INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest: **No.**

Effects of artemisinin on proliferation and apoptosis of human liver cancer HepG2 cells: a protocol of systematic review and meta-analysis

Li, J[1]; Liu, ZY[2]; Yu, HB[3]; Xue, Q[4]; Qu, XS[5].

Review question / Objective: **Is artemisinin effective on proliferation and apoptosis of human liver cancer HepG2 cells(HLCHG-2C)?**
Condition being studied: **Artemisinin; human liver cancer HepG2 cells.**
Information sources: **Electronic databases will be systematically searched potential studies in MEDLINE, Scopus, Web of Science, Cochrane Library, EMBASE, WANGFANG and China National Knowledge Infrastructure from their initiation to the February 29, 2020, regardless language and publication time restrictions. We will include all potential case-controlled studies (CCSs) or randomized controlled studies (RCSs) that identified the effects of artemisinin on proliferation and apoptosis of HLCHG-2C. A search strategy sample for MEDLINE is summarized. We will also provide similar search strategies for other electronic databases. In addition, we will examine other sources to avoid missing more potential studies, such as Google Scholar, reports on related agencies, conference proceedings, and reference lists of relevant reviews.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 April 2020 and was last updated on 13 April 2020 (registration number INPLASY202040075).

INTRODUCTION

Review question / Objective: **Is artemisinin effective on proliferation and apoptosis of human liver cancer HepG2 cells(HLCHG-2C)?**

Condition being studied: **Artemisinin; human liver cancer HepG2 cells.**

METHODS

Participant or population: **This study will include HLCHG-2C as its targeted subject.**

Intervention: **In the experimental group, all HLCHG-2C were managed using artemisinin. However, we will exclude**

studies that utilized combination of artemisinin with other treatments.

Comparator: In the control group, all treatments options were available for HLCHG-2C. However, we will not consider studies employed any types of artemisinin as their control managements.

Study designs to be included: e will include case-controlled studies(CCSs) or randomized controlled studies(RCSs) that explore effects of artemisinin on HLCHG-2C.

Eligibility criteria: This study will include all potential CCSs or RCSs exploring the effects of artemisinin vs. other comparators on proliferation and apoptosis of HLCHG-2C.

Information sources: Electronic databases will be systematically searched potential studies in MEDLINE, Scopus, Web of Science, Cochrane Library, EMBASE, WANGFANG and China National Knowledge Infrastructure from their initiation to the February 29, 2020, regardless language and publication time restrictions. We will include all potential case-controlled studies (CCSs) or randomized controlled studies (RCSs) that identified the effects of artemisinin on proliferation and apoptosis of HLCHG-2C. A search strategy sample for MEDLINE is summarized. We will also provide similar search strategies for other electronic databases. In addition, we will examine other sources to avoid missing more potential studies, such as Google Scholar, reports on related agencies, conference proceedings, and reference lists of relevant reviews.

Main outcome(s): Primary outcome is proliferation and apoptosis of HLCHG-2C. Its proliferation is examined by cell viability test, and its apoptosis is detected by flow cytometry.

Additional outcome(s): Secondary outcomes are included HLCHG-2C proliferation and apoptosis related-proteins and genes expression. The proteins (including β-catenin, PTEN, Akt, CyclinD1, P27, Bax, Bcl-2, Caspase-3, Caspase-9, Cytochrame-C, and PCNA) are measured by immunofluorescence or western blot test. The genes (including Mcl-1 and Caspase-3) are identified by Real-time polymerase chain reaction or relevant test.

Data management: Before data collection, a standardized data extraction sheet will be developed to collect relate study data from all eligible studies. Two investigators will independently collect following data: publication information (along with author name and publication time), HLCHG-2C information, study setting and design, interventions and comparators (such as names and types of managements, dosage, et al), outcomes, results, findings, and conflict of interest. Any disagreements will be worked out by consultation with another investigator. Any insufficient or missing information will be obtained from original authors by email or telephone.

Quality assessment / Risk of bias analysis: The study quality will be independently appraised by two investigators using Newcastle-Ottawa Scale for CCSs and Cochrane risk of bias tool for RCSs. Any different opinions will be arbitrated with another investigator.

Strategy of data synthesis: This study will apply RevMan 5.3 software to synthesize and analyze extracted data. We will calculate treatment effects of pooled dichotomous data as risk ratio and 95% confidence intervals (CIs), and synthesized continuous data as weighted mean difference or standardized mean difference and 95% CIs. Heterogeneity across studies will be assessed using Higgins I^2 statistic. $I^2 \leq 50\%$ is considered as having minimal heterogeneity and data will be pooled using a fixed-effects model, while $I^2 > 50\%$ is regarded as suggesting substantial heterogeneity and data will be synthesized using a random-effects model. When there is minimal heterogeneity, we will arrange to conduct a meta-analysis if possible. Otherwise, when there is significant heterogeneity, we will carry out a subgroup analysis to investigate possible sources of substantial heterogeneity.

Subgroup analysis: If necessary, this study will carry out a subgroup analysis to test the sources of heterogeneity in accordance with the different types of studies, study quality, and intervention and controls.

Sensibility analysis: Whenever possible, this study will also conduct a sensitivity analysis to examine the robustness and stability of study findings by removing low quality studies.

Country(ies) involved: China.

Keywords: Artemisinin; human liver cancer HepG2 cells; effect.