Iran Red Crescent Med J. 2019 October; 21(10):e94743. doi: 10.5812/ircmj.94743.

Published online 2019 November 2. **Review Article**

Silymarin in Preventing Anti-Tuberculosis and Antipsychotic Drug-Induced Liver Injury at Different Doses and Treatment Times: A Systematic Review

Ying Kun Sheng [1], Lu Zhang [1, **] and Yin Hong [1, *]

[1] Zhejiang Chinese Medicine University, Hangzhou, China

[*] *Corresponding author*: Zhejiang Chinese Medicine University, 311400, Hangzhou, China. Tel: +86-13588159037, Email: georgehongyin@126.com
[**] *Corresponding author*: Zhejiang Chinese Medicine University, 311400, Hangzhou, China. Email: 2738293215@qq.com

Received 2019 June 01; **Revised** 2019 October 09; **Accepted** 2019 October 15.

Abstract

Context: The therapeutic effect, the optimal treatment time, and the dose of silymarin for preventing anti-tuberculosis and antipsychotic drug-induced liver injury (anti-TB/antipsychotic DILI) remains controversial. We conducted the first systematic review and meta-analysis study to evaluate the clinical efficacy of silymarin in the treatment of anti-TB/antipsychotic DILI in several subgroups based on follow-up time and dose.

Evidence Acquisition: We searched the keywords and free words of "silymarin (silibinin)" and "Anti-tuberculosis or antipsychotic drug-induced liver injury" in PubMed, Web of Science, Cochrane, Scopus, and clinicaltrials.gov for full text English articles and China Journal Full-text Database (CNKI) and China Medical Bio-Document Database (CBM) for full text Chinese articles. The searched papers were reserved for randomized controlled trials (RCTs). The Jadad quality scale was used to conduct quality assessments. Two observers (SY and HY) independently extracted the data. MD and OR values were calculated to evaluate the clinical efficacy of silymarin in anti-TB/antipsychotic DILI. The Q test and chi-square test were used for heterogeneity analysis.

Results: Nine RCTs with 2,712 participants (1,351 in the silymarin group and 1,361 in the control group) satisfying the inclusion criteria were finally examined. Compared to the placebo group, silymarin at less than 300 mg/d dose significantly reduced the occurrence of anti-TB/antipsychotic DILI and serum liver enzymes AST and ALT whether for two weeks, four weeks, or eight weeks [pooled OR: 0.53, 95% CI: 0.35 - 0.78, P = 0.42, I^2 = 3%; pooled MD: -4.47, 95% CI: -7.00, -1.93, P = 0.70, I^2 = 0%, AST; pooled MD: -3.50, 95% CI: -6.08, -0.91, P = 0.58, I^2 = 0%, ALT]. However, no significant difference was found in serum liver enzyme TBIL compared to the control group [pooled MD: -0.02, 95% CI: -0.07, -0.04, P = 0.69, I^2 = 0%]. Silymarin at 315 mg/d significantly reduced the occurrence of anti-TB/antipsychotic DILI and serum liver enzymes AST, ALT, and TBIL for eight weeks [subtotal OR: 0.17, 95% CI: 0.08 - 0.39, I^2 = 76%] but no significant difference was found between the over 400 mg/d silymarin group and the control group [subtotal OR: 0.93, 95% CI: 0.20 - 4.39, I^2 = 76%]. No significant difference was found in the occurrence of adverse events compared to the control group [pooled OR: 0.94, 95% CI: 0.71 - 1.25, I^2 = 0%]. Compared to the control group, silymarin prolonged the occurrence of anti-TB/antipsychotic DILI [pooled SMD: 1.78, 95% CI: 1.65 - 1.91, I^2 = 42%].

Conclusions: Silymarin prolonged the occurrence of anti-TB/antipsychotic DILI and reduced the incidence of anti-TB/antipsychotic DILI without significant adverse effects. The optimal treatment time of silymarin to prevent anti-TB/antipsychotic DILI was related to its dose.

Keywords: Anti-Tubercular Agents, Antipsychotic, China, Drug-Induced Liver Injury, Liver Function Tests, Silybin, Silymarin, Systematic Review, Treatment Outcome

1. Context

Drug-induced liver injury (DILI) is a worldwide health problem and is the fifth leading cause of death associated with liver disease (1). It is essentially an adverse reaction to conventional drugs, herbs, dietary supplements, etc. during treatment, especially with anti-tuberculosis and antipsychotic drugs (2, 3). About 1.7 million cases of death in 10.4 million cases of tuberculosis were estimated by the World Health Organization (WHO) (4). The incidence of DILI will continue to increase in the future due to the use of anti-tuberculosis drugs (5, 6).

Silymarin is a remedy for hepatoprotection with antioxidant, anti-inflammatory, anti-fibrotic, and liver protection effects (7-9). Animal and in vitro experiments have demonstrated significant hepatoprotective effects of sily-

Copyright © 2019, Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited

marin on DILI. Ramanathan and Sivanesan reported that 100 mg/kg silymarin significantly improved zidovudine and isoniazid-induced hepatotoxicity in rats (10). Silymarin reduced hepatotoxicity caused by resorcinol and rifampicin by inhibiting glutathione reductase and glutathione peroxidase activity in mice (11). Tasduq et al. (12) confirmed that silymarin could reverse the abnormal increase of liver enzyme indices (including AST and ALT) in anti-tuberculous DILI rats. However, clinically, the therapeutic effect of silymarin on antituberculosis DILI remains controversial. Asgarshirazi et al. (13) reported that silymarin could significantly improve anti-epileptic DILI. Chen et al. (14) reported that silymarin had a preventive effect on DILI due to thioacetamide. A previous study (15) reported that silymarin significantly improved anti-TB DILI. Conversely, randomized clinical trials designed by Marjani et al. (16), Heo et al., Zhang et al. (17) and Gu et al. (18) showed no significant effect of silymarin on anti-TB DILI. Therefore, it is necessary to systematically evaluate the hepatoprotective effect of silymarin on anti-TB DILI.

Recently, Tao et al. (19) in a systematic review, reported that silymarin effectively reduced the occurrence of anti-TB DILI, and the best effect was obtained after four weeks of treatment. However, it is well known that the clinical efficacy of a drug is related not only to the duration of treatment, but also to the administration dose. According to reports, silymarin at 720 mg/d significantly reduced the serum levels of liver enzymes in patients with hepatitis C, while 420 mg/d silymarin had no significant effect (20), suggesting that the dose is a key factor in the hepatoprotective effect of silymarin. Therefore, it is necessary to clarify the role of dose and treatment time in the anti-TB DILI effect of silymarin. Besides, the uncontrolled dose and treatment time of antipsychotic drugs can often cause adverse reactions (21). To date, there is no study evaluating the clinical efficacy of silymarin in preventing antipsychotic DILI. It seems it is time to systematically evaluate the role of dose and treatment time in the anti-TB/antipsychotic DILI effects of silymarin.

We conducted the first systematic review and meta-analysis study to evaluate the clinical efficacy of silymarin in the treatment of anti-TB/antipsychotic DILI in several subgroups based on follow-up time and dose.

2. Evidence Acquisition

2.1. Date Source

Two authors independently searched the literature in PubMed, Scopus, Web of Science, Cochrane, EBSCOhost, clinicaltrials.gov, China Journal Full-text Database (CNKI), Wanfang Database, and China Medical Bio-Documentary Database (CBM). Keywords and free words were as follows: “silymarin” or “silibinin” or “silybum” or “silybin” or “silydianin” or “silychristin” or “milk thistle”, “antituberculosis drug-induced liver injury, antipsychotic drug-induced liver injury” and all results intersected with “randomized controlled trial OR randomized”. The search time was from the establishment of the library to September 2019. The detail of the literature search process is summarized in Figure 1.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) randomized clinical trial, (2) patients receiving antituberculosis treatment, (3) test group treated with silymarin and control group with accepted placebo, (4) Chinese language literature with observations or control groups of more than 100 patients, and (5) incidence, side effects, time of occurrence, AST, ALT, and TBIL with at least one outcome indicator. Meta-analyses, reviews on outcome indicators, meeting abstracts, duplicated studies, and editorial comments were excluded. Two reviewers independently screened relevant articles, and inconsistency was discussed with the third author. The Kappa coefficient was 0.8134.

2.3. Data Extraction

The first author, sample size, intervention methods, treatment time, dosage, and outcome indicators were extracted by two authors (SK and HY). Differences and inconsistencies between the two reviewers were coordinated by the third author (ZL). The Jadad quality scale was used to evaluate the quality of the literature in terms of random sequence generation, allocation concealment, double-blinding, and description of withdrawals and drop-outs. Scores 0 - 3 indicated a low quality and 4 - 7 indicated a high quality.

2.4. Statistical Analysis

The meta-analysis was performed using RevMan 5.0 software. Dichotomous variables of count data were calculated by the Mantel-Haenszed (M-H) method, and the effect size was expressed by the odds ratio (OR) and the 95% confidence interval (CI). Continuous variables were analyzed by the Inverse Variance (IV) method, and the effect value was expressed by the Mean Difference (MD) or Standard Mean Difference (SMD) and 95% CI. The Q test and chi-square test were used for heterogeneity analysis. $P \geq 0.1$, $I^2 \leq 50\%$, combined analysis using the fixed-effect model; $P \leq 0.1$, $I^2 \geq 50\%$, using the random-effects model for combined analysis. Sensitivity analysis was performed to test the influence of a single study on the overall effect size by the leave-one-out method.

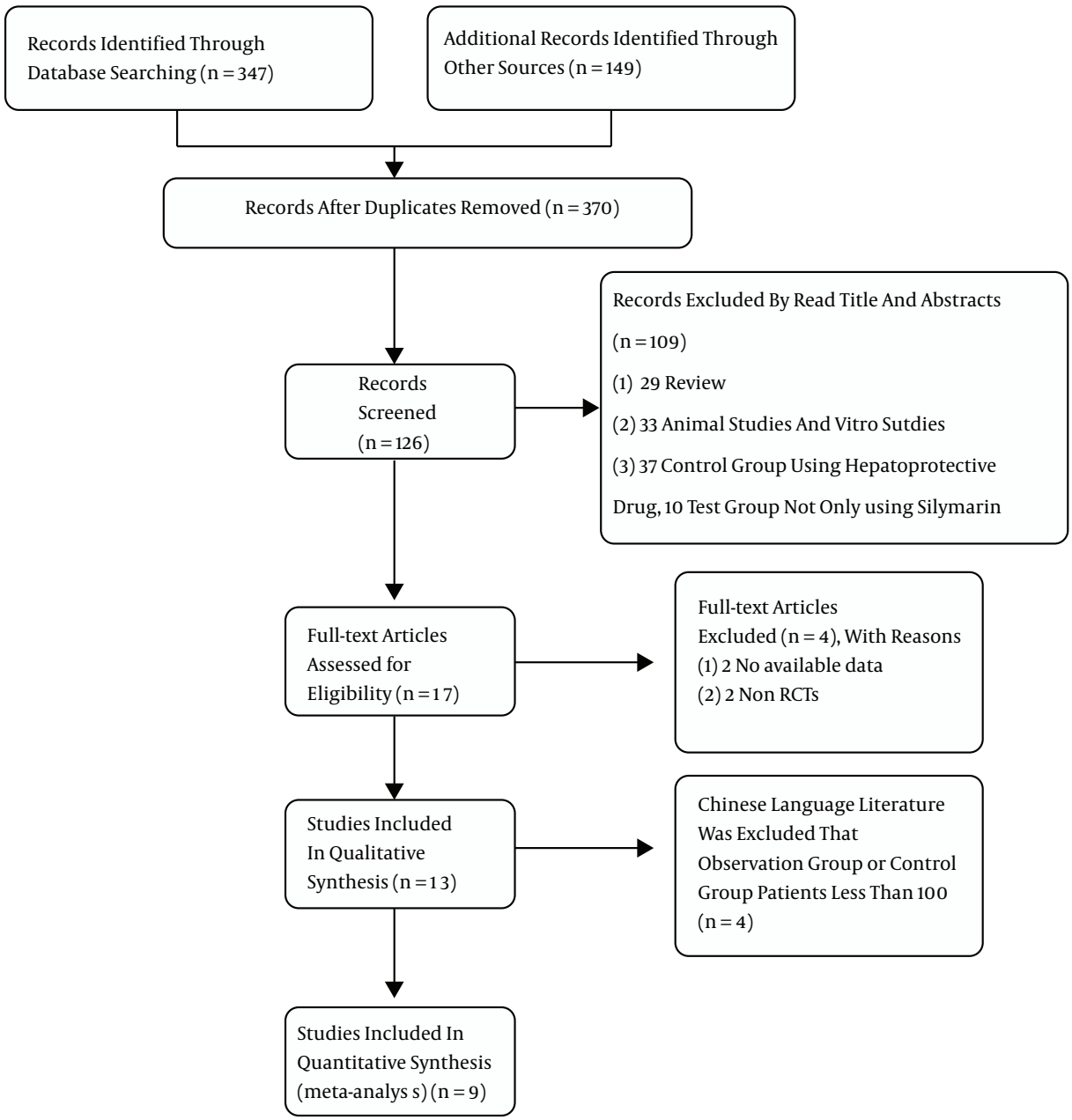

Figure 1. Flow diagram of the study selection process in the meta-analysis

3. Results

3.1. Outcome Studies

Our search retrieved 496 articles related to silymarin or anti-TB/antipsychotic DILI. However, 370 duplicate articles were excluded. By reading the title and the abstract of articles, 109 articles were excluded because of being a review study, animal study, or doing an inappropriate intervention. After reading the full texts, eight articles did not meet the inclusion criteria (no available data, non-RCT, and observations or control groups of less than 100 patients in Chinese language literature), as shown in Table 1. In total, nine studies were included. RCTs were screened independently by two authors (SY and HY) through all databases, as shown in Figure 1.

Table 1. Summary of Quality Evaluation by the Jadad Scale for Clinical Trials of Silymarin Anti-TB/Antipsychotic DILI

Trials	Random Sequence Generation	Allocation Concealment	Double Blinding	Description of Withdrawals and Drop-outs	Score
Luangchosiri et al. (22)	2	2	2	1	7
Marjani et al. (16)	1	2	2	1	6
Heo et al. (15)	2	0	2	1	5
Gu et al. (18)	2	1	0	1	4
Wu et al. (23)	2	1	0	1	4
Ni (24)	1	1	0	1	3
Zhang et al. (17)	2	0	0	1	3
Duan (25)	1	1	0	1	3
Zhang et al. (26)	1	0	0	1	2

3.2. Basic Characteristics of the Study

Nine RCTs with 2,712 participants (1,351 cases in the silymarin group and 1,361 cases in the control group) were evaluated. The first author, study design, sample size, intervention measures, follow-up, dosage, and related outcome indicators are shown in Table 2.

3.3. Result of Data Analysis

Nine studies contributed to the occurrence of anti-TB/antipsychotic DILI analysis and participants were separated into five subgroups with different dosages and follow-up periods. Sensitivity analysis showed that silymarin at less than 300 mg/d significantly reduced the occurrence of anti-TB/antipsychotic DILI, whether it was applied for two weeks, four weeks, or eight weeks [subtotal OR: 0.78, 95% CI (0.41, 1.32), P = 0.56, I^2 = 0% for two weeks; subtotal OR: 0.28, 95% CI (0.13, 0.60), P = 0.28, I^2 = 22% for four weeks; subtotal OR: 0.65, 95% CI (0.31, 1.35), P = 0.60, I^2 = 0% for eight weeks; pooled OR: 0.53, 95% CI (0.35, 0.78), P = 0.42, I^2 = 3%] (Figure 2). Silymarin at 315 mg/d significantly reduced the occurrence of anti-TB/antipsychotic DILI [subtotal OR: 0.17, 95% CI (0.08, 0.39), P = 0.04, I^2 = 76%] for eight weeks but no significant difference was found between the over 400 mg/d silymarin group and the control group [subtotal OR: 0.93, 95% CI (0.20, 4.39), P = 0.02, I^2 = 76%] (Figure 2). No significant difference was found in the occurrence of adverse events between the control and silymarin groups [pooled OR: 0.94, 95% CI (0.71, 1.25), P = 0.46, I^2 = 0%] (Figure 3).

Compare to the control group, 315 mg/d silymarin significantly reduced serum liver enzymes AST, ALT, and TBIL in eight weeks [subtotal MD: -29.00, 95% CI (-31.57, -26.43) for AST; subtotal MD: -124.00, 95% CI (-126.76, -121.24) for ALT; subtotal MD: -12, 95% CI (-12.72, -11.28) for TBIL], all with low heterogeneity (P = 1.00, I^2 = 0%). Silymarin at less than 300 mg/d significantly reduced serum liver enzymes AST and ALT in two weeks, four weeks, and eight weeks [AST subtotal MD: -2.89, 95% CI (-6.87, 1.09) for two weeks; AST subtotal MD: -5.74, 95% CI (-10.69, -0.80) for four weeks; AST subtotal MD: -5.22, 95% CI (-9.92, -0.51) for eight weeks, with low heterogeneity (P > 0.29, I^2 < 10%); ALT subtotal MD: -3.30, 95% CI (-7.15, 0.56) for two weeks; ALT subtotal MD: -3.55, 95% CI (-10.91, 3.80), P = 0.07, I^2 = 70% for four weeks; ALT subtotal MD: -3.48, 95% CI (-10.58, 3.62) for eight weeks, with low heterogeneity (P > 0.61, I^2 = 0%)]. No significant difference was found between the silymarin and placebo groups in terms of TBIL change [TBIL subtotal MD: 0.02, 95% CI (-0.07, 0.11) for two weeks; TBIL subtotal MD: -0.12, 95% CI (-0.50, 0.25) for four weeks; TBIL subtotal MD: -0.02, 95% CI (-0.12, 0.08) for eight weeks, with low heterogeneity (P > 0.61, I^2 = 0%)], as shown in Figure 4.

The time of the occurrence of anti-TB/antipsychotic DILI in the silymarin group and control group was analyzed. The results showed that silymarin prolonged the occurrence time of DILI, which was 1.78 times that of the control group (Figure 5).

3.4. Evaluation of Publication Bias

Considering all nine RCTs, the funnel plot of the occurrence of liver injury in each subgroup was basically symmetrical (Figure 6) with no significant publication bias. However, heterogeneity was found in the subgroups of 315 mg/d for eight weeks and over 400 mg/d.

4. Conclusions

Recently, the hepatoprotective effect of silymarin as a liver-protecting drug has been controversial. Heo et al. (15) reported that silymarin significantly reduced serum biochemical parameters in patients with anti-TB DILI. Fathalah et al. (20) reported that 720 mg/d silymarin significantly reduced the serum liver enzyme index in patients with hepatitis C. However, clinical trial results by Fried et

Table 2. Basic Characteristics of the Included Studies[a]

First Author	Treatment	Control	Follow-up, wk	Dose, mg/d	T/C	Outcome
Wu (23)	Anti-TB+SM	Anti-TB	8	210	118/114	1, 2, 3
Gu (18)	Anti-TB+SM	Anti-TB	8	210	253/255	1, 2, 3
Marjani (16)	Anti-TB+SM	Anti-TB+placebo	2	420	35/35	1, 2
Luangchosiri (22)	Anti-TB+SM	Anti-TB+placebo	4	420	27/28	1, 2
Heo (15)	Anti-TB+SM	Anti-TB+placebo	8	280	45/58	1
Zhang (17)	Anti-TB+SM	Anti-TB	8	400	56/44	1, 2
Ni (24)	Anti-TB+SM	Anti-TB	8	315	216/200	1, 3
Zhang (26)	Anti-TB+SM	Anti-TB	8	315	312/309	1, 2, 3
Duan (25)	Anti-TB+SM	Antipsychotic	8	210	110/108	1

[a]Anti-TB, 2HRZE/4HR; SM, Silymarin; 1, Incidence of liver injury; 2, Adverse event; 3, Liver function indicators.

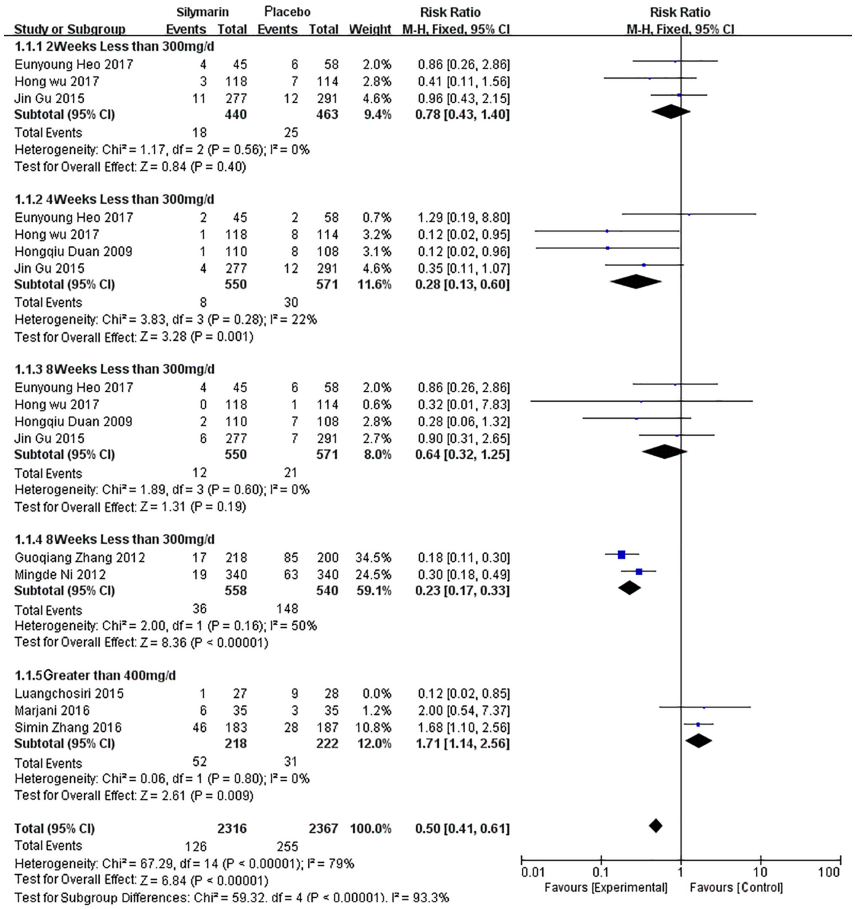

Figure 2. Effect of different dosages and treatment times of silymarin on the occurrence of anti-TB/antipsychotic DILI

al. (27) showed that high doses of silymarin did not significantly reduce the serum ALT levels in patients with chronic hepatitis. A meta-analysis showed that silymarin did not significantly improve serum biochemical parameters in patients with liver disease (28). Therefore, it was important to evaluate whether silymarin has a liver-protecting

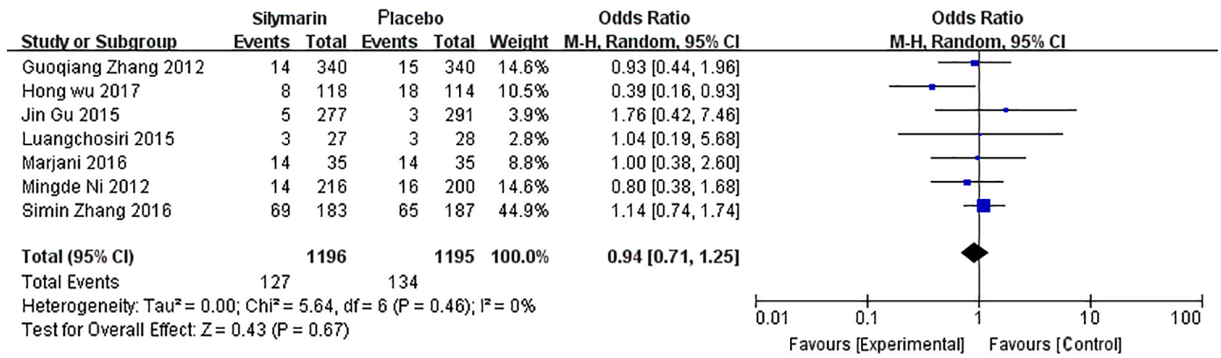

Figure 3. The occurrence of adverse events by silymarin

effect and to determine the dosage of silymarin. Besides, Zhang et al. (17) reported that silymarin had no significant effect on anti-TB DILI, but instead it caused liver damage, suggesting that silymarin may be ineffective in anti-TB DILI. However, Tao et al. (19) reported that silymarin significantly reduced the incidence of anti-TB DILI and for four-week treatment was the best duration to protect the liver. It indicated that the treatment time is one of the effective factors in the treatment of anti-TB DILI with silymarin. Our meta-analysis aimed to systematically evaluate the clinical efficacy of silymarin in the treatment of anti-TB/antipsychotic DILI divided into several subgroups based on follow-up time and dose.

Overall, silymarin significantly reduced the occurrence of anti-TB/antipsychotic DILI compared to the control group and no significant adverse reaction was found. Under the premise of consistent doses, the results were similar to those reported by Tao et al. (19). The optimal treatment time for silymarin for preventing anti-TB/antipsychotic DILI was four weeks. The occurrence of anti-TB/antipsychotic DILI significantly reduced by treatment with 315 mg/d silymarin for eight weeks. It was worth to mention that no significant change was found by treatment with a dose of greater than 400 mg/d (including 400 mg/d and 420 mg/d). There are two possible explanations for the difference. The small sample size may be one of the reasons. Additionally, over 400 mg/d subgroup underwent treatment for two weeks, four weeks, and eight weeks. Different treatment times may have led to inconsistencies between the results obtained by Marjani et al. (16), Zhang et al. (17), and Luangchosiri et al. (22) reported that silymarin effectively inhibited the occurrence of anti-TB DILI, while Marjani et al. (16) and Zhang et al. reported no effect.

Besides, we performed a subgroup analysis of serum liver enzyme indicators in anti-TB/antipsychotic DILI patients. The results showed that the patients' serum liver enzymes significantly reduced by treatment with 315 mg/d silymarin for eight weeks. Serum AST and ALT levels significantly reduced after two weeks, four weeks, and eight weeks by treatment with less than 300 mg/d and TBIL levels significantly reduced after four weeks by treatment with less than 300 mg/d. However, serum TBIL did not change significantly after two weeks and eight weeks by treatment with less than 300 mg/d. It was suggested that silymarin could improve the serum liver enzyme index of anti-TB/antipsychotic DILI patients to a certain extent, which was related to the treatment time. The duration of four weeks was the best time for silymarin to treat anti-TB/antipsychotic DILI without considering the dosage. It may be related to the presence of autoimmunity in anti-TB/antipsychotic DILI patients. According to reports, DILI patients have autoimmune properties, mostly in the first month of treatment for anti-TB DILI (29, 30). That is, the autoimmunity of anti-TB/antipsychotic DILI patients prolonged the time of DILI and silymarin had a little effect on treatment in two weeks.

Indeed, this meta-analysis had some limitations. The RCTs Jadad rating scale scores for the subgroup of 315 mg/d silymarin treatment for eight weeks showed low literature quality (Table 1). In addition, the > 400 mg/d silymarin subgroup comprised of treatment times of two weeks, four weeks, and eight weeks, reducing the reliability of the results. Heterogeneity was found in the subgroup of silymarin treated with 315 mg/d silymarin for eight weeks and a dose of greater than 400 mg/d (Figure 5). Last but not least, five of nine RCTs did not report serum liver enzymes, and only reported the incidence of anti-TB/antipsychotic DILI. Therefore, the efficacy of 315 mg/d and > 400 mg/d silymarin in preventing anti-TB/antipsychotic DILI remains to be further studied.

Above all, silymarin significantly reduced the occurrence of anti-TB/antipsychotic DILI compared to the control group and no significant adverse reaction was found. The optimal treatment time for < 300 mg/d silymarin to

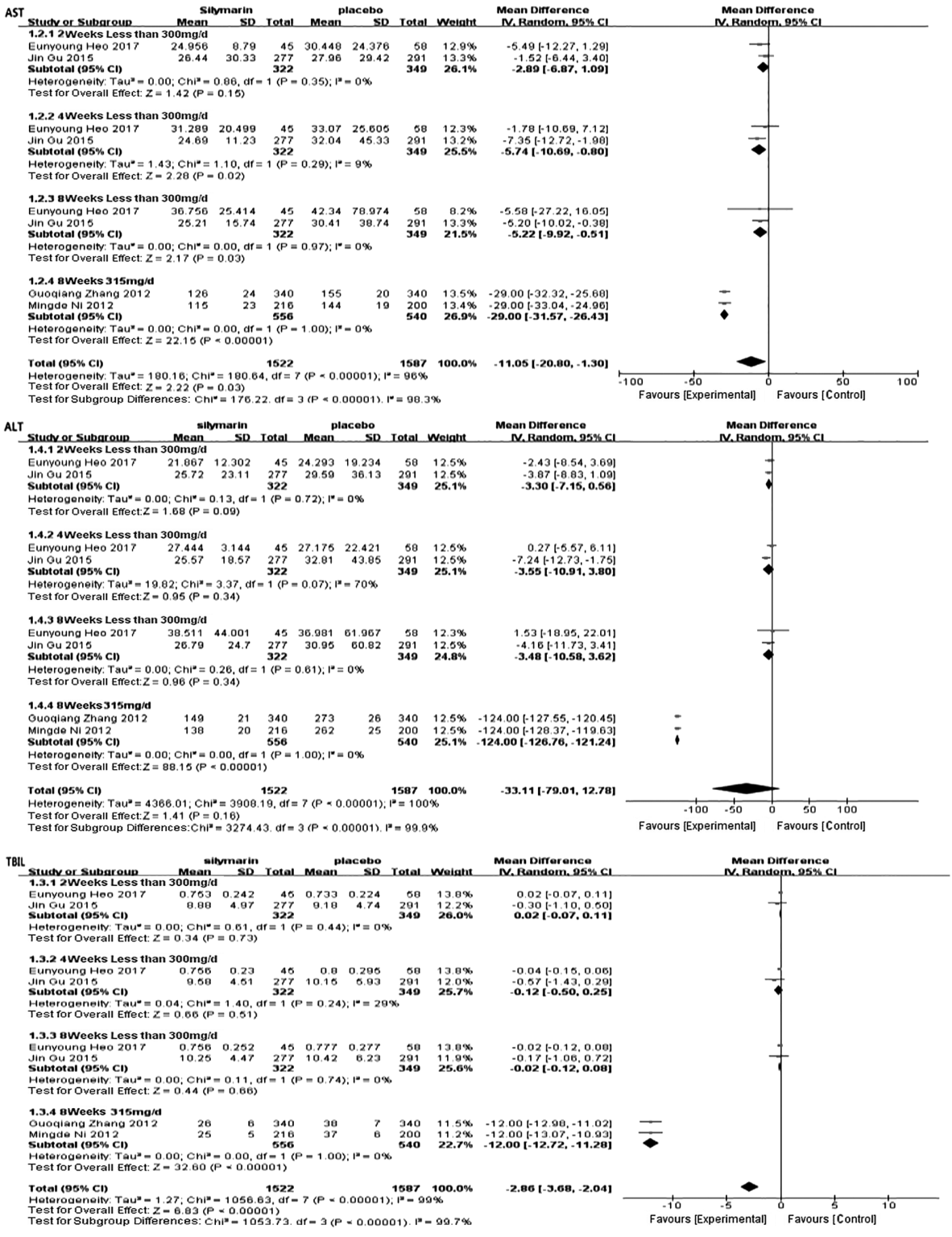

Figure 4. Effect of silymarin on serum liver enzymes AST, ALT, and TBIL

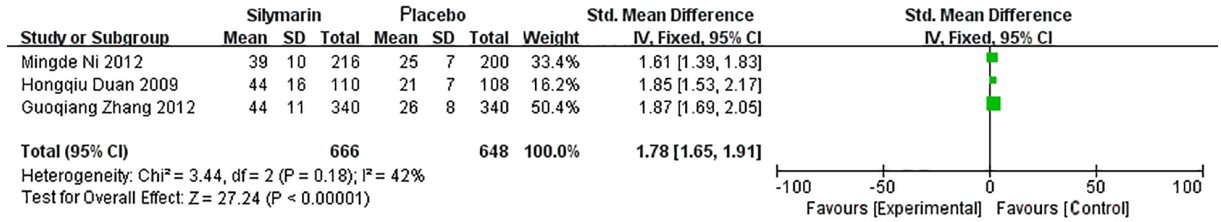

Figure 5. Time of occurrence of anti-TB/antipsychotic DILI in silymarin group and control group

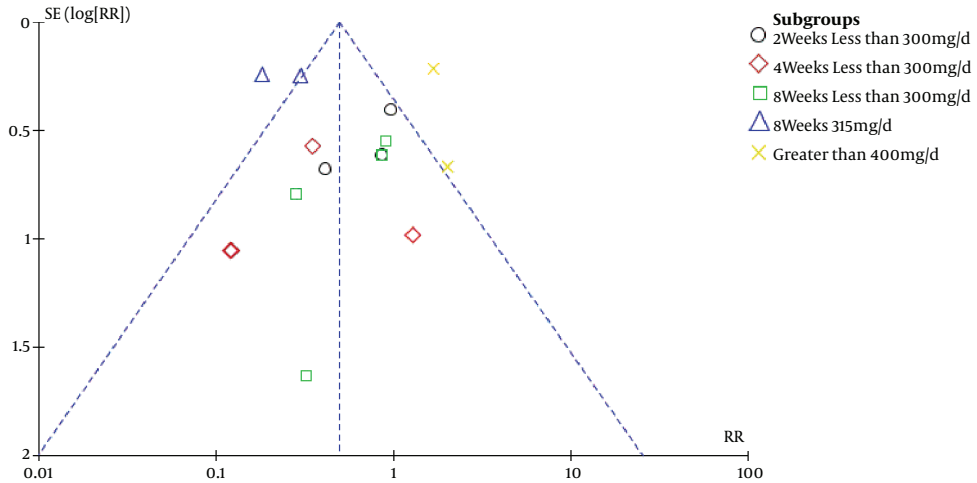

Figure 6. Publication bias of RCTs

prevent anti-TB/antipsychotic DILI was four weeks. Silymarin treatment with 315 mg/d for eight weeks was the best choice and the quality of RCTs was not considered. The optimal treatment time of silymarin to prevent anti-TB/antipsychotic DILI was related to its dose.

Footnotes

Authors' Contribution: Ying Kun Sheng and Lu Zhang proposed the meta-analysis. Ying Kun Sheng and Yin Hong extracted and analyzed the data independently. Lu Zhang was responsible for the potential of disagreements and discordances between Ying Kun Sheng and Yin Hong. Ying Kun Sheng wrote the first draft with the guidance of Yin Hong. Ying Kun Sheng was the guarantor.

Conflict of Interests: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Funding/Support: This study was supported by the Zhejiang Natural Science Foundation of China (LY16H280008).

References

1. Luo G, Shen Y, Yang L, Lu A, Xiang Z. A review of drug-induced liver injury databases. *Arch Toxicol*. 2017;**91**(9):3039–49. doi: 10.1007/s00204-017-2024-8. [PubMed: 28717830].
2. Kuna L, Bozic I, Kizivat T, Bojanic K, Mrso M, Kralj E, et al. Models of drug induced liver injury (DILI) - current issues and future perspectives. *Curr Drug Metab*. 2018;**19**(10):830–8. doi: 10.2174/1389200219666180523095355. [PubMed: 29788883]. [PubMed Central: PMC6174638].
3. Saini N, Bakshi S, Sharma S. In-silico approach for drug induced liver injury prediction: Recent advances. *Toxicol Lett*. 2018;**295**:288–95. doi: 10.1016/j.toxlet.2018.06.1216. [PubMed: 29981923].
4. World Health Organization. *Global Tuberculosis Report 2017*. World Health Organization; 2017.
5. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol*. 2019;**70**(1):151–71. doi: 10.1016/j.jhep.2018.09.014. [PubMed: 30266282].
6. Garcia-Cortes M, Ortega-Alonso A, Lucena MI, Andrade RJ, Spanish Group for the Study of Drug-Induced Liver Disease L. Drug-induced liver injury: A safety review. *Expert Opin Drug Saf*. 2018;**17**(8):795–804. doi: 10.1080/14740338.2018.1505861. [PubMed: 30059261].
7. Hackett ES, Twedt DC, Gustafson DL. Milk thistle and its derivative compounds: A review of opportunities for treatment of liver disease. *J Vet Intern Med*. 2013;**27**(1):10–6. doi: 10.1111/jvim.12002. [PubMed: 23140176].

8. Demiroren K, Basunlu MT, Erten R, Cokluk E. A comparison of the effects of thymoquinone, silymarin and N-acetylcysteine in an experimental hepatotoxicity. *Biomed Pharmacother*. 2018;**106**:1705–12. doi: 10.1016/j.biopha.2018.07.125. [PubMed: 30119245].
9. Hsiang CY, Lin LJ, Kao ST, Lo HY, Chou ST, Ho TY. Glycyrrhizin, silymarin, and ursodeoxycholic acid regulate a common hepatoprotective pathway in HepG2 cells. *Phytomedicine*. 2015;**22**(7-8):768–77. doi: 10.1016/j.phymed.2015.05.053. [PubMed: 26141764].
10. Ramanathan R, Sivanesan K. Evaluation of ameliorative ability of Silibinin against zidovudine and isoniazid-induced hepatotoxicity and hyperlipidaemia in rats: Role of Silibinin in Phase I and II drug metabolism. *Chem Biol Interact*. 2017;**273**:142–53. doi: 10.1016/j.cbi.2017.06.008. [PubMed: 28619387].
11. Upadhyay G, Singh AK, Kumar A, Prakash O, Singh MP. Resveratrol modulates pyrogallol-induced changes in hepatic toxicity markers, xenobiotic metabolizing enzymes and oxidative stress. *Eur J Pharmacol*. 2008;**596**(1-3):146–52. doi: 10.1016/j.ejphar.2008.08.019. [PubMed: 18789925].
12. Tasduq SA, Peerzada K, Koul S, Bhat R, Johri RK. Biochemical manifestations of anti-tuberculosis drugs induced hepatotoxicity and the effect of silymarin. *Hepatol Res*. 2005;**31**(3):132–5. doi: 10.1016/j.hepres.2005.01.005. [PubMed: 15777701].
13. Asgarshirazi M, Shariat M, Sheikh M. Comparison of efficacy of folic acid and silymarin in the management of antiepileptic drug induced liver injury: A randomized clinical trial. *Hepatobiliary Pancreat Dis Int*. 2017;**16**(3):296–302. doi: 10.1016/S1499-3872(16)60142-X. [PubMed: 28603098].
14. Chen IS, Chen YC, Chou CH, Chuang RF, Sheen LY, Chiu CH. Hepatoprotection of silymarin against thioacetamide-induced chronic liver fibrosis. *J Sci Food Agric*. 2012;**92**(7):1441–7. doi: 10.1002/jsfa.4723. [PubMed: 22102319].
15. Heo E, Kim DK, Oh SH, Lee JK, Park JH, Chung HS. Effect of prophylactic use of silymarin on anti-tuberculosis drugs induced hepatotoxicity. *Tuberc Respir Dis (Seoul)*. 2017;**80**(3):265–9. doi: 10.4046/trd.2017.80.3.265. [PubMed: 28747959]. [PubMed Central: PMC5526953].
16. Marjani M, Baghaei P, Kazempour Dizaji M, Gorji Bayani P, Fahimi F, Tabarsi P, et al. Evaluation of hepatoprotective effect of silymarin among under treatment tuberculosis patients: A randomized clinical trial. *Iran J Pharm Res*. 2016;**15**(1):247–52. [PubMed: 27610165]. [PubMed Central: PMC4986122].
17. Zhang S, Pan H, Peng X, Lu H, Fan H, Zheng X, et al. Preventive use of a hepatoprotectant against anti-tuberculosis drug-induced liver injury: A randomized controlled trial. *J Gastroenterol Hepatol*. 2016;**31**(2):409–16. doi: 10.1111/jgh.13070. [PubMed: 26243373].
18. Gu J, Tang SJ, Tan SY, Wu Q, Zhang X, Liu CX, et al. An open-label, randomized and multi-center clinical trial to evaluate the efficacy of Silibinin in preventing drug-induced liver injury. *Int J Clin Exp Med*. 2015;**8**(3):4320–7. [PubMed: 26064348]. [PubMed Central: PMC4443182].
19. Tao L, Qu X, Zhang Y, Song Y, Zhang SX. Prophylactic therapy of silymarin (milk thistle) on antituberculosis drug-induced liver injury: A meta-analysis of randomized controlled trials. *Can J Gastroenterol Hepatol*. 2019;**2019**:3192351. doi: 10.1155/2019/3192351. [PubMed: 30733935]. [PubMed Central: PMC6348824].
20. Fathalah WF, Abdel Aziz MA, Abou El Soud NH, El Raziky MES. High dose of silymarin in patients with decompensated liver disease: A randomized controlled trial. *J Interferon Cytokine Res*. 2017;**37**(11):480–7. doi: 10.1089/jir.2017.0051. [PubMed: 29135373].
21. Amaral L, Kristiansen JE, Viveiros M, Atouguia J. Activity of phenothiazines against antibiotic-resistant Mycobacterium tuberculosis: A review supporting further studies that may elucidate the potential use of thioridazine as anti-tuberculosis therapy. *J Antimicrob Chemother*. 2001;**47**(5):505–11. doi: 10.1093/jac/47.5.505. [PubMed: 11328759].
22. Luangchosiri C, Thakkinstian A, Chitphuk S, Stitchantrakul W, Petraksa S, Sobhonslidsuk A. A double-blinded randomized controlled trial of silymarin for the prevention of antituberculosis drug-induced liver injury. *BMC Complement Altern Med*. 2015;**15**:334. doi: 10.1186/s12906-015-0861-7. [PubMed: 26400476]. [PubMed Central: PMC4580123].
23. Wu H, Li W, An Q, Zhang S, Shen L. Therapeutic effect of shuifeiqibin capsule on prevention of liver injury caused by anti-tuberculosis drugs. *Chin J Antituberc*. 2017;**39**(7):757–60.
24. Ni M. Silibinin capsule for prevention of liver function damage caused by tuberculosis drugs. *Contemp Med*. 2012;**18**(27):7–8.
25. Duan H. Clinical effect of shuifeiqibin capsule on prevention of drug-induced liver injury in hepatitis B VIRUS CARRIERS. *Zhongguo Zhong Yi Yao Zi Xun*. 2009;**1**(4):88.
26. Zhang G, Jia Y, Zhang Y, Dong F. Clinical observationof the effect of Shuifeiqibin Capsule (Shui Linjia) on prevention of liver function damage caused by anti-tuberculosis drugs in hospitalized patients with tuberculosis. *Chin Commun Med*. 2012;**14**(3):77.
27. Fried MW, Navarro VJ, Afdhal N, Belle SH, Wahed AS, Hawke RL, et al. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: A randomized controlled trial. *JAMA*. 2012;**308**(3):274–82. doi: 10.1001/jama.2012.8265. [PubMed: 22797645]. [PubMed Central: PMC3683986].
28. de Avelar CR, Pereira EM, de Farias Costa PR, de Jesus RP, de Oliveira LPM. Effect of silymarin on biochemical indicators in patients with liver disease: Systematic review with meta-analysis. *World J Gastroenterol*. 2017;**23**(27):5004–17. doi: 10.3748/wjg.v23.i27.5004. [PubMed: 28785154]. [PubMed Central: PMC5526770].
29. deLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. *Semin Liver Dis*. 2014;**34**(2):194–204. doi: 10.1055/s-0034-1375959. [PubMed: 24879983].
30. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: Mechanisms and management. *J Clin Exp Hepatol*. 2013;**3**(1):37–49. doi: 10.1016/j.jceh.2012.12.001. [PubMed: 25755470]. [PubMed Central: PMC3940184].