INPLASY PROTOCOL

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None declared.

The effect and toxicity equilibrium of matrine for liver injury: An evidence construction process based on meta-analysis

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Review question / Objective: **The aim of this systematic review is to compare toxicity and protection of matrine in the liver to better inform clinical practice. To this end, the proposed systematic review will address the following question: How to use the matrine more safely and effectively ?**
Condition being studied: **DILI is an adverse reaction of the liver to a drug or its metabolites(Andrade et al., 2019). Epidemiological surveys show that there are about 23.8 cases per 100,000 people of DILI in China, about 19.1 of 100,000 in Iceland and about 13.9 of 100,000 in France (Bjornsson et al., 2013; Sgro et al., 2002; Shen et al., 2019) DILI may cause acute liver failure (ALF) and other serious adverse consequences, even death. In the United States, DILI has become the main cause of ALF, accounting for about 50%(Reuben et al., 2010). Therefore, the efficacy and toxicity of drugs are like a double-edged sword. How to use the double-edge sword more safely and effectively is an urgent problem to solve.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 April 2023 and was last updated on 30 April 2023 (registration number INPLASY202340114).

INTRODUCTION

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Rationale: Meta-analysis, a method of synthesizing multivariate data, allows the results of multiple previous studies to be combined to clarify development patterns. Thus, meta-analysis, combined with dose-time-effect and mechanistic analysis, was used in this study to systematically analyze the hepatoprotective and hepatotoxic effects of MT. This study filled the gap in the current cognition of pharmacology and toxicological effects of MT in liver, and provided strong evidence for follow-up research and safer clinical application.

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METHODS

Participant or population: Rats and mice.

Intervention: Control groups: without matrine; model groups: use matrine.

Comparator: Normal animals or animals with liver injury.

Study designs to be included: The included literature on the bidirectional effects of MT met the following criteria: (1) Population: Rats or mice. (2) The intervention(I) groups received only MT monotherapy. (3) The control(C) groups did not receive treatment or receive non-functional intervention. (4) The included studies contained at least one C group and one I group. (5) There are several studies which links the expression of ALT, AST, SOD, as well as the MDA of liver tissue to the severity of LI. Serum TG, Serum TC, IL-6, TNF-α and CAT were chosen for future investigation as new secondary markers of LI.

Eligibility criteria: The included literature on the bidirectional effects of MT met the following criteria: (1) Population: Rats or mice. (2) The intervention(I) groups received only MT monotherapy. (3) The control(C) groups did not receive treatment or receive non-functional intervention. (4) The included studies contained at least one C group and one I group. (5) There are several studies which links the expression of ALT, AST, SOD, as well as the MDA of liver tissue to the severity of LI. Serum TG, Serum TC, IL-6, TNF-α and CAT were chosen for future investigation as new secondary markers of LI.

Information sources: The retrieved databases included four English databases: PubMed, Web of science, Cochrane library, Embase, as well as four Chinese databases: China National Knowledge Infrastructure (CNKI), WanFang Med Online (WanFang), China Science and Technology Journal Database (VIP), and China Biomedical Literature Service System (SinoMed).

Main outcome(s): Primary outcomes are ALT, AST, SOD and MDA.

Additional outcome(s): Additional outcomes are TG, TC, IL-6, TNF-a, and CAT.

Quality assessment / Risk of bias analysis: Based on the 10-point Collaborative Meta-Analytical Methods and Review of Animal Research Data (CAMARADES) grading scale, which was created in 2004(Macleod et al., 2004), the methodological quality of investigations was appropriate evaluated. Independent assessments of bias risk and methodological quality were performed by two researchers. According to the specificity of this study, the quality metrics were adjusted. When there was a disagreement in the assessment, the correspondence author reached consensus or arbitration.

Strategy of data synthesis: The researchers used STATA version 16.0 software for meta-analysis. Moreover, the p-value should below 0.05 (p50%] or fixed-effects model [I2≤50%]). And when I2 was greater than 50%, the result was judged to have significant heterogeneity. To determine the source of heterogeneity, researchers performed subgroup analyses for animal species (rat, mouse), dose administered (low (L)≤25mg/kg, 2550mg/kg), and time of administration (<4w and ≥4w). Sensitivity analysis was used to determine whether the results were reliable enough to draw conclusions. Besides, the Egger's test was used to identify publication bias and in the presence of publication bias, |t|-value should be less than 0.05.

Subgroup analysis: To determine the source of heterogeneity, researchers performed subgroup analyses for animal species (rat, mouse), dose administered (low (L)≤25mg/kg, 2550mg/kg), and time of administration (<4w and ≥4w).

Sensitivity analysis: In mouse models, the sensitivity of ALT, AST, SOD, and MDA levels to detect LI was not significantly different. Egger's test was approximated to determine publication bias using the |t|-value. The |t| values of these four indicators did not lead to publication bias in studies on LI. (ALT, |t| = |-1.79|; AST, |t|= |-1.92|; SOD, |t| = |3.26|; MDA, |t| = |-4.08|).

Country(ies) involved: China.

Keywords: Matrine; Natural products; Hepatotoxicity; Hepatoprotection; Meta-analysis

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