INPLASY PROTOCOL

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None declared.

The efficacy and toxicity equilibrium of emodin for liver injury: A dynamic systematic review and meta-analysis

Hu, SH[1].

Review question / Objective: **To study the efficacy and toxicity equilibrium of emodin in liver injury and review its mechanisms, so as to provide guidance for clinic.**
Condition being studied: **Liver injury is a common pathological process of liver disease, mainly caused by alcohol, drug toxicity, viral infection etc. After exposure to the causative agents of liver injury, a series of corresponding inflammatory signaling pathways will be activated, triggering oxidative stress response, leading to the activation of hepatic stellate cells (HSCs) and the production of excess extracellular matrix (ECM). If the above process is not effectively controlled, it may further develop into fibrosis, cirrhosis and even liver cancer. Currently, liver disease is affecting the life and health of human beings around the world. Given that the early symptoms of liver disease are not obvious, diagnosis is usually made when the disease has already entered the stage of fibrosis or even cirrhosis, at which time the appropriate treatment becomes limited and difficult. Advanced liver disease is usually only effectively treated with liver transplantation. In conclusion, finding promising new drugs and taking timely interventions to prevent or treat liver injury in the early stage or before the occurrence of it are meaningful directions for clinical prevention and treatment for liver disease.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2023 and was last updated on 31 March 2023 (registration number INPLASY202330123).

INTRODUCTION

Review question / Objective: **To study the efficacy and toxicity equilibrium of emodin in liver injury and review its mechanisms, so as to provide guidance for clinic.**

Rationale: The effects of emodin on treatment and induction of liver injury were quantitatively synthesized by meta-analysis, and the potential mechanisms of its hepatoprotect orion hepatotoxicity were systematically reviewed, time/dose and efficacy/toxicity analyses were performed to further delineate the effective and toxic range.

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METHODS

Search strategy: In order to obtain objective, accurate and persuasive research results, and facilitate other researchers to retrieve and repeat this study, four English databases with overall high-quality literature were selected for retrieval. All the potential preclinical studies on Cochrane library, EMBASE, PubMed and Web of Science were searched from the establishment of the database to April 2023. A combination of free-text and mesh terms were used to identify diseases and intervention agent: “Liver Injury” and “Emodin”. Ultimately, studies will be classified according to whether emodin is used to treat or induce liver injury for subsequent analysis.

Take pubmed retrieval as an example:

#1: (Emodin) OR "Emodin"[Mesh] OR (Frangulic Acid[Title/Abstract]) OR (Frangula Emodin[Title/Abstract])) OR (Emodin, Frangula[Title/Abstract])) OR (Rheum Emodin[Title/Abstract])) OR (Emodin, Rheum[Title/Abstract])) OR (Archin[Title/Abstract])) OR (Peristim[Title/Abstract])

#2: (Chemical and Drug Induced Liver Injury) OR "Chemical and Drug Induced Liver Injury"[Mesh]OR(Chemically-Induced Liver Toxicity[Title/Abstract]) OR (Chemically Induced Liver Toxicity[Title/Abstract])) OR (Chemically-Induced Liver Toxicities[Title/Abstract])) OR (Liver Toxicities, Chemically-Induced[Title/Abstract])) OR (Liver Toxicity, Chemically-Induced[Title/Abstract])) OR (Toxicities, Chemically-Induced Liver[Title/Abstract])) OR (Toxicity, Chemically-Induced Liver[Title/Abstract])) OR (Drug-Induced Acute Liver Injury[Title/Abstract])) OR (Drug Induced Acute Liver Injury[Title/Abstract])) OR (Liver Injury, Drug-Induced, Acute[Title/Abstract])) OR (Acute Liver Injury, Drug-Induced[Title/Abstract])) OR (Acute Liver Injury, Drug Induced[Title/Abstract])) OR (Hepatitis, Toxic[Title/Abstract])) OR (Toxic Hepatitis[Title/Abstract])) OR (Hepatitides, Toxic[Title/Abstract])) OR (Toxic Hepatitides[Title/Abstract])) OR (Drug-Induced Liver Disease[Title/Abstract])) OR (Disease, Drug-Induced Liver[Title/Abstract])) OR (Diseases, Drug-Induced Liver[Title/Abstract])) OR (Drug Induced Liver Disease[Title/Abstract])) OR (Drug-Induced Liver Diseases[Title/Abstract])) OR (Liver Disease, Drug-Induced[Title/Abstract])) OR (Liver Diseases, Drug-Induced[Title/Abstract])) OR (Drug-Induced Liver Injury[Title/Abstract])) OR (Drug Induced Liver Injury[Title/Abstract])) OR (Drug-Induced Liver Injuries[Title/Abstract])) OR (Injuries, Drug-Induced Liver[Title/Abstract])) OR (Injury, Drug-Induced Liver[Title/Abstract])) OR (Liver Injuries, Drug-Induced[Title/Abstract])) OR (Liver Injury, Drug-Induced[Title/Abstract]))

OR (Liver Injury, Drug Induced[Title/Abstract])) OR (Hepatitis, Drug-Induced[Title/Abstract])) OR (Drug-Induced Hepatitides[Title/Abstract])) OR (Drug-Induced Hepatitis[Title/Abstract])) OR (Hepatitides, Drug-Induced[Title/Abstract])) OR (Hepatitis, Drug Induced[Title/Abstract])
#3: #1 AND #2 (This is the retrieval formula).

Participant or population: Since there are two analyses, they are divided as follows. Hepatoprotection studies: rodent models of liver injury established in recognized manners; Hepatotoxicity studies: healthy rodents (no liver injury modeling).

Intervention: The group of interventions received monotherapy with emodin at any dose (the dose here will then be counted and divided into high and low doses), whether for hepatoprotection and hepatotoxicity studies.

Comparator: In the study of hepatoprotection of emodin, it was compared with animals given the same amount of non-functional substance or no treatment on the basis of liver injury model; in the study of hepatotoxity of emodin, it is the same.

Study designs to be included: All potential preclinical studies investigating emodin for treatment of liver injury, induction of liver injury, or both will be included.

Eligibility criteria: As shown below, inclusion criteria based on the PICO principles were used to identify appropriate researches: (1) Participant(P): in hepatoprotection studies, participants should be rodent models of liver injury established in recognized manners; in hepatotoxicity studies, it should be healthy rodents (no liver injury modeling) (2) Intervention(I): the experimental group received monotherapy with emodin at any dose; (3) Control(C): in the study of emodin treating liver injury, it was compared with animals given the same amount of non-functional substance or no treatment on the basis of liver injury model; in the study of emodin aggravating liver injury, healthy animals were used as controls. in the study of emodin treating liver injury, the model group was given the same amount of non-functional substances or no treatment on the basis of the liver injury model; while in the study of emodin aggravating liver injury, liver injury model was used as control; (4) Outcome(O): in the study of emodin in the treatment of liver injury, the primary outcome indicators were ALT, AST, TBIL and ALP, and the secondary outcome indicators were serum TNF-α, SOD, MDA, TG, IL-1β and IL-6; in the study of emodin aggravating liver injury, the primary outcome indicators were ALT, AST, and TBA, while the secondary outcome indicators was MPR2.The following were the exclusion criteria: (1) Participant (P): target disease was not liver injury, or animal models were non-rodent ; (2) Intervention：not treated with emodin alone; (3) Control (C): compared with other treatment options with unclear efficacy (such as western medicine, Chinese medicine or combination therapy) (4) Results (O): prespecified primary or secondary outcome indicators were missing or data were unavailable; (5) Research design and form: clinical trials, reviews, conference reports and other non-targeted preclinical studies in vivo; (6) unpublished data or duplicated literature.

Information sources: All the potential preclinical studies on Cochrane library, EMBASE, PubMed and Web of Science were searched from the establishment of the database to Aprial 2022. If information is missing or in doubt, attempts will be made to contact the corresponding author to refine the information.

Main outcome(s): Appropriate criteria (for example, if there are more than three groups of data for an indicator, input and analysis will be made) will be formulated according to the data obtained from the exclusion to extract the data. The main potential outcome indicators are: Serum ALT level; Serum AST leve; Serum TBiL level; Serum TBA level; …etc
These data will be recorded in detail, including the corresponding dosing time

and dose, and if different doses (e.g. 20/40/60 mg/kg) exist in the same study, only the maximum dose set will be recorded.
Ultimately, the systematic review will be based on the included animal studies and other relevant and necessary literature to sort out the potential mechanisms of the hepatoprotection and hepatotoxicity of emodin as comprehensively as possible.

Additional outcome(s): Outcome indicators such as specific target pathways related to this study will be included as secondary outcome indicators. In order to ensure scientific statistics, the criteria are consistent with the above primary outcome indicators.

Quality assessment / Risk of bias analysis: The SYstematic Review Center for Laboratory Animal Experimentation (SYRCLE) animal laboratory bias risk assessment tool was used to assess the risk of bias in the preclinical literature on hepatoprotection/hepatotoxicity of emodin in liver injury.
It is composed of ten projects, the final evaluation results for "yes" and "no" and "uncertain". "Yes" indicates a low risk of bias, "no" indicates a high risk of bias, and " uncertain " indicates that there is an uncertain risk of bias. The quality assessment of preclinical studies includes the following 10 aspects: (1) generation or full application of allocation sequence; (2) the baseline of each group was the same; (3) adequate concealment of allocation; (4) animals were randomly placed during the experiment; (5) the researchers were blinded; (6) animals were randomly selected; (7) assessors were blinded; (8) complete processing of incomplete data; (9) The selective outcomes of these studies were not reported; (10) there were no other issues in the study that might cause a high risk of bias. When faced with disagreements in the research, the corresponding author will give consensus or arbitration.

Strategy of data synthesis: STATA 16 was used for statistical analyses. The extracted outcome measures were continuous variables, so their combined total effect size was expressed as standardized mean difference (SMD) and 95% confidence interval (CI). P-value<0.05 (P<0.05) indicated that the difference between the experimental group and the control group was statistically significant. I-square (I2) was used to evaluate the heterogeneity of researches. When I2 was higher than 50%, the results were considered to have high heterogeneity. Given the exploratory nature of the animal studies, random effects models were used regardless of whether I2 was greater than or less than 50%.

Subgroup analysis: Subgroup analysis will be conducted based on the species of the animal model (rat or mouse), dose of administration (high or low dose), and duration of administration (long or short time).

Sensitivity analysis: Sensitivity analyses will b performed to assess whether the study results were robust enough to draw conclusions.

Language restriction: Yes, only the four main databases listed above were searched, which means the language is mostly English.

Country(ies) involved: China.

Keywords: Emodin; Hepatoprotection; Hepatotoxicity; Meta-analysis; Preclinical studies.

Contributions of each author:
Author 1 - Sihan Hu.

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