

# INPLASY PROTOCOL

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

**Conflicts of interest:**  
None declared.

## The Effect of Curcumin Differs on Individual Cognitive Domains across Different Patient Populations: a Systematic Review and Meta-analysis

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**Review question / Objective:** To summarize the existing evidence from randomized controlled trials of curcumin supplement ( $\geq 8$  weeks) on overall cognitive function, individual cognitive domains, and adverse events.

**Condition being studied:** The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis are going to be: (1) P: human adult participants ( $\geq 20$  years old); (2) I: curcumin oral supplement; (3) C: placebo; and (4) O: changes in the scores of the selected cognitive function tests.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 September 2021 and was last updated on 24 September 2021 (registration number INPLASY202190085).

### INTRODUCTION

**Review question / Objective:** To summarize the existing evidence from randomized controlled trials of curcumin supplement ( $\geq 8$  weeks) on overall cognitive function, individual cognitive domains, and adverse events.

**Rationale:** Curcumin is a polyphenol with strong antioxidant and anti-inflammatory effect and has been shown effective in ameliorating cognitive decline in animal studies. However, the clinical effectiveness was inconclusive and relevant

gastrointestinal adverse events were reported.

**Condition being studied:** The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis are going to be: (1) P: human adult participants ( $\geq 20$  years old); (2) I: curcumin oral supplement; (3) C: placebo; and (4) O: changes in the scores of the selected cognitive function tests.

## METHODS

**Search strategy:** The combinations of the following keywords will be used for literature search, including curcumin, turmeric, ginger, curcuma longa, curcuminoid, cognitive, cognition, memory, learning, dementia, and Alzheimer.

**Participant or population:** Human adult participants ( $\geq 20$  years old).

**Intervention:** Curcumin oral supplement.

**Comparator:** Placebo.

**Study designs to be included:** Randomized controlled trials.

**Eligibility criteria:** To generate a recruited study list, the following inclusion criteria will be used: (1) RCTs with adult human participants ( $\geq 20$  years old), (2) RCTs investigating the difference in results of cognitive function tests after curcumin supplement or placebo regimens, (3) RCTs with an intervention duration greater than or equal to 8 weeks, and (4) placebo-controlled trials. To be specific, we will choose the least treatment duration to be 8 weeks, which is the recommended length of for curcumin supplement to take effect.

**Information sources:** A systemic literature search will be conducted in PubMed (US National Library of Medicine) and Embase (Wolters Kluwer Ovid) for randomized controlled trials investigating cognitive outcomes of curcumin intervention. The reference lists or bibliographies of the available review articles and meta-analyses will be scrutinized for additional

candidates. Animal studies, non-randomized studies, and studies with intervention period less than 8 weeks will be excluded from the present meta-analysis.

**Main outcome(s):** The primary outcomes will be the changes in the cognitive function tests following at least 8-weeks of use of curcumin or placebo regimens. The cognitive function tests will be categorized into nine domains, including overall performance, working memory, processing speed, language, episodic memory / visual learning, verbal memory, cognitive flexibility / problem solving, social cognition and fluid cognition.

**Additional outcome(s):** The secondary outcomes will be: (1) overall withdrawal rates, (2) specific withdrawal rates related to adverse effects, (3) overall adverse event rates, and (4) gastrointestinal adverse event rates.

**Data management:** Two independent authors (I.-C.T. and K.-V.C.) will extract data from the recruited studies, including demographic data, study design, details of curcumin supplement and placebo regimens and the primary and secondary outcomes. In situations where the data is unavailable in the published articles and clinical trial registries, we will contact the corresponding authors to request original data.

**Quality assessment / Risk of bias analysis:** The version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) will be used for methodological quality assessment. RoB 2 includes 6 main items: randomization process, intervention adherence, missing outcome data, outcome measurement, selective reporting, and overall risk of bias. In RoB 2's intervention adherence section, one of the two options should be selected for literature assessment: intention-to-treat (intervention assignment) or per-protocol (intervention adherence). In this meta-analysis, we will use the per-protocol evaluation.

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**Strategy of data synthesis:** The current meta-analysis will be conducted with a random-effects model. The meta-analysis procedure will be performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ). We will use Hedges' g and 95% confidence intervals as the main effect size effect size of the primary outcomes (cognitive function changes in different domains). An Hedges' g of 0.2, 0.5, and 0.8 is considered a small, moderate, and large effect size, respectively. We will use odds ratios and their 95% confidence intervals to investigate the secondary outcomes (rates of withdrawal and adverse events). The I<sup>2</sup> and Cochran's Q statistics will be used to evaluate the degree of heterogeneity among studies. An I<sup>2</sup> value of 25%, 50%, and 75% is considered low, moderate, and high heterogeneity, respectively.

**Subgroup analysis:** The subgroup analysis will be performed based on the difference in the target populations, such as older adults, Alzheimer's disease, and schizophrenia.

**Sensitivity analysis:** Sensitivity analysis will also be performed by substituting the representative test with other similar assessments. The results will be re-analyzed to check whether the association between the intervention and outcomes changes significantly.

**Language:** No language limit.

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

**Keywords:** curcumin, turmeric, Curcuma Longa, cognition, cognitive function.

**Contributions of each author:**

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