The Efficacy and Safety of Wuling Powder on Cirrhotic Ascites: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract. Objective To evaluate the efficacy and safety in patients with cirrhotic ascites treated by Wuling Powder. Methods PubMed, Web of science, The Cochrane library, EMBase, CNKI, WAFANG, VIP and SinoMed database were searched. Randomized controlled studies of cirrhotic ascites were collected from the establishment of the database to February 20, 2020. EndNote was used for literature screening, RevMan 5.3 was used for data analysis, GRADEpro was used to evaluate the evidence quality. Results 11 studies with 1054 patients were analyzed. Meta-analysis: ① Total effective rate: The Wuling powder group was higher (P <0.01)). ② Liver function: The serum ALT, AST and TBIL in Wuling powder group were significantly lower (P <0.01), the ALB (Albumin) was significantly higher (P <0.05). ③ The incidence of adverse events: There was no significant difference (P=0.72>0.05). ④ Recurrence rate: The Wuling powder group was lower (P <0.01). ⑤ GRADE evaluation: The quality of evidence in the total effective rate, ALB index and incidence of adverse reactions was intermediate, the others were low or very low. Conclusions The Wuling powder combined with basic western medical treatment for cirrhotic ascites can significantly improve clinical efficiency, liver function and reduce recurrence rate, the adverse events were not obvious. However, due to the low quality of the included studies, it should be used with caution in the clinic.

Keywords: Wuling Powder, Cirrhotic Ascites, Meta-Analysis, Efficacy, Liver Function, GRADE Evaluation

1. Introduction
Cirrhotic ascites is a common end-stage complication of liver disease, which can be caused by viral hepatitis, alcoholic hepatitis, cholestatic liver disease, etc. [1]. Viral hepatitis is the main cause of liver cirrhosis, there are currently more than 250 million chronic hepatitis B virus infected people.
worldwide, but only 10% of them are diagnosed and only 1% are adequately treated, most of these patients develop cirrhosis [2]. Cirrhotic ascites patients account for about 67.3% of hospitalized patients with liver cirrhosis, the 1-year mortality rate is 15%, the 5-year mortality rate can be as high as 44%. Therefore, the treatment of cirrhotic ascites should attract great attention for the medical professions [3].

At present, the methods of Western medicine treated cirrhotic ascites were mainly diuretic drugs and surgical treatment. But diuretic resistance occurs in 20% ~ 30% of patients, there were many side effects of diuretics. For example, the combined use of spironolactone and furosemide may cause renal insufficiency. Furosemide can cause hypokalemia, hypochloric alkalosis, hyponatremia and hypovolemia. Long-term use of spironolactone can cause gynecomastia [4].

Wuling powder was from "Treatment on Febrile Diseases", which was used for bladder water storage certificates, the Wuling powder prescription was combined with Zhuling, Poria, Atractyloides, Zexie, and Guizhi. Nowadays it was used as a "water-saving prescription" [5], many studies have reported that wuling powder has a very good clinical effect in treating cirrhotic ascites, but each study is a small sample, the statistical power is insufficient. So far, there is no systematic review was published.

2. Methods

2.1 Search Strategies
PubMed, The Cochrane library, Web of science, EMBase, CNKI, Wanfang, VIP and SinoMed were retrieved, search terms: Wuling, cirrhosis, ascites, cirrhotic ascites. “wuling and (cirrhosis or ascites or cirrhotic ascites)” from the establishment of each database to February 20, 2020.

2.2 Eligibility Criteria

2.2.1 Type of study: Only RCTs reporting the efficacy and safety of wuling powder for cirrhotic ascites were eligible, including the use of blind and non-blind methods.

2.2.2 Type of participants: All the participants were needed met the Chinese and Western diagnostic criteria for cirrhotic ascites [6,7], there was no restriction on race, age, or gender.

2.2.3 Type of intervention: The control group were all used basic western medicine. Patients restricted water and salt intake and mainly took a high-calorie diet. Hepatoprotective drugs were multivitamins, diphenyl biphenyl esters and ganlixin, etc. The anti-hepatitis B drug was mainly lamivudine tablets, the diuretics drug were mainly furosemide and spironolactone, etc. Most of them were supplemented with human albumin, the infected patients were given antibiotics. On the basis of the control group, the experimental group was treated with Wuling powder.

2.2.4 Type of outcome measures: The Major outcomes were total clinical effective rate, incidence of adverse events, Recurrence rate and liver function. The minor outcomes were include ALT, AST, ALB (Albumin), TBIL. The basis of total clinical effective rate includes the improvement in abdominal circumference, 24-hour urine output, weight, and TCM syndrome scores.

2.3 Exclusion Criteria:
① Repeated publication or apparently similar articles;② reviews, case series, animal researches, pharmacological experiments and observation study; ③ combined with other TCM therapy, e.g. acupuncture, moxibustion and other traditional Chinese medicine prescriptions; ①Studies with incomplete data, unreliable or inaccessible full text.

2.4 Study Selection
This study was contacted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [19]

2.5 Data Extraction
①The first authors’ names and publication year, ②The characteristics of participants, including number, mean age, sex; ③treatment information about interventions management, follow-up period and course of treatment. ④ Key elements of bias risk assessment ⑤outcome measurement.

2.6 Quality Assessment
The bias risk assessment was evaluated by the tool in the Cochrane Evaluation Manual Handbook 5.1.0, and the study was finally judged as "high risk of bias", "low risk of bias", and "unclear ".

2.7 Data Analysis
Binary categorical and continuous variables were expressed as mean difference (MD) or standardized mean difference (SMD) whereas dichotomous variables were reported as Relative risk (RR) and Mean Differences (MD) with their 95% confidence limits (CI); When qualitative (P > 0.10, I² <50%), a fixed effect model is used for meta-analysis.

3 Results

3.1 Literature Screening Results.
679 studies were retrieved by searching the eight databases. 332 records remained after removed the duplication., 276 records were excluded by screening the titles and abstracts.; By reading the full article, 45 records were excluded with reasons:8 records were reviews, 21 records were combined with other TCM therapy, 3 records were the repeat research;13 records were poor quality or significant data errors. Ultimately, 11 eligible studies were included for this study. The search process and study selection were depicted by a PRISMA flow chart.

3.2 Characteristics of Included Studies
In each study, the baseline comparisons were performed which included sample size, age, and intervention (P=0.72>0.05). 538 in the experimental group and 516 in the control group. All of the control groups were treated with basic western medicine, All of the experimental groups were added with Wuling powder (One dose, twice a day), the Observation were ranged from 24 days to 6 months. The primary outcomes:①Total clinical effective rate;②ALT;③AST;④ALB;⑤TBIL;⑥Incidence of adverse events, ⑦Recurrence rate and liver function. 11 studies [8-18] reported total clinical effectiveness, 8 studies[9,11-17] reported the ALT index, 5 studies [8,11-12,14,16] reported the AST index, 6 studies [8-9,13-15,17] reported the TBIL index, 4 studies [9,13,15,17] reported the ALB index, 4 studies [8,11,14,16] reported the incidence of adverse reactions, and 2 studies [10,17] reported the recurrence rate (Table 1).
Table 1. Basic characteristics of included studies

| Study ID | Sample Size (Experimental/control) | Age | Intervention Experimental treatment | Observation | Outcomes | Risk of bias (low/unclear/high) |
|----------|-------------------------------------|-----|--------------------------------------|-------------|----------|---------------------------------|
| Xu 2018[8] | 45/45 | 48.2±2.2 | 48.3±2.2 | Wuling powder combined with basic western treatment | 1 month | ①③⑤⑥ | High |
| Hu 2007[9] | 36/36 | NA | NA | Wuling powder combined with basic western treatment | 3 months | ①②④⑤ | High |
| He 2013[10] | 60/60 | 46.35±9.34 | 26.1±17.08 | Wuling powder combined with basic western treatment | 3 months | ①③④⑥ | low |
| Gao 2012[11] | 36/17 | 46.9 ± 7.2 | 48.1 ± 6.4 | Wuling powder combined with basic western treatment | 6 months | ①②③④⑤ | unclear |
| Yang 2019[12] | 44/44 | 57.04±5.6 | 49.8±5.2 | Wuling powder combined with basic western treatment | 6 months | ①②③④ | unclear |
| Hou 2019[13] | 67/67 | 59.48±5.9 | 59.5±5.8 | Wuling powder combined with basic western treatment | 24 days | ①②③④⑤ | High |
| Zhao 2013[14] | 56/56 | 49.1±5.1 | 48.9±5.2 | Wuling powder combined with basic western treatment | 6 months | ①②③④⑤ | low |
| Wan 2018[15] | 45/45 | 48.13±2.78 | 48.11±2.74 | Wuling powder combined with basic western treatment | 4 weeks | ①②③④⑤ | unclear |
| Gao 2005[16] | 44/22 | 46.8±2.6 | NA | Wuling powder combined with basic western treatment | 3 months | ①②③④⑤ | unclear |
| Shang 2016[17] | 65/65 | 53.7±4.2 | 53.9±4.1 | Wuling powder combined with basic western treatment | 6 months | ① | low |

3.3 Quality Assessment of Included Studies

The 11 studies [8-18] all reported by randomized, 4 studies [10,14,16,18] were by random number table, 7 studies were not [8-9,10-13,15,17] reported random methods. All studies were not reported random concealment and blinding methods, 2 studies [9,16] reported the shedding cases (Figure 1).

3.3 Results of Meta-Analysis

3.3.1 Total efficacy rate. 11 studies [8-18] reported total efficacy rate, Heterogeneity (P=0.61, I²=0), the wuling powder group can significantly improve clinical efficacy [FE, RR=1.28, 95% CI (1.20, 1.35), P<0.000 1] (Figure 2).
3.3.2 Liver function. In order to ensure the consistency of the study baseline, the study was not included when the liver function indexes of two groups were significantly different before treatment.  

①ALT: 8 studies [9,11-17] reported ALT index, heterogeneity (I²=98%), The ALT in the experimental group was significantly lower [RE,MD=-38.65, 95%CI(-49.10, -28.20), P<0.00001] (Figure 3).  

②AST: 5 studies [8,11-12,14,16] reported AST index, heterogeneity (I²=99%), the AST in the experimental group was significantly lower [RE,MD=-21.83, 95%CI(-39.46, -4.21), P=0.02<0.05](Figure4).  

③TBIL: 6 studies [8-9,13-15,17] reported TBIL, heterogeneity (P<0.00001, I²=88%), the TBIL in the experimental group was significantly lower [RE,MD=-48.98, 95%CI(-73.12, -24.85), P<0.00001] (Figure 5).  

④ALB: 4 studies [9,13,15,17] reported ALB, heterogeneity (P=0.24, I²=28%), the ALB in the experimental group was significantly higher [RE,MD=5.33, 95%CI(4.22,6.43), P<0.00001] (Figure 6).
3.3.3 Incidence of adverse events. 4 studies [8,11,14,16] reported adverse events and adverse reactions. Heterogeneity (P=0.95, I² =0), there was no statistics differences between the two groups(FE,P=0.72>0.05), (Figure 7).

3.3.4 Recurrence rate. 2 studies [10,17] reported recurrence rate, heterogeneity (P=0.95, I² = 0), It was showed that reduce the recurrence rate significantly (FE,P <0.000 01)(Figure 8).

3.3.5 Publication Bias. Funnel plots was reviewed for total efficacy rate , there was a significant bias with Egger’s test (P=0.003<0.05).

4. Discussion
This is a systematic review of 11 RCTs with 1054 participants, The course of treatment was from 24 days to 6 months. The present study indicated that wuling powder can improve the total clinical
efficacy rate, liver function and recurrence rate significantly without significant adverse events, Wuling powder could be used as an alternative drug for the symptom treatment of cirrhotic ascites.

Previous studies showed that if liver cells were damaged, ALT, AST and TBIL will be released in the blood, which will increase the AST and ALT index. In addition, liver function damage will affect ALB synthesis, ALB index will decrease if liver was damaged [20]. This study showed that serum ALT, AST, and TBIL significantly decreased and the ALB index increased in the experimental group after treatment (P < 0.05), it proves that Wuling Powder has a significant improvement on liver function.

The problems of this research: ① Small sample size; ② The risk bias assessment of the included research has a low quality, there was no study used a double-dummy technique to reduce the difference between the two groups ③ Because the follow-up period was ranged from 24 days to 6 months, the long-term safety of Wuling powder for cirrhotic ascites could not be determined. ④ All RCTs were in Chinese and conducted in Chinese population, the generalizability was restricted.

5. Conclusion
Wuling powder combined with basic western medical treatment on cirrhotic ascites can improve clinical effectiveness, liver function and reduce the recurrence rate without significant adverse events. Due to the limited number of patients included in the study and the lack of blindness, more high-quality randomized controlled trials are needed to support it.

Acknowledgments
This work were supported by National Key Research and Development Program Fund (2020YFE0201800); Henan scientifical and technological research project (202102310173); Henan engineering research Center of modern Technology of Zhongjiing Prescription.

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