INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy of Artemisinin and its derivatives in animal models of type 2 diabetes mellitus: A protocol for systematic review and meta-analysis

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Review question / Objective: **The aim of this study is to conduct a comprehensive systematic evaluation and meta-analysis to analyze the antidiabetic effects and safety of artemisinin and its derivatives on T2DM by pooling relevant animal studies.**

Eligibility criteria: **The following inclusion criteria based on PICO principle will be used to identify appropriate studies: (1) Participants: T2DM model animals; (2) intervention: artemisinin or artemisinin derivatives; (3) comparison: the control group was untreated- controlled or vehicle-controlled; (4) outcomes: outcome parameter included at least one of fasting plasma glucose (FPG), glycated hemoglobin A1c(HbA1c), 2h plasma glucose in intraperitoneal glucose tolerance test (2hPG in IPGTT), 2h plasma glucose in intraperitoneal insulin tolerance test (2hPG in IPITT), area under the curve in intraperitoneal glucose tolerance test (AUC in IPGTT), area under the curve in intraperitoneal insulin tolerance test (AUC in IPITT), serum insulin, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), urine volume, body weight. The exclusion criteria are: (1) in-vitro studies or clinical trials; (2) the test group was treated concurrently with OHAs or insulin; and (3) the control group was treated with any other therapeutic drugs.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 July 2021 and was last updated on 26 July 2021 (registration number INPLASY202170084).

INTRODUCTION

Review question / Objective: **The aim of this study is to conduct a comprehensive systematic evaluation and meta-analysis to analyze the antidiabetic effects and safety of artemisinin and its derivatives on T2DM by pooling relevant animal studies.**

Condition being studied: **According to the IDF Diabetes Atlas (9th edition), approximately 463.0 million adults aged**

20-79 years worldwide (9.3% of all adults in this age group) have diabetes mellitus (DM), and it is estimated that this number will increase to 700.2 million (10.9%) in 2045. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for approximately 90% of all diabetes worldwide. The etiology and pathogenesis of T2DM are not completely understood, but its most significant pathophysiology is characterized by insulin resistance and pancreatic β-cells dysfunction. T2DM and its complications are strongly associated with an increasing burden of disability and mortality worldwide, approximately 4.2 million adults are estimated to die as a result of DM and its complications in 2019, which is equivalent to one death every eight seconds. Oral hypoglycemic agents (OHAs) are the main treatment for T2DM, but these OHAs are often associated with various adverse events and secondary failures. Artemisinin was first extracted from Artemisia annua L. by Chinese scientist Youyou Tu, and is considered as the first prioritized recommendation for malaria treatment by the World Health Organization. For her contribution to the extraction, purification and testing of artemisinin, Youyou Tu was awarded the 2015 Nobel Prize in Physiology or Medicine. As research continues, a variety of artemisinin derivatives have been discovered (including artemether, artesunate, artelinic acid, dihydroartemisinin, and arteether), and all of them have shown antimalarial potential. Interestingly, increasing evidence has shown that artemisinin and its derivatives also exhibit therapeutic effects on T2DM. The antidiabetic effects of artemisinin family were mainly studied mainly in animal and cell models, current evidence suggests that artemisinin and its derivatives can alleviate T2DM by improving insulin resistance, restoring the function of islet cells, and promoting the trans-differentiation of islet α-cells to β-cells. To date, there is no meta-analysis based on preclinical studies to synthesize evidence on the effects of artemisinin and its derivatives in treating T2DM.

METHODS

Search strategy: Two authors will independently search fourteen electronic databases (PubMed, Embase, Web of Science, Scopus, CINAHL, OpenGrey, Google Scholar, PsycInfo, British Library Ethos, ProQuest Dissertations & Theses, China National Knowledge Internet, VIP Information Chinese Periodical Service Platform, Chinese Biomedicine Literature Database, and Wanfang Data Knowledge Service Platform) to identify relevant animal studies from inception till July 2021. The search will be performed with MeSH and free-text words appropriately adapted for each database. There will be no restrictions on the language and year of publication.

Participant or population: T2DM model animals.

Intervention: Artemisinin or artemisinin derivatives.

Comparator: The control group was untreated- controlled or vehicle-controlled.

Study designs to be included: Animal studies.

Eligibility criteria: The following inclusion criteria based on PICO principle will be used to identify appropriate studies: (1) Participants: T2DM model animals; (2) intervention: artemisinin or artemisinin derivatives; (3) comparison: the control group was untreated- controlled or vehicle-controlled; (4) outcomes: outcome parameter included at least one of fasting plasma glucose (FPG), glycated hemoglobin A1c(HbA1c), 2h plasma glucose in intraperitoneal glucose tolerance test (2hPG in IPGTT), 2h plasma glucose in intraperitoneal insulin tolerance test (2hPG in IPITT), area under the curve in intraperitoneal glucose tolerance test (AUC in IPGTT), area under the curve in intraperitoneal insulin tolerance test (AUC in IPITT), serum insulin, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), urine volume, body weight. The exclusion criteria are: (1) in-vitro studies or clinical trials; (2)

the test group was treated concurrently with OHAs or insulin; and (3) the control group was treated with any other therapeutic drugs.

Information sources: Two authors will independently search fourteen electronic databases (PubMed, Embase, Web of Science, Scopus, CINAHL, OpenGrey, Google Scholar, PsycInfo, British Library Ethos, ProQuest Dissertations & Theses, China National Knowledge Internet, VIP Information Chinese Periodical Service Platform, Chinese Biomedicine Literature Database, and Wanfang Data Knowledge Service Platform) to identify relevant animal studies.

Main outcome(s): Fasting plasma glucose (FPG).

Additional outcome(s): Glycated hemoglobin A1c(HbA1c), 2h plasma glucose in intraperitoneal glucose tolerance test (2hPG in IPGTT), 2h plasma glucose in intraperitoneal insulin tolerance test (2hPG in IPITT), area under the curve in intraperitoneal glucose tolerance test (AUC in IPGTT), area under the curve in intraperitoneal insulin tolerance test (AUC in IPITT), serum insulin, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), urine volume, and body weight.

Data management: EndNote software (Version X9) will be used to manage the retrieved literature. After deduplication, two independent authors will screen the retrieved studies according to the inclusion and exclusion criteria. First, the titles and abstracts will be investigated, and then the full-texts of relevant studies will be reviewed to assess their suitability for meta-analysis. Any discrepancies will be resolved by discussion with the corresponding author. Subsequently, an Excel form will be created based on the following items: year of publication, first author, country, species of model, age, weight, types of artemisinins, intervention (dosage form, dosage, and duration of treatment), sample size (test group/control group), outcomes at the baseline and at the end of the intervention, safety parameter and adverse event. For the outcome indicators presented graphically, GetData Graph Digitizer software (Version 2.26) will be used to extract the data.

Quality assessment / Risk of bias analysis: Two investigators will independently assess the quality of the included studies using the SYRCLE's risk of bias tool. The contents of the evaluation will cover five domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each entries will be assigned a judgment of low, high, or unclear risk of bias. Any discrepancies will be resolved by consultation with the corresponding author.

Strategy of data synthesis: All meta-analyses will be performed using Revman software (Version 5.3). The random-effect model will be applied to pool the effect sizes due to the differences in the experimental design of animal studies. As the major outcomes are continuous variables, the effect sizes will be expressed using the weighted mean difference (WMD) and 95% confidence interval (95% CI). Statistical significance will be set at $P < 0.05$. I2 and Cochrane's Q statistics will be used to assess the heterogeneity of the included studies, $I2 > 50\%$ and PQ-test < 0.1 indicate that there is significant heterogeneity. Potential publication bias will be assessed via Egger's linear regression test using Stata software (Version 15.0).

Subgroup analysis: Subgroup analyses will be conducted based on species of model and type of artemisinins when heterogeneity is significant.

Sensitivity analysis: Sensitivity analysis will be used to evaluate the stability of the overall results by sequentially removing each trial.

Language: There will be no restrictions on the language.

Country(ies) involved: China.

Keywords: Artemisinin; artemisinin derivatives; type 2 diabetes mellitus; meta-analysis.

Dissemination plans: All the results of this meta-analysis will be published in a peer-reviewed journal.

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