

# INPLASY PROTOCOL

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**Conflicts of interest:**  
None declared.

## Flavonoids for viral acute respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials

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**Review question / Objective:** To date, there are some RCTs conducted on patients concerning the efficacy of flavonoids against viral ARTIs. However, the findings are inconsistent and the evidence of the antiviral activity of flavonoids against viral ARTIs remains decentralized. Therefore, the purpose of this current systematic review and meta-analysis of the available evidence is to investigate the efficacy of flavonoids on viral respiratory tract infections (ARTIs).

**Information sources:** The Medline, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Wanfang and VIP information databases will be searched from inception time to date. The ClinicalTrials.gov registry will be also searched for unpublished trials and the authors were contacted for additional information if necessary. Relevant references from included studies were sought to retrieve additional eligible studies.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 August 2021 and was last updated on 28 August 2021 (registration number INPLASY202180107).

### INTRODUCTION

**Review question / Objective:** To date, there are some RCTs conducted on patients concerning the efficacy of flavonoids against viral ARTIs. However, the findings

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flavonoids on viral respiratory tract infections (ARTIs).

**Condition being studied:** To date, there are some studies conducted on patients concerning the efficacy of flavonoids against respiratory tract infections. Preclinical studies have showed evidence of antiviral activity of quercetin-type flavonols with significantly reduced mortality rate of infected animals and a reduction in the average viral load. Furthermore, a meta-analysis in 2016 conducted by Somerville et al. included 14 studies and found that flavonoid supplementation decreased upper respiratory tract infections incidence by 33% compared with control, with no apparent adverse effects. However, the evidence of the antiviral activity of flavonoids against viral ARTIs remains decentralized.

## METHODS

**Participant or population:** Patients who suffered from virus-induced ARTIs.

**Intervention:** The interventions for treating vital ARTIs could be any kinds of flavonoids.

**Comparator:** The control group without flavonoids.

**Study designs to be included:** RCTs.

**Eligibility criteria:** Meet the PICOS principles of our research.

**Information sources:** The Medline, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Wanfang and VIP information databases will be searched from inception time to date. The ClinicalTrials.gov registry will be also searched for unpublished trials and the authors were contacted for additional information if necessary. Relevant references from included studies were

sought to retrieve additional eligible studies.

**Main outcome(s):** (1) the incidence of ARTIs; (2) the overall clinical effectiveness.

**Additional outcome(s):** (1) time to viral clearance; (2) time to symptom resolution or clinical improvement; (3) measures of immune status with the use of the following biomarkers: IL-6, IL-8, IL-10, TNF-a; (4) admission to hospital; (5) duration of hospital stay; (6) intensive care unit (ICU) length of stay; (7) duration of mechanical ventilation; (8) mortality; (9) incidence of potential adverse reactions to flavonoids.

**Quality assessment / Risk of bias analysis:** For each eligible trial, reviewers, following training and calibration exercises, will use a revision of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2.0) to rate trials as either at i) low risk of bias, ii) some concerns—probably low risk of bias, iii) some concerns—probably high risk of bias, or iv) high risk of bias, across the following domains: bias arising from the randomisation process; bias owing to departures from the intended intervention; bias from missing outcome data; bias in measurement of the outcome; bias in selection of the reported results, including deviations from the registered protocol; bias due to competing risks; and bias arising from early termination for benefit. We will rate trials at high risk of bias overall if one or more domains will be rated as some concerns—probably high risk of bias or as high risk of bias and as low risk of bias if all domains will be rated as some concerns—probably low risk of bias or low risk of bias. Reviewers will resolve discrepancies by discussion and, when not possible, with adjudication by a third party.

**Strategy of data synthesis:** Stata, version 16.0 (StataCorp LLC) will be used for statistical analysis. Dichotomous data will be used the odds ratios (OR) with 95% confidence intervals (CI). Continuous data will be used the weighted mean difference (WMD) with 95% CI after the units were standardized. Missing data were dealt with according to the Cochrane Handbook for

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**Systematic Reviews of Interventions.**  $P < 0.05$  will be considered statistically significant.

**Subgroup analysis:** Subgroup analyses will be used to explore possible sources of heterogeneity, based on the following: Trial characteristics: author, publication year, design, sample size. Patient characteristics: country, age, sex, smoking habits, comorbidities. Types of intervention drugs: which kind of flavonoids; whether single or multifactorial interventions such as antiviral western medicine. Duration: long or short intervention time.

**Sensitivity analysis:** Sensitivity analysis will be conducted by excluding studies one by one, so that we can determine the source of heterogeneity.

**Country(ies) involved:** China.

**Keywords:** flavonoids, viral acute respiratory tract infections, systematic review, meta-analysis.

**Contributions of each author:**

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