Effect of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy
A protocol of systematic review and meta-analysis
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Abstract
Background: This systematic review aims to assess the effect of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy.
Methods: We will search Cochrane Library, PUBMED, EMBASE, CINAHL, Web of Science, Google Scholar, PsycINFO, WANGFANG, VIP, CBM, and CNKI from their inceptions to the March 31, 2020, without language restrictions. Two authors will independently carry out searching literature records, scanning titles and abstracts, full texts, collecting data, and assessing risk of bias. RevMan 5.3 software will be used for statistical analysis.
Results: This systematic review will investigate whether cinnamaldehyde is effective on Cav-1 and Survivin expression in epilepsy.
Conclusion: Its findings will provide helpful evidence for the effect of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy.
Systematic review registration: INPLASY202040152.
Abbreviations: CCSs = case-controlled studies, CIs = confidence intervals, RCTs = randomized controlled trials.
Keywords: Cav-1, cinnamaldehyde, effect, epilepsy, survivin

1. Introduction
Epilepsy is one of the most common chronic neurological diseases,[1−4] which is characterized by an enduring predisposition to generate seizures.[5] It can affect people of any ages, irrespective their races, economic status, educational background, social class, and geographical locations.[6−11] Many factors can provoke and induce this condition, including neurobiologic, cognitive, psychological, and social consequences.[12−15] Although lots of treatments are available for seizures, its efficacy is limited.[16−19] Thus, it is still very important to explore more effective medications for this disorder.
Previous studies have found that Cav-1 and Survivin has association with epilepsy, [20−25] and several studies have examined cinnamaldehyde the affect Cav-1 and Survivin expression in epilepsy, [25,26] which can help find out new potential medications for epilepsy. However, all their conclusions are based on the single study and no study has been conducted to address this topic comprehensively and systematically. Thus, this study will explore the effect of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy.

2. Methods
2.1. Study registration
This study was registered and funded on INPLASY202040152. It has been reported based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol statement.[27,28]

2.2. Criteria for considering studies for this review
2.2.1. Types of studies. This study will only consider case-controlled studies (CCSs) of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy. However, studies of nonclinical studies and noncontrolled trials will be excluded in this study.
2.2.2. Types of subjects. This systematic review will include subjects who were diagnosed as epilepsy.
2.2.3. Types of exposures. In the experimental group, all epilepsy subjects received cinnamaldehyde in this study.
In the control group, all epilepsy subjects did not receive any treatment in this study.
2.3.1. Electronic databases. We will carry out comprehen-

We will utilize a

addition, we will adapt similar detailed search strategy to the

All these electronic databases will be searched from their inceptions to the March 31, 2020, without

CINAHL, Web of Science, Google Scholar, PsycINFO, WANG-

study information, such as title, time of publication,

divergences between 2 authors will be solved by a third author

independent authors will conduct data collection, and any

previous designed data collection form to extract the data. Two

whole process of study selection is

opinions occur between 2 authors, we will invite a third author to

remaining studies will be further identi

2.4.4. Assessment of risk of bias of included studies. Two

authors will independently conduct the risk of bias for each
eligible study using Cochrane risk of bias. It has 7 domains, and
each field is further assigned as low, unclear, and high risk of bias.

Any disagreements between the 2 authors will be solved by a third
author through discussion. We will summarize the results of risk
of bias assessments in Risk of Bias Table.

2.4.5. Measurement of treatment effect. For dichotomous
values, we will calculate them as risk ratio and 95% confidence
intervals. For continuous values, we will calculate them as mean
difference or standardized mean difference and 95% confidence
intervals.

2.4.6. Assessment of heterogeneity. We will use I² statistics to
check the heterogeneity among eligible studies. The value of I² ≤
50% means low heterogeneity; and the value of I² > 50%
indicates substantial heterogeneity.

2.4.7. Data synthesis. We will apply RevMan 5.3 software for
statistical analysis in this study. A meta-analysis will be
conducted if low heterogeneity exists among included studies
on the same interventions and outcomes. A fixed-effects model
will be utilized if the heterogeneity is low. On the contrary, a
random-effect model will be employed if the heterogeneity is
significant. Then, subgroup analysis and meta-regression test will
be performed to explore sources of substantial heterogeneity.

2.4.8. Publication bias. We will carry out Funnel plot and Egger
regression test to check if there is any publication bias when more
than 10 studies are included.²⁹

2.4.9. Subgroup analysis. We will undertake subgroup analysis
based on the different interventions, controls, and outcome tools.

2.4.10. Sensitivity analysis. We will exclude studies with a high
risk of bias to identify the robustness and stability of pooled
outcomes.

2.5. Dissemination and ethics

No ethical approval is needed, because this is a literature-based
study. We are expected to publish this study at peer-reviewed
journals.

3. Discussion

Several studies have reported the effect of cinnamaldehyde on
Cav-1 and Survivin expression in epilepsy. However, no
systematic review with sufficient evidence has investigated this
issue. Therefore, this study will systematically appraise the effect
of cinnamaldehyde on Cav-1 and Survivin expression in epilepsy.
The findings of this study may fulfill the gap in this field and may
provide evidence to further explore potential medicine for
epilepsy, which may benefit both future research and clinical
practice.

Table 1

| Number | Search terms |
|--------|--------------|
| 1      | Mesh descriptor (epilepsy) explode all trees |
| 2      | (Cav-1) explode all trees |
| 3      | (Survivin) explode all trees |
| 4      | (epilepsy) or (seizure) or (disorder) or (recurrence) or (epilepsy symptom) or (Cav-1) or (Survivin) ti, ab, kw |
| 5      | Or 1–4 |
| 6      | (cinnamaldehyde) explode all trees |
| 7      | (cinnamaldehyde) or (aldehyde) or (cinnamon) or (cinnamic aldehyde) or (trans-cinnamaldehyde) |
| 8      | Or 6–7 |
| 9      | MeSH descriptor: (randomized controlled trials) explode all trees |
| 10     | (random) or (allocation) or (placebo) or (blind) or (clinical trials) or (controlled clinical trials) ti, ab, kw |
| 11     | 9 and 10 |
| 12     | 5 and 8 and 11 |

2.2.4. Types of outcome measurements. Primary outcomes
are gene and protein expressions of Cav-1 and Survivin. Gene
expression was measured by real-time quantitative real-time
polymerase chain reaction. Protein expression was detected by
immunofluorescence or western blot test.

Secondary outcomes are patch-clamp whole-cell mode voltage
clamp recording, and survivin apoptosis factor, as measured by
flow cytometry.

2.3. Search methods for identification of studies

2.3.1. Electronic databases. We will carry out comprehen-
sively search from Cochrane Library, PUBMED, EMBASE,
CINAHL, Web of Science, Google Scholar, PsycINFO, WANG-
FANG, VIP, CBM, and CNKI. All these electronic databases will
be searched from their inceptions to the March 31, 2020, without
language and publication status restrictions. We will present a
detailed search strategy for Cochrane Library in Table 1. In
addition, we will adapt similar detailed search strategy to the
other electronic databases.

2.3.2. Searching other resources. This study will also search
ongoing studies, clinical registry, and reference lists of relevant
studies.

2.4. Data collection and analysis

2.4.1. Study selection. We will carry out study selection
according to the pre-designed eligibility criteria. Two authors
will independently screen the titles and abstracts of all literature
records. We will exclude all irrelevant studies, and full-text of all
remaining studies will be further identified. If any different
opinions occur between 2 authors, we will invite a third author to
solve it via discussion. The whole process of study selection is
demonstrated in the flowchart.

2.4.2. Data collection and management. We will utilize a
previous designed data collection form to extract the data. Two
independent authors will conduct data collection, and any
divergences between 2 authors will be solved by a third author
though discussion. The following information will be extracted:
study information, such as title, time of publication, first author,
and so on; patient characteristics, such as race, age, and so on;
study methods, such as sample size, randomization, blind,
Author contributions

Conceptualization: Jia-nan Yu, Cai-fang Yue, Ke-jian Wang, Nan-nan Chi, Xin Li.
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Investigation: Xin Li.
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