing for heterogeneity showed results of $p$=0.09 and $I^2$=37%; thus the random-effects model was used for the meta-analysis, revealing a significant overall effect ($p$=0.004). This suggested with strong statistical evidence that ITP patients treated with integrated-CHM treatments would have a significantly lower chance of having side effects than those treated with CWM alone.

***Gui Pi Tang* (GPT) Compared to Conventional Western Medicine**

The risk ratio (with 95% CI) in each of the 6 studies(appendix-y) reporting effective rate was calculated (Figure 13). Testing for heterogeneity did not show significant heterogeneity among studies ($p$=0.15). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$=0.001), which is sufficient to conclude statistical significance; suggesting that ITP patients treated with GPT have a higher effective rate than those treated with CWM.

For the 3 studies[104,107,109] reporting PLT statistics, the standardized mean group differences (with 95% CI of the mean) were calculated (Figure 14). Testing for heterogeneity did not show significant heterogeneity among studies ($p$=0.11). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), which is sufficient to conclude statistical significance; suggesting that ITP patients treated with GPT have greater platelet counts than those treated with CWM.

**Integrated *Gui Pi Tang* and Conventional Western Medicine Compared to Conventional Western Medicine**

Included in this meta-analysis were 9 randomized controlled studies that compared treatment effect of integrative GPT with CWM against CWM alone. Among these studies, 7 studies(appendix-z) reported effective rate, 2 studies[25,48] reported side effect rate, 6 studies(appendix-aa) reported platelet counts, 1 study[48] reported IL-10, $CD4^+$,

$CD8^+$, and $CD4^+/CD8^+$, and 2 studies[32,40] reported PAIgG. Based on the criterion described earlier, only meta-analyses based on effective rate and platelet count, were conducted.

The risk ratio (with 95% CI of the mean) for each of the 7 studies reporting effective rate was calculated (Figure 15). Testing for heterogeneity did not show significant heterogeneity among the studies ($p$=0.80). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), suggesting that ITP patients treated with GPT and CWM resulted in a greater effective rate than those treated with CWM alone.

For each of the 6 studies reporting PLT, the standardized mean group difference (with 95% CI of the mean) was calculated for meta-analysis (Figure 16). Testing for heterogeneity showed significant heterogeneity among studies ($p$<0.0001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$<0.00001), suggesting that ITP patients treated with GPT and CWM together resulted in higher platelet count than those treated with CWM alone.

### *Liang Xue Hua Yu Tang* (LHT) Compared to Conventional Western Medicine

There were 4 randomized controlled studies that compared treatment effect between LHT and CWM that qualified for this meta-analysis. Among these studies, all 4 reported[94,98,99,101] an effective rate, and 3 reported[94,98,99] PLT. Two meta-analyses were therefore conducted: one based on effective rate and the other based on platelet count.

The risk ratio (with 95% CI) from each of the 4 studies reporting effective rate was calculated (Figure 17). Testing for heterogeneity did not show significant heterogeneity among the studies ($p$=0.68). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$=0.0010), suggesting that ITP patients treated with LHT have a higher effective rate than those treated with CWM.

For each of the 3 studies reporting PLT, the standardized mean group difference (with 95% CI of the mean) was calculated (Figure 18). Results of testing for heterogeneity were $p$=0.10 and $I^2$=56%. The random-effects model was thus used for the meta-analysis. A strong significant overall effect ($p$<0.00001) demonstrated that ITP patients treated with LHT have greater platelet counts than those treated with CWM.

### Integrated *Liang Xue Hua Yu Tang* and Conventional Western Medicine Compared to Conventional Western Medicine

Included in this meta-analysis were 4 randomized controlled studies that compared treatment effect between LHT and CWM. Among these studies, all 4 studies[37,67,69,74] reported effective rate, 3 studies[67,69,74] reported platelet counts, and 1 study [37] reported IL-10, TNF-α, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$. Two meta-analyses were therefore conducted: one based on effective rate and the other based on platelet count.

The risk ratio (with 95% CI of the mean) from each of the 4 studies reporting effective rate was calculated for meta-analysis (Figure 19). Testing for heterogeneity did not show significant heterogeneity among studies ($p$=0.43). The fixed-effects model of the meta-analysis revealed a significant overall effect ($p$=0.0010). This result demonstrated sufficient evidence to conclude statistical significance at a 0.05 level, suggesting that ITP patients treated with LHT and CWM can expect a greater effective rate than those treated with CWM alone.

The standardized mean group difference (with 95% CI of the mean) was calculated for each of the 3 studies reporting PLT (Figure 20). Testing for heterogeneity showed significant heterogeneity among studies ($p$<0.00001). The random-effects model of the meta-analysis revealed a significant overall effect ($p$=0.006); which suggested that ITP patients treated with LHT and CWM together, could expect higher platelet counts than those treated with CWM alone.

## DISCUSSION

Immune-mediated thrombocytopenia is an autoimmune disease characterized by increased platelet destruction and decreased platelet production, creating an increased bleeding tendency. Western medical treatment, which mainly focuses on glucocorticoids and immuno-suppressive agents, can be challenging with adverse side effects, and likelihood of relapse. This systematic review and meta-analysis, using 91 and 89 peer-reviewed articles respectively, investigated whether there exists sufficient scientific evidence that Chinese herbal medicine either alone or integrated with conventional Western medicine can improve treatment for patients with ITP. Study findings demonstrated that both Chinese herbal medicine alone or combined with conventional medicine had significantly better outcomes compared to conventional medicine only, on overall effective rate, post-treatment platelet numbers (PLT), and incidence of adverse side effects (all $p$<0.0001). Studies specifically evaluating the classic Chinese herbal medicine formulas, *Gui Pi Tang* and *Liang Xue Hua Yu Tang*, used alone or integrated with conventional medicine, demonstrated significantly better outcomes when compared to conventional medicine on overall effective rate and post-treatment PLT (all $p$<0.01). Several frequently occurring immune function indicators (IL-10, TNF-α, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$) included in studies were selected for meta-analysis. Findings for these parameters demonstrated significant differences between treatment with Chinese herbal medicine both alone and integrated therapy when compared to conventional therapy, suggesting CHM treatment had greater benefit treating the immune dysregulation occurring in ITP patients. The overall results from this systematic review and meta-analysis suggest that Chinese herbal medicine either by itself or as part of an integrative therapy for ITP is more effective than conventional treatment only. These findings substantiated the study hypothesis that Chinese herbal medicine therapy is beneficial when treating cases of ITP.

A meta-analysis published by Zhang and Jiang in 2014 on the clinical efficacy of integrating Chinese herbal medicine with conventional treatment for ITP, indicated that combination therapy significantly increased peripheral platelet counts and bone marrow megakaryocyte values in ITP patients. It was also shown there were significant advantages for long-term efficacy (reduced relapse rate) and decreased adverse reactions.[112] The authors concluded from study findings that the overall effectiveness of integrated Chinese and Western medicine treatments had significant clinical advantages compared to single Western medicine therapy, similar to the findings of the present study.

In the studies included in this report, ITP patients experienced varying degrees of adverse reactions during conventional treatment. Commonly encountered treatment side effects included gastrointestinal reactions (anorexia, diarrhea, vomiting), headaches, fatigue, skin symptoms, as well as liver and kidney function impairment.[23,25,64] Conventional treatment and its attendant problems have motivated clinical investigations to find effective treatments with less adverse effects. Consistent with Zhang's 2014 findings, the results of this meta-analysis demonstrated that herbal medicine integrated with conventional therapy can significantly reduce the incidence of these adverse reactions compared to using conventional treatment only ($p$=0.004).[23] Additionally, the current study concluded that Chinese herbal medicine when used alone, could have significantly lower incidence of adverse events, when compared to conventional treatment alone ($p$<0.00001).

With the in-depth progress made in ITP mechanism research, it is believed that there is a close association between ITP and dysregulation of cellular and humoral immune mechanisms.[32] Although etiology is unclear in most cases, particularly primary ITP, antibody-mediated and/or T-cell mediated platelet destruction are key processes.[113] In addition, further immune system dysfunction described in various studies may include impairment of T cells, reduction of T regulatory cell numbers (i.e. important for immune tolerance), Th1/Th2 imbalance (tends to Th1 phenotype), cytokine imbalances, increased cytotoxic $CD8^+$ T cells, and impaired megakaryocyte function in the bone marrow.[113,114] The composite of these effects is to enhance platelet clearance through phagocytosis by exposure of platelet surface antigens and loss of tolerance, leading to a profound thrombocytopenia in many cases with dysfunctional megakaryocytes unable to restore normal platelet numbers.

Helper T cells (Th cells, $CD4^+$), which can be affected in this disease, are particularly important as they are required for almost all adaptive immune responses. They activate B cells to secrete antibodies, macrophages to ingest microbes, and help activate cytotoxic T cells ($CD8^+$) for targeted destruction of abnormal cells. Proliferating helper T cells that develop into effector cells differentiate into subtypes such as Th1 and Th2. The Th1 cells mainly secrete cytokines such as IFN-γ, TNF-α and IL-2, while Th2 cells mainly secrete cytokines such as IL-10, IL-5, IL-4. The inflammatory cytokine, TNF-α, secreted by Th1 cells reflects the severity of an inflammatory response; while IL-10 is an inhibitory cytokine secreted by Th2 cells. It plays a role in suppressing immune responses by directly inhibiting the proliferation and activation of autoreactive T cells and macrophages, maintaining immune homeostasis.[53] Meta-analysis results from this study indicated that the Chinese herbal medicines evaluated can effectively reduce TNF-α and increase IL-10.

Commonly used indicators to investigate the imbalance of T lymphocyte subsets include $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ overall levels.[115] Studies have shown that lymphocyte immune dysfunction in ITP patients is characterized by decreased numbers of $CD4^+$ cells, decreased ratio of $CD4^+/CD8^+$ and increased numbers of $CD8^+$ cells, which are consistent with the findings from the meta-analyses in this study. After Chinese herbal medicine treatment, the number of $CD4^+$ cells increased, the $CD4^+/CD8^+$ cell ratio increased, and the number of $CD8^+$ cells decreased; demonstrating significant statistical differences compared to conventional treatment. These findings suggest that Chinese herbal medicine improves the dysregulated state of T lymphocytes in patients. The results of these studies, demonstrating immune factor changes, suggest that the actions of the herbal medicines evaluated may be associated with improvement of overall immune function, although the specific targets still require further research.

Although different from human clinical trials, there were interesting investigations with ITP animal models comparing Chinese herbal medicine and conventional therapy that were found during the systematic literature review.[116-120] Of note were studies that investigated the underlying mechanisms of herbal medicine enhanced peripheral platelet numbers similar to glucocorticoid therapy.[116-119] Processes illustrated to achieve this effect included both improved platelet production and immunomodulation. Increased platelet counts were achieved by CHM promoting the differentiation of megakaryocytes, increasing the proportion of platelet-producing megakaryocytes, or enhancing the expression of certain growth factors and their receptors to facilitate platelet production.[116-118] By regulating the immune system and consequently regulating the levels of IL-10 and TNF-α in mouse peripheral blood serum, murine experiments demonstrated that Chinese herbal medicine could normalize the $CD8^+$ levels and improve the function of T-cell subsets in model mice without damaging the thymus and adrenal glands as seen with the use of prednisone.[116] Additionally, evidence from the experimental models demonstrated herbal medicine treatment can adjust the balance between platelet production and serum levels of thrombopoietin (TPO) and reticulated platelets in mice.[120]

From the perspective of TCM/TCVM, immune function is related to the body's *Wei Qi* (Defense *Qi*), which is a component of *Zheng Qi* (Antipathogenic *Qi*) responsible for defending and maintaining the body's homeostasis. This concept is reflected in *Huang Di Nei Jing*, which states: "As *Zheng Qi* is stored within, evil *Qi*

cannot invade." By intervening with Chinese medicine to improve the patient's self-immune status, a good clinical recovery can be achieved.[35] Traditional Chinese medicine emphasizes a holistic approach and individualized treatment based on pattern differentiation. Different types of TCM herbal medicine formulas can be used to treat ITP patients with different TCM patterns, demonstrating individualized medicine with the characteristic of "treating the same disease with different personalized treatments". In addition to the overall Chinese herbal medicine treatment strategies, the current study also selected studies with relatively consistent herbal medicine formulas for ITP treatment of specific TCM patterns, for a categorized meta-analysis. These formulas included *Gui Pi Tang*, *Liang Xue Hua Yu Tang*, *Sheng Xue Xiao Ban* capsule, and *Er Zhi Sheng Ban Tang*. These representative classic TCM prescriptions studied in this research share similar results to those in Qin et al.'s report in 2022 based on a data mining method of ITP clinical medications.[16]

*Gui Pi Tang*, a widely available Chinese herbal medicine, is a tonifying formula used to treat Deficiency of the Heart and Spleen, and Spleen *Qi* failure to control Blood. Meta-analysis showed that both GPT alone and its integration with conventional medicine were more effective than conventional therapy alone, in terms of improving platelet count and overall effective rate, suggesting better clinical efficacy for ITP patients with *Qi* and Blood Deficiency. These results are consistent with the findings of Zhang, who conducted a meta-analysis of 9 randomized controlled trials (RCTs) and found that GPT (or combined with Western medicine) had a higher overall response rate than Western medicine treatment only.[121] Furthermore, these researchers explored the active components of GPT using network pharmacology methods, suggesting that GPT may treat ITP by inhibiting viruses, regulating immunity, and improving inflammation.

Similar to GPT, treatment of ITP patients with *Liang Xue Hua Yu Tang*, showed significant efficacy in improving overall effective rate and platelet count when used alone or in combination with Western medicine, based on the TCM principles of clearing Heat, detoxification, cooling Blood, and resolving Blood Stasis. Meta-analysis results suggest that it also has a significant clinical effect in treating ITP, and this result is similar to previous reports with the same treatment principles.[122]

A meta-analysis in 2022, which included 27 RCTs, indicated that the combination of *Sheng Xue Xiao Ban* capsule (SXXBC) and glucocorticoid treatment for ITP was significantly more effective compared to glucocorticoid treatment alone in terms of treatment efficacy, platelet relapse time, and relapse rate.[122] *Sheng Xue Xiao Ban* capsule mainly consists of *Qing Dai* (Indigo), *Mu Dan Pi* (Moutan), *Lian Qiao* (Forsythia), *Xian He Cao* (Agrimony), and *Gan Cao* (Licorice), with TCM functions of clearing Heat, detoxification, cooling Blood, and resolving Blood Stasis.

Although the representative formulas for two other TCM patterns (*Yin* Deficient Heat and Blood Stasis) included in the literature were insufficient for meta-analysis, the literature review indicates that Chinese herbal medicine based on principles of nourishing *Yin* and clearing Heat, as well as harmonizing *Shao-Yang* and regulating Liver to clear Heat, have shown significant effectiveness in treating ITP.[24,76] As for ITP patients with false Heat due to *Yin* Deficiency, the use of *Er Zhi Sheng Ban Tang* has shown a significantly higher overall effective rate and platelet count recovery compared to treatment with prednisone, and the clinical outcomes have been favorable.[102,117] In another study on patients with *Yin* Deficiency and excessive Fire pattern of ITP, although the overall effective rate did not reach the level of statistical significance, the self-formulated herbal medicine demonstrated better improvements in TCM syndrome manifestations compared to prednisone (e.g. restlessness, night sweats, dizziness, thirst).[45]

It is worth noting that a mouse model investigation clearly demonstrated the lack of significant therapeutic effect when a non-pattern-based herbal medication was used for the treatment of ITP. In this experiment, *Xi Jiao Di Huang Tang* (the classical herbal formula targeting Blood Heat and reckless movement of Blood) was used to treat ITP mice with Spleen *Qi* failing to control Blood. The results indicated that TCVM treatments, without taking individualized pattern diagnosis into account, had no significant therapeutic effect on ITP, reflecting the importance of accurate TCM/TCVM pattern differentiation in treatment.[119]

There are several study limitations to be considered in the present meta-analysis. The majority of the controlled trials had low methodological quality, lacking detailed descriptions of random allocation methods, study designs, concealed allocation plans, and information on loss to follow-up. Moreover, the trials primarily involved human subjects, with a lack of controlled trials focusing on the use of Chinese herbal medicine in veterinary medicine. And it's important to acknowledge the distinction between a disease induced in a laboratory animal and one that occurs naturally. The absence or non-implementation of single-blind, double-blind, or triple-blind methods in the trials may have introduced subjective bias into the results. Additionally, some of the included randomized controlled trials had small sample sizes, which may impact the reliability and generalizability of the findings.

In summary, the present meta-analysis demonstrated significant benefit when incorporating Chinese herbal medicine into the medical treatment protocol for ITP patients. The specific mechanisms of action for individual herbal prescriptions, however, remain unclear due to the diverse and individualized nature of pattern differentiation in TCM. Future research should aim for more specific and comprehensive investigations into the effects of various types of CHM prescriptions. To promote the use of CHM clinically, it is necessary to conduct more large-sample, multi-center, randomized double-blind studies to enhance the quality of evidence that supports CHM's therapeutic efficacy, particularly in the field of veterinary medicine.

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The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this paper and the author did not receive any specific grant of funding from any organization in the public, commercial or non-profit sectors.

## FOOTNOTES

[a.] Review Manager (RevMan 5.4), Cochrane Collaboration, London, England

[b.] Risk of bias software, Cochrane Collaboration, London, England

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121. Zhang T. Clinical efficacy and potential mechanism exploration of Modified Guipi Decoction in the treatment of immune thrombocytopenia in children with syndrome of Qi failing to control Blood. Nanjing University of Chinese Medicine 2022. (In Chinese). https://doi.org/10.27253/d.cnki.gnjzu.2022.000054
122. Ding M, Li B, Yang M et al. Effectiveness of Shengxuexiaoban Capsules combined with glucocorticoid therapy for immune thrombocytopenia: A meta-analysis. PLoS One 2022; 17(9):e0275122. https://doi.org/10.1371/journal.pone.0275122

## FOREST PLOTS (Figures 2-20)

**Legend for Forest Plots:** The solid horizontal lines represent 95% confidence interval. Each horizontal line within the plot represents a separate study being analyzed; the vertical line represents an odds ratio of 1 (i.e. no association). A point estimate of the study result is represented by a square (blue square-dichotomous/binary variable, green square-continuous variable). The diamond shape represents the pooled results calculated from all studies in the plot (the meta-analysis), with the two ends of the diamond representing the 95% relative confidence interval.

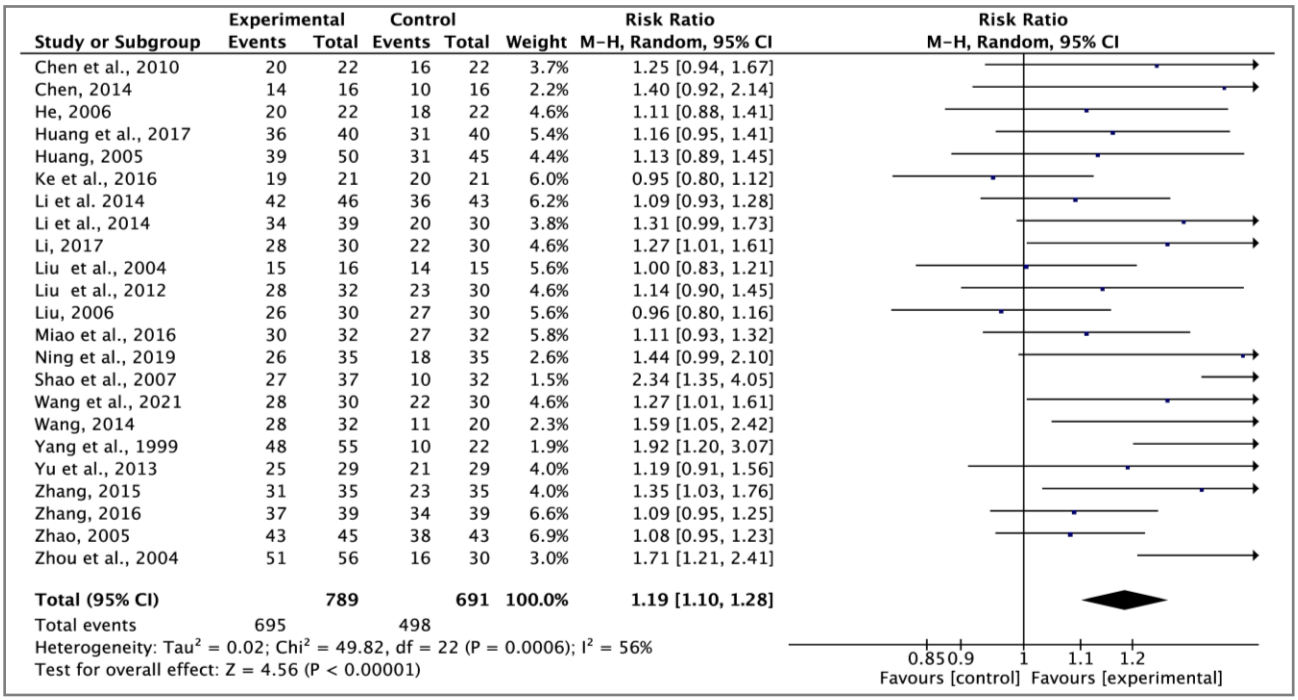


**Figure 2:** Effect size meta-analysis with forest plot from 23 studies reporting effective rate statistics for CHM treatment efficacy compared to CWM in treating ITP patients.[appendix-n] "Experimental" = CHM treatment; "Control" = CWM; M-H=Mantel-Haenszel analysis method for visual representation of a meta-analysis.

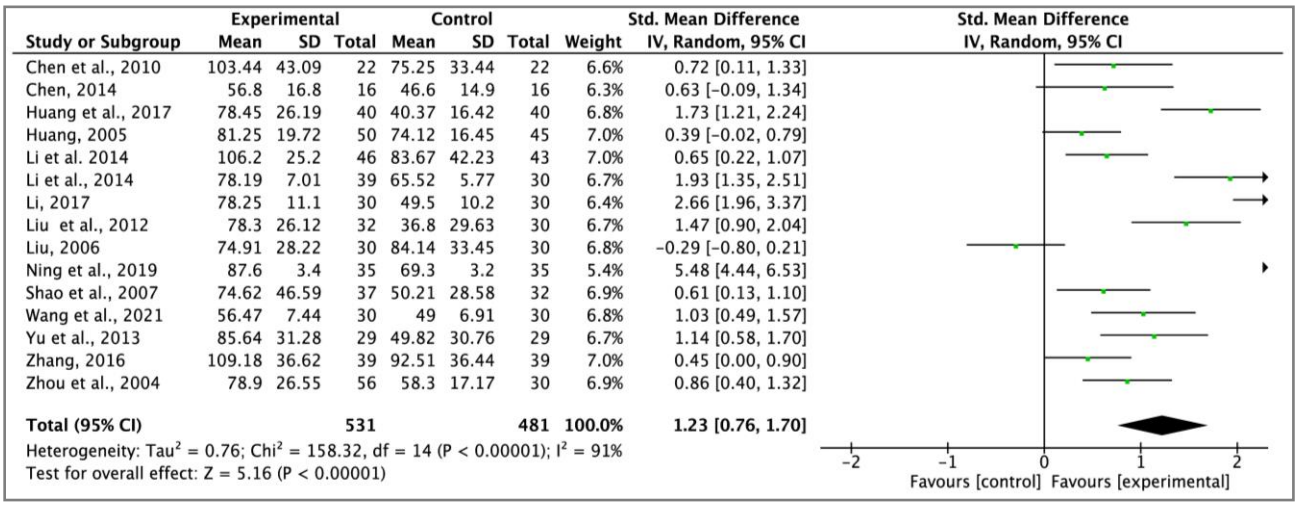


**Figure 3:** Effect size meta-analysis with forest plot from 15 studies reporting platelet count statistics for CHM treatment efficacy compared to CWM in treating ITP patients.[appendix-o] Note the diamond shape which represents the pooled results of the meta-analysis and sums up study results, which equals 1.23 which is greater than 1 and falls within the "favors experimental" result. "Experimental" = CHM treatment; "Control" = CWM.

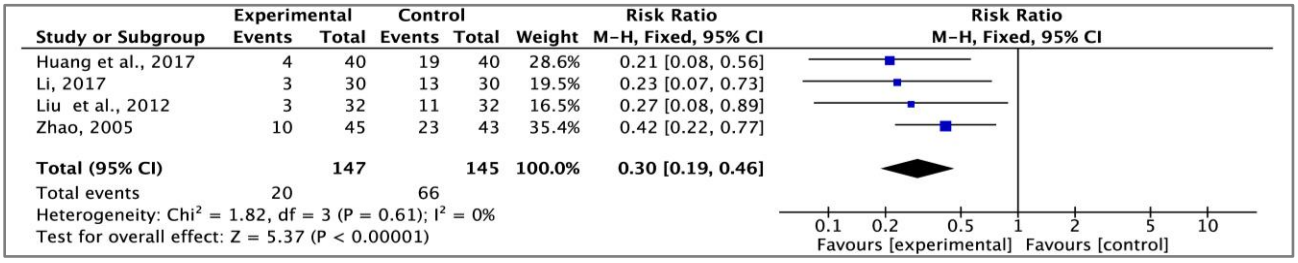


**Figure 4:** Effect size meta-analysis with forest plot from 4 studies reporting side effect rate statistics for CHM treatment versus CWM in treating ITP patients.[94,99,100,110] Note diamond shows study result favors experimental. "Experimental" = CHM treatment; "Control" = CWM.

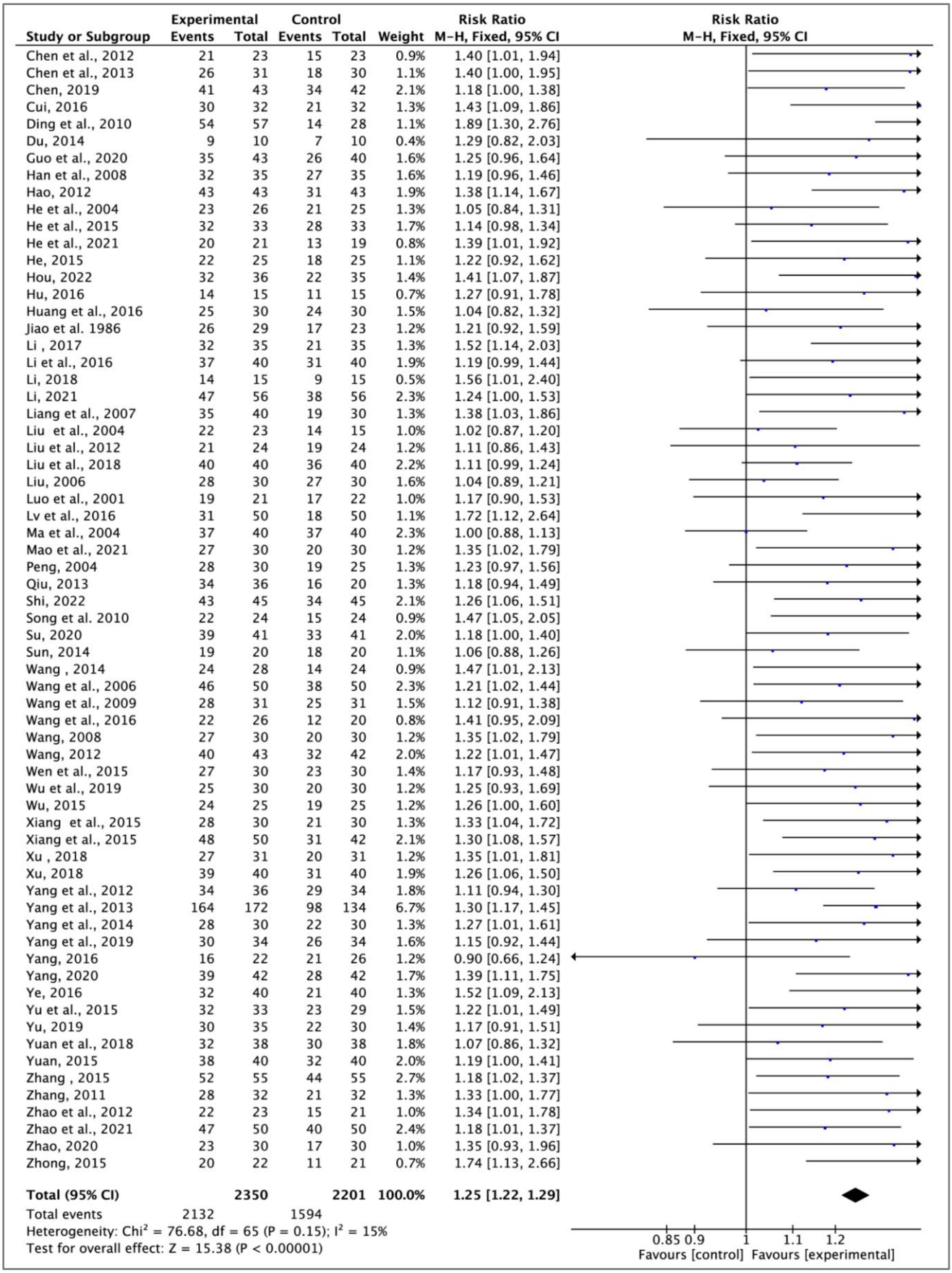


**Figure 5:** Effect size meta-analysis with forest plot from 66 studies reporting effective rate statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-p] "Experimental" = CHM+CWM; "Control" = CWM.

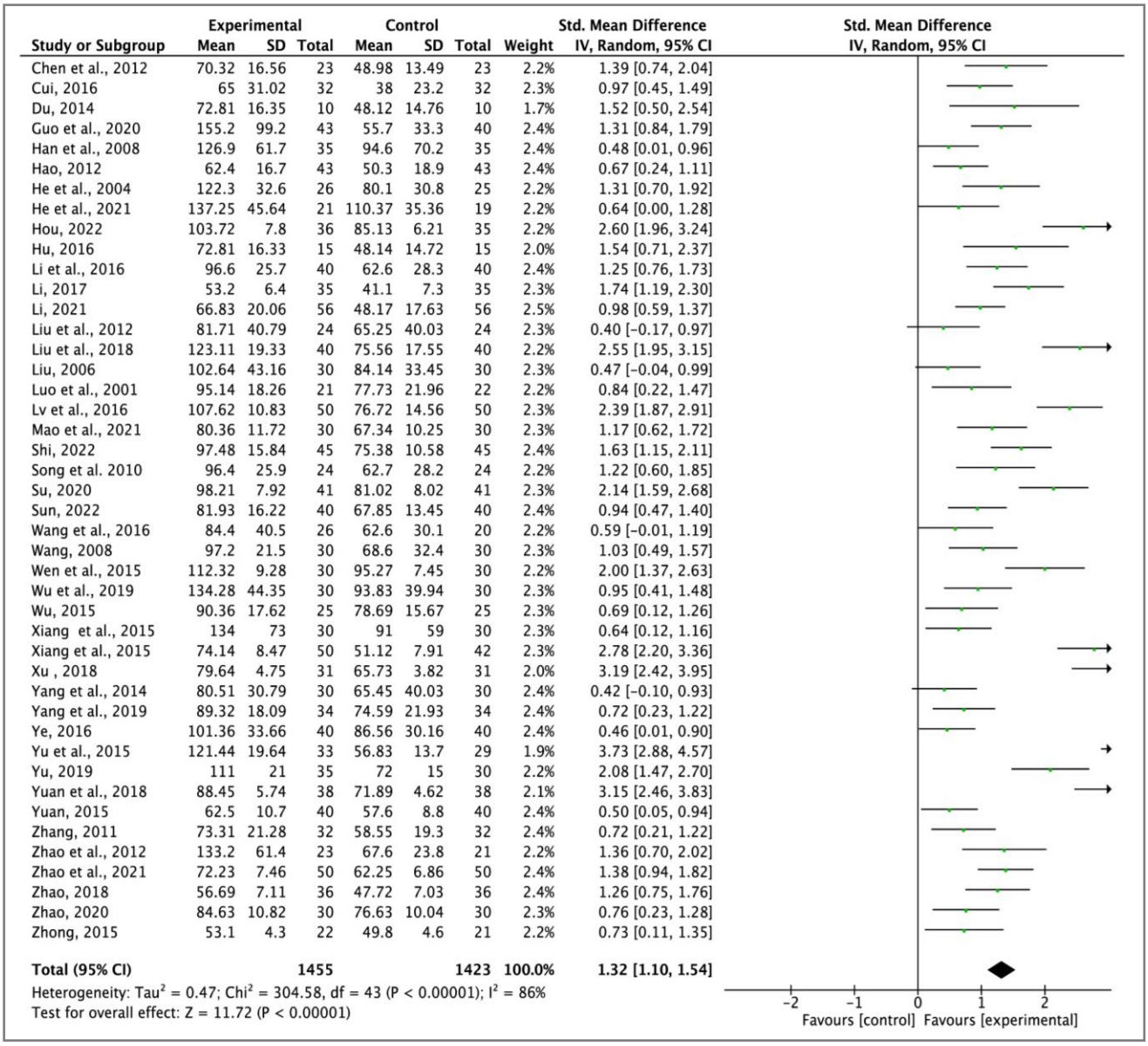


**Figure 6:** Effect size meta-analysis with forest plot from 44 studies reporting platelet count statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-q] "Experimental" = CHM+CWM; "Control" = CWM.

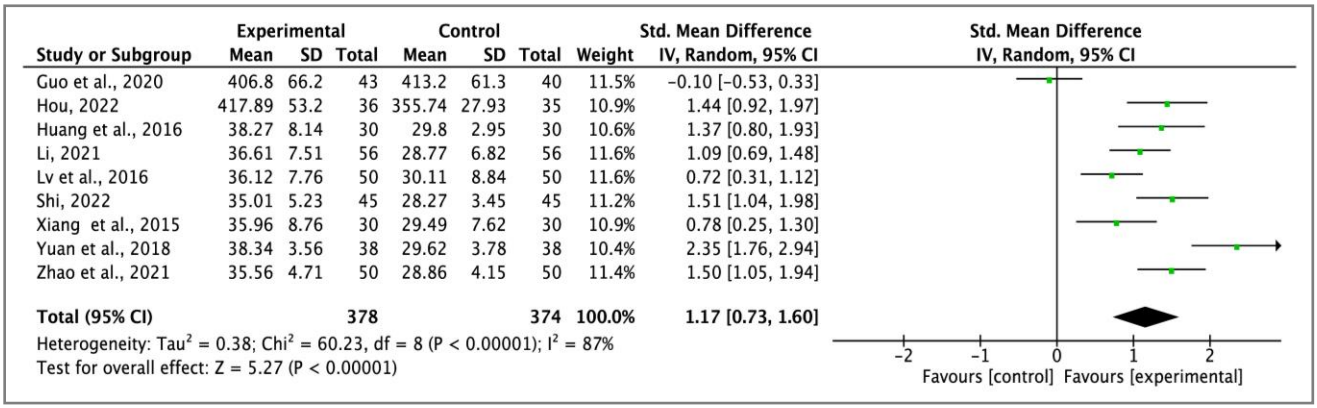


**Figure 7:** Effect size meta-analysis with forest plot from 9 studies reporting IL-10 statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-r] "Experimental" = CHM+CWM; "Control" = CWM.

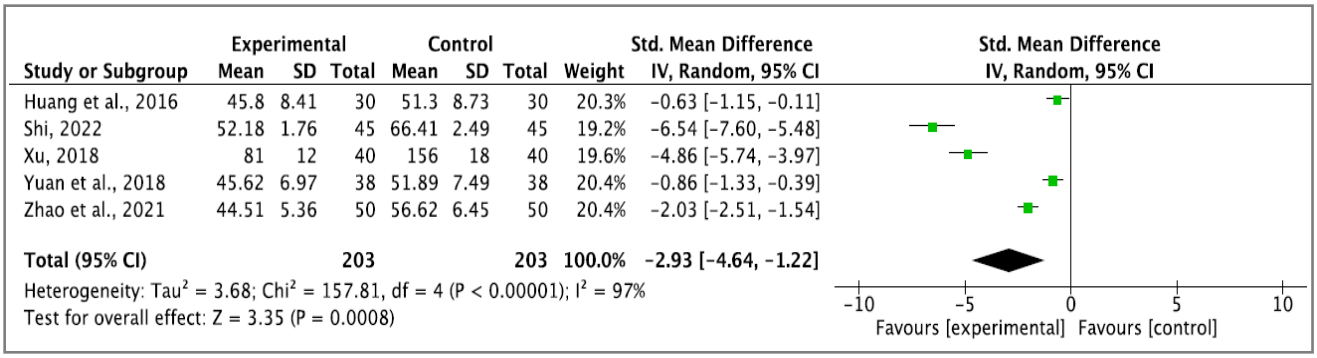


**Figure 8:** Effect size meta-analysis from 5 studies reporting TNF-α statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-s] "Experimental" = CHM+CWM; "Control" = CWM.

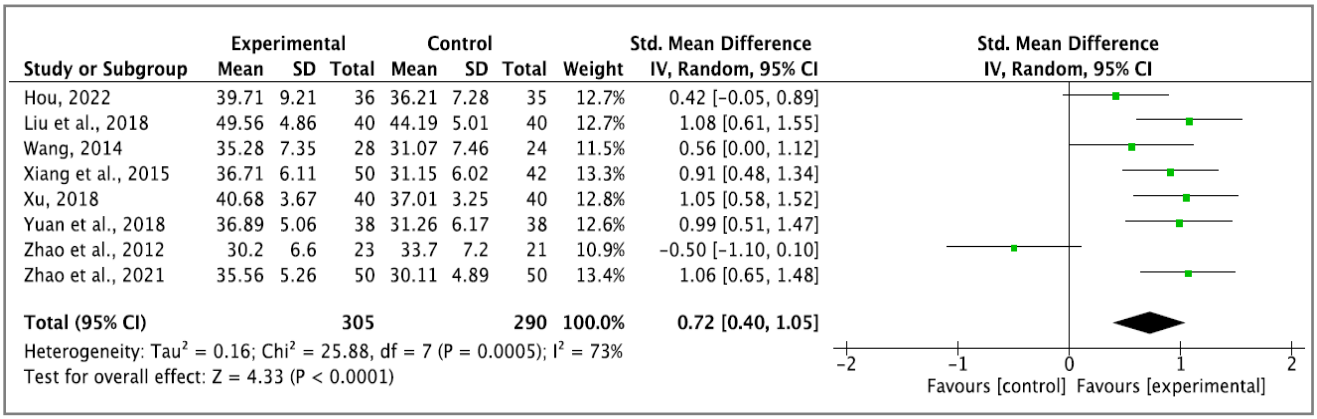


**Figure 9:** Effect size meta-analysis with forest plot from 8 studies reporting $CD4^+$ statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-t] "Experimental" = CHM+CWM; "Control" = CWM.

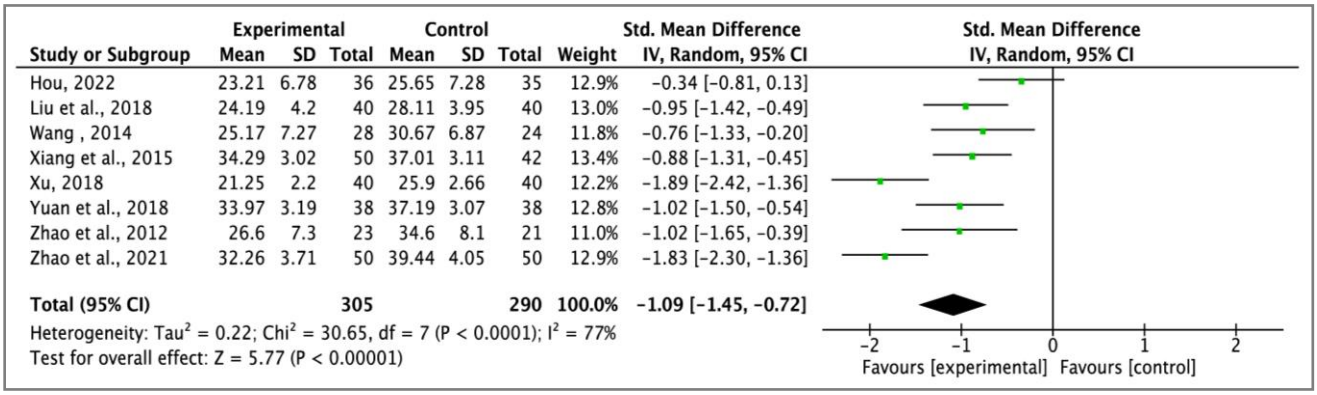


**Figure 10:** Effect size meta-analysis from 8 studies reporting $CD8^+$ statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-u] "Experimental" = CHM+CWM; "Control" = CWM.

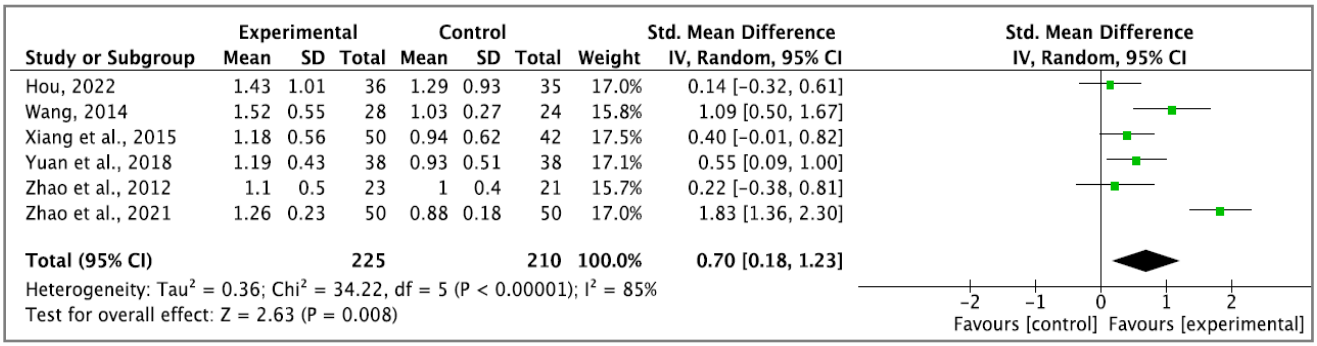


**Figure 11:** Effect size meta-analysis with forest plot from 6 studies reporting $CD4^+/CD8^+$ statistics for CHM+CWM compared to CWM in treating ITP patients.[appendix-v] "Experimental" = CHM+CWM; "Control" = CWM.

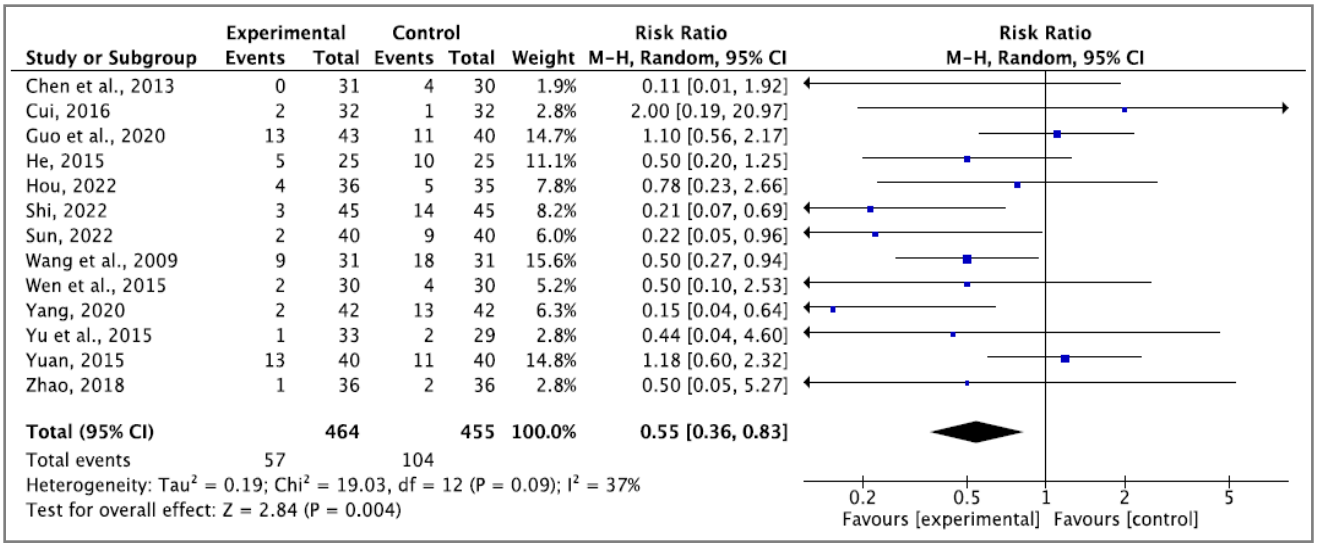


**Figure 12:** Effect size meta-analysis with forest plot from 13 studies reporting side effect rate statistics for CHM+CWM versus CWM in treating ITP patients.[appendix-w] "Experimental" = CHM+CWM; "Control" = CWM.

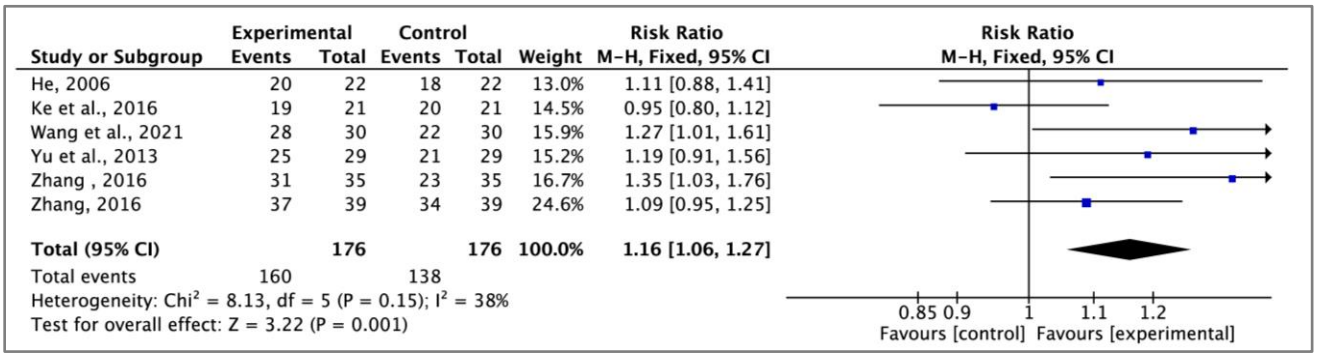


**Figure 13:** Effect size meta-analysis with forest plot from 6 studies[appendix-y] reporting effective rate statistics for GPT treatment compared to CWM in treating ITP patients. "Experimental" = GPT treatment; "Control" = CWM.

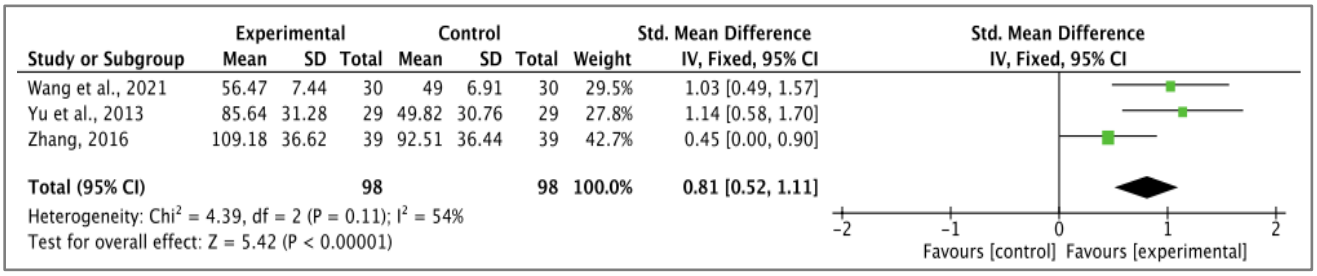


**Figure 14:** Effect size meta-analysis with forest plot from 3 studies reporting platelet count statistics for GPT treatment compared to CWM in treating ITP patients. "Experimental" = GPT treatment; "Control" = CWM.

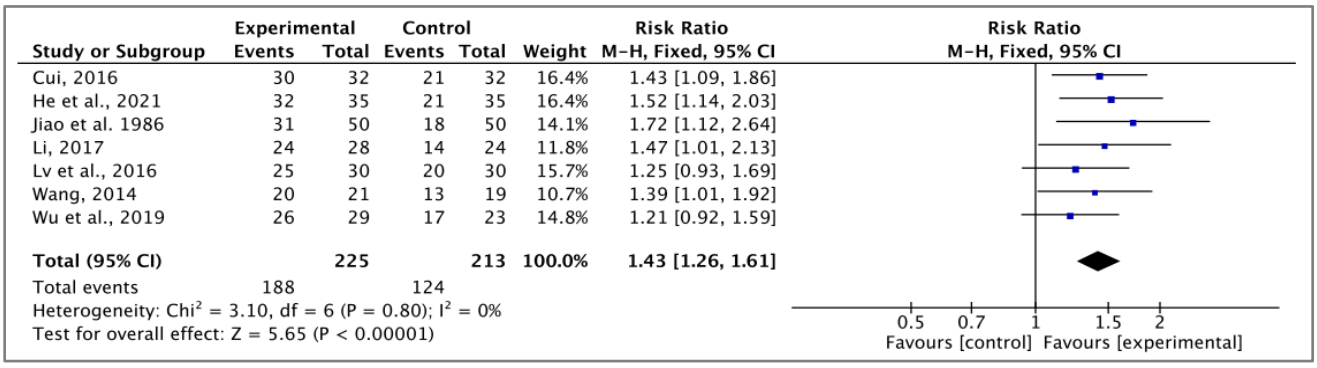


**Figure 15:** Effect size meta-analysis with forest plot from 7 studies reporting effective rate statistics for GPT+CWM compared to CWM alone in treating ITP patients.[appendix-z] "Experimental" = GPT+CWM; "Control" = CWM.

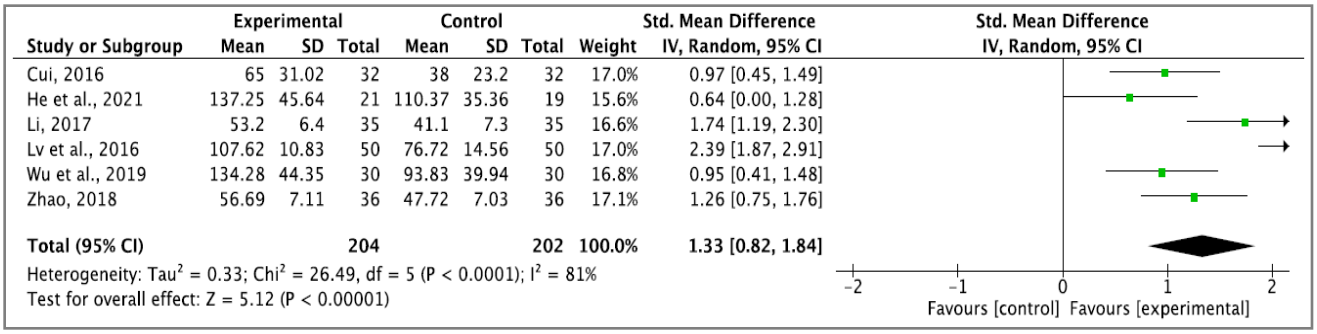


**Figure 16:** Effect size meta-analysis with forest plot from 6 studies reporting platelet count statistics for GPT+CWM efficacy compared to CWM alone in treating ITP patients.[appendix-aa] "Experimental" = GPT+CWM; "Control" = CWM

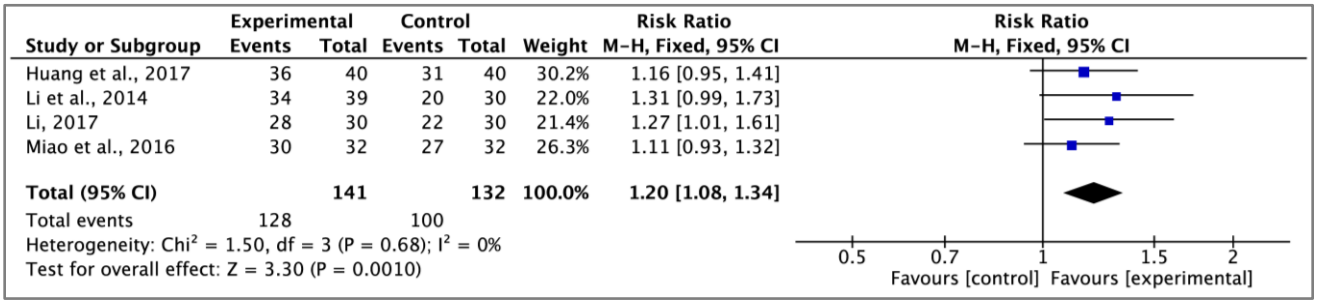


**Figure 17:** Effect size meta-analysis with forest plot from 4 studies reporting effective rate statistics for LHT treatment compared to CWM in treating ITP patients.[94,98,99,101] "Experimental" = LHT treatment; "Control" = CWM

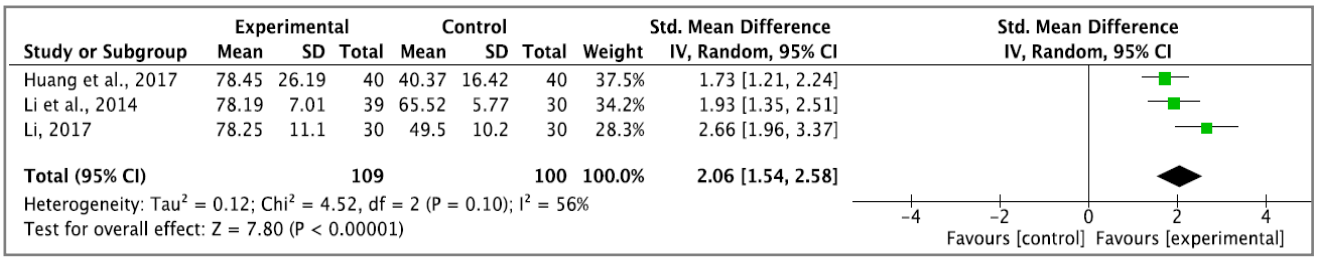


**Figure 18:** Effect size meta-analysis with forest plot from 3 studies reporting platelet count statistics for LHT treatment compared to CWM in treating ITP patients.[94,98,99] "Experimental" = LHT treatment; "Control" = CWM.

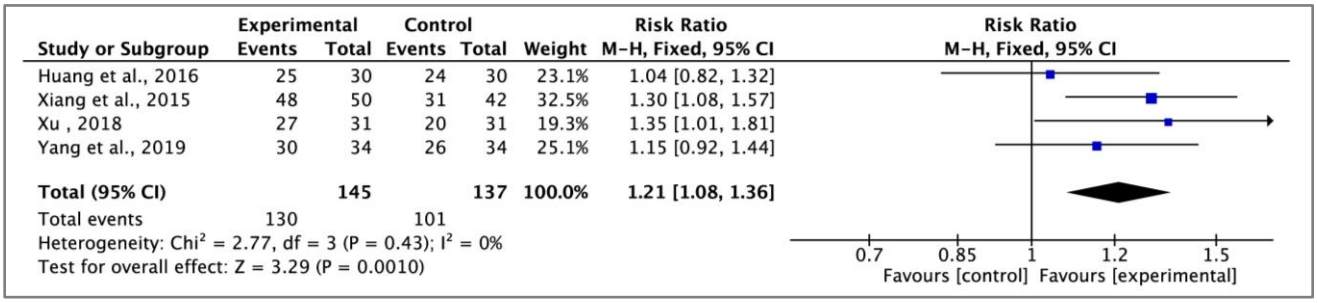


**Figure 19:** Effect size meta-analysis with forest plot from 4 studies reporting effective rate statistics for LHT+CWM compared to CWM alone in treating ITP patients.[37,67,69,74] "Experimental" = LHT+CWM; "Control" = CWM alone.

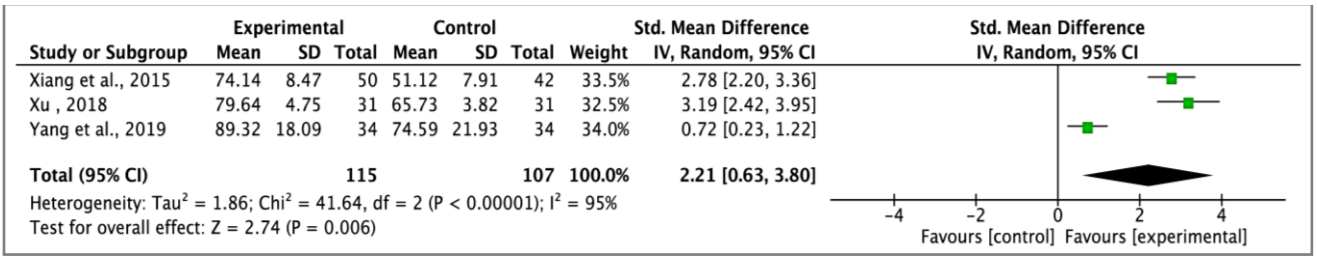


**Figure 20:** Effect size meta-analysis with forest plot from 3 studies reporting platelet count statistics for LHT+CWM efficacy compared to CWM alone in treating ITP patients.[67,69,74] "Experimental" = LHT+CWM; "Control" = CWM alone.

## APPENDIX

**List of Article References Used When Greater Than Five Reference Numbers are Cited for Systematic Review and Meta-analysis Results**

*a.* Retrospective Studies [28,35,38,49,51,53,67,72,97,106]
*b.* (CHM + CWM) vs. CWM [22-43,45-61,63-87,89]
*c.* Efficacy of *Gui Pi Tang* [24,33,38,40,48,63,65,86,93,96,104,107-109]
*d.* Integrative *Gui Pi Tang* (GPT + CWM) vs CWM [24,33,38,40,48,63,65,86]
*e.* *Gui Pi Tang* vs CWM [93,96,104,107-109]
*f.* Randomized controlled clinical trials (Jadad Scale assessment) [17,22-27,29-34,36,37,39-48,50,52,54-66,68-71,73-87,89-91,93-96,98-105,107-111]
*g.* Articles describing randomization [24,27,32,33,39,42,45,48,50,55,57,62,64,65,74,76,80-86,89,94,98-100,102-105,108,110,111]
*h.* Articles describing fate of subjects [23,37,63,64,75,81,100]
*i.* Articles scoring 2 on Jadad Scale [24,27,32,33,37,39,40,42,45,46,48,50,55,57,61-63,65,74-76,80,82-86,89,94,98,99,101-105,110,111]
*j.* Articles scoring 1 on Jadad Scale [17,22,25,26,29-31,34,36,41,43,44,47,52,54,56,58-60,66,68,69-71,73,77-79,87,90,91,93,95,96,107,109]
*k.* Articles with random allocation [24,27,32,33,35,42,45,48,50,55,57,62,64,65,74,81,82-86,89,92,94,98-100,102-105,108-111]
*l.* Outcome data in outline (all data measured and reported) [17,22,25,26,31-34,36,37,39,40,42,44,46-48,50,52,55,57,63-66,68-70,73-87,89,91,93-96,98-105,107-111]
*m.* Recorded loss to follow-up/drop out conditions [37,63,64,81,100,108]
*n.* CHM vs CWM (Effective rate) [17,44,90,91,93-111]
*o.* CHM vs CWM (PLT) [17,90,91,94,95,97-100,102-104,107,109,111]
*p.* CHM + CWM vs CWM (Risk ratio from studies reporting effective rate) [17,22-56,58-85,87,89]
*q.* Studies reporting PLT [17,22,25,27-31,33,35,36,39,40,42,45-48,50,53-55,57,60,61,64-69,73,74,77-81,83-87,89]
*r.* Studies reporting IL-10 [28,35,37,42,48,53,68,80,85]
*s.* Studies reporting TNF-α [37,53,70,80,85,88]
*t.* Studies reporting $CD4^+$ [35,46,63,67,70,80,84,85]
*u.* Studies reporting $CD8^+$ [35,46,63,67,70,80,84,85]
*v.* Studies reporting $CD4^+/CD8^+$ [35,63,67,80,84,85]
*w.* Studies reporting side effect rate [23,25,28,34,35,53,57,59,64,76,78,81,86]
*x.* Risk ratio < 1 demonstrating integrated CHM had smaller side effect rate than CWM[23,34,35,53,57,59,64,76,78,86]
*y.* *Gui Pi Tang* vs CWM (Effective rate) [93,96,104,107-109]
*z.* Integrated *Gui Pi Tang* vs CWM (Effective rate) [25,33,38,40,48,63,65]
*aa.* Integrated *Gui Pi Tang* vs CWM (PLT) [25,33,40,48,63,65]