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Original Study

Clinical Use of Curcumin in Depression: A Meta-Analysis

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A B S T R A C T

Introduction: There is growing interest in the use of curcumin, a plant polyphenol with potent anti-inflammatory, anti-oxidant, and neuroprotective properties, as a novel antidepressant. Clinical trials have yielded conflicting conclusions pertaining to its effectiveness in depression. A meta-analysis of the topic, which has not been done until now, is therefore necessary to summarize current evidence and generate hypotheses for further research.

Methods: Using the keywords [curcumin OR diferuloylmethane OR curcuminoid OR turmeric OR Indian saffron] AND [depression OR MDD OR suicide], a preliminary search on the PubMed, Ovid, Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANTR), and Cochrane Field for Complementary Medicine database yielded 2081 articles published in English between January 1, 1960, and August 1, 2016.

Results: Six clinical trials with a total of 377 patients were reviewed, comparing the use of curcumin to placebo. In patients with depression, the pooled standardized mean difference from baseline Hamilton Rating Scale for Depression scores (pooled standardized mean difference −0.344, 95% confidence interval −0.558 to −0.129; $P = .002$) support the significant clinical efficacy of curcumin in ameliorating depressive symptoms. Significant anti-anxiety effects were also reported in 3 of the trials. Notably, no adverse events were reported in any of the trials. Most trials had a generally low risk of bias, except for an open trial of curcumin and a single-blinded study.

Limitations: Because of the small number of studies available, a funnel plot or sensitivity analysis was not possible. Evidence on the long-term efficacy and safety of curcumin is also limited as the duration of all available studies ranged from 4 to 8 weeks.

Conclusions: Curcumin appears to be safe, well-tolerated, and efficacious among depressed patients. More robust randomized controlled trials with larger sample sizes and follow-up studies carried out over a longer duration should be planned to ascertain its benefits.

According to the World Health Organization, depression is a highly prevalent and debilitating mental disorder affecting more than 350 million people worldwide.[1] It is the leading cause of disability and a major contributor to the overall global burden of disease.[2] Depression is common in patients living with chronic diseases, and patients with depression are also at increased risk of suicide and have higher rates of medical and psychiatric comorbidities.[3] Furthermore, approximately one-half of patients with major depressive disorder fail to respond to first-line treatment, and initial response to standard first-line medications such as selective serotonin reuptake inhibitors (SSRIs) may take as long as 4 to 6 weeks.[4–6] Even with successful treatment of depression, there is often only partial remission of symptoms.[7] There is a pressing need to research newer and more effective treatments for major depressive disorder.

Traditional medicine is often a fertile ground for new drug candidates and the development of modern medicines.[8] Curcumin (diferuloylmethane) is a bright yellow plant pigment, and the principal curcuminoid present in Indian saffron or turmeric (*Curcuma longa*), a popular spice and food additive widely used in South Asian and Middle Eastern countries.[9] Curcumin is also used in Ayurvedic

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medicine to treat various inflammatory conditions (eg, arthritis and ulcers).[10] Curcumin is also an important active ingredient found in the traditional Chinese medicine Jieyu-wan and Xiaoyao-san, which have been used for centuries to manage stress, depression, and other mood disorders.[11]

Previous studies have reported the potent anti-oxidant,[12] anti-inflammatory,[13] and neuroprotective[14] effects of curcumin. Many preclinical trials have also highlighted curcumin's potential antidepressant-like effects in rat[15] and mice[11] models of depression, with similar effects to conventional antidepressants like fluoxetine and imipramine.[16] These results are promising for they support the possible use of curcumin to treat depressive disorders. Clinical trials have also been conducted but have yielded conflicting conclusions pertaining to the effectiveness of curcumin in major depressive disorder.[17–19] A meta-analysis of the topic, which has not been done until now, is, thus, timely and necessary to summarize current evidence and generate hypotheses for further research.

Methods

Patient Involvement

This article does not contain any studies with human participants performed by any of the authors. Patients/service users/carers/lay people were not involved in the design or course of this study.

Search Strategy

Literature search was done in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Using the keywords [curcumin OR diferuloylmethane OR curcuminoid OR turmeric OR Indian saffron] AND [depression OR MDD OR suicide], a preliminary search on the PubMed, Ovid, Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANTR), and Cochrane Field for Complementary Medicine database yielded 2081 articles published in English between January 1, 1960, and August 1, 2016. Gray literature was not searched. Title/abstract screening were performed independently by the researchers to identify articles of interest. For relevant abstracts, full articles were obtained, reviewed, and also checked for references of interest. The authors of the articles were not contacted to provide additional data.

Full articles were obtained for all selected abstracts and reviewed by all researchers for inclusion. Any disagreement was resolved by discussion and consensus among the 3 researchers. The inclusion criteria for this review were (1) published randomized controlled trial; (2) specified dose of curcumin was administered as an active intervention; (3) study participants had clinically diagnosed major depressive disorder; and (4) available outcome measures for treatment efficacy and safety.

Methodological quality of the eligible clinical trials was appraised using the Jadad scale[20] by all investigators (consensus). Trials were scored between 0 (very poor) and 5 (rigorous). Cochrane Collaboration's tool for assessing risk of bias[21] of randomized controlled trials was also applied.

Data such as study design, study population and demographics, and outcome measures were extracted. The primary outcome measures of interest were treatment response and safety/incidence of adverse effects. Treatment response was quantified using standardized mean difference (SMD) for mean reduction in Hamilton Rating Scale for Depression (HAM-D) score from baseline with treatment. Estimates were pooled and where appropriate, 95% confidence intervals (CIs) and *P* values were calculated.

Heterogeneity among the different studies pooled was examined using the I^2 statistic and Cochran Q test. If heterogeneity was small ($I^2 \leq 50\%$), a fixed effects model was applied for the meta-analysis. Because of the small number of studies available, publication bias was not assessed using a funnel plot or Egger test, and a sensitivity analysis was not done. All analyses were done using MedCalc Statistical Software v 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

A total of 2081 records were identified through PubMed, Ovid, Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANTR), and Cochrane Field for Complementary Medicine database search. Of these, 11 full text articles were reviewed and considered for inclusion. The abstraction process and the reason(s) for exclusion of each study after full-text review were detailed in Figure 1. Altogether, 6 studies were included in the meta-analysis. The key study characteristics and findings were summarized in Table 1.

The studies were assessed using the Cochrane Collaboration's tool for bias. The results were detailed in Table 2. Most studies had a low risk of bias, except for an open trial of curcumin,[24] which did not blind the assessors or patients about the treatment received. Another study[25] was only single-blinded.

Because of the small number of studies available, a funnel plot or sensitivity analysis was not feasible.

The pooled SMD from baseline HAM-D scores (pooled SMD −0.344, 95% CI −0.558 to −0.129; $P = .002$) supports the clinical efficacy of curcumin in ameliorating depressive symptoms when compared with placebo/control. This was illustrated in a forest plot (Figure 2).

Insufficient outcome data were available to analyse the risk or odds ratio of adverse events related to curcumin use. It is, however, encouraging that no adverse events were reported in any of the trials.

Discussion

The available clinical trials generally support the antidepressant effects of curcumin administration in depressed patients. The pooled SMD from baseline HAM-D scores (pooled SMD −0.344, 95% CI −0.558

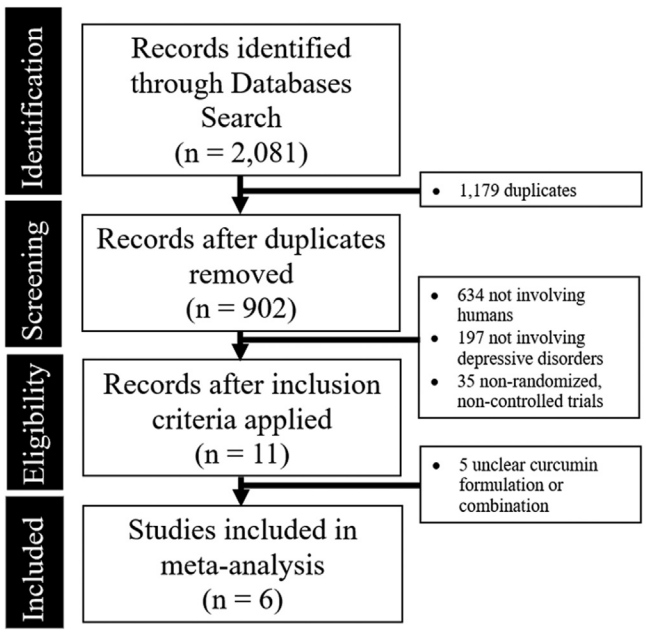

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the studies identified during the literature search and abstraction process.