REVIEW
The Role of Curcumin Administration in Patients with Major Depressive Disorder: Mini Meta-Analysis of Clinical Trials

Dalia Al-Karawi,1,∗ Doaa Alem Al Mamoori2 and Yaman Tayyar3
1Al-Kadhimiya Teaching Hospital, Baghdad, Iraq
2Department of Emergency Medicine, Baghdad Medical City, Baghdad, Iraq
3Griffith University, Gold Coast, Queensland, Australia

Major depression is a common, recurrent, and chronic disease that negatively affects the quality of life and increases the risk of mortality. Several studies have demonstrated that curcumin, the yellow-pigmented substance of the turmeric, possesses antidepressant properties. The aim of this review is to meta-analytically assess the antidepressant effect of curcumin in patients with major depressive disorders. We extensively searched the literature until August 2015. The random-effect model was used to calculate the pooled standardized difference of means (SMD). Subgroup analyses were also performed to examine the effect of different study characteristics on the overall model. Six clinical trials met the inclusion criteria. Overall, curcumin administration showed a significantly higher reduction in depression symptoms [SMD = −0.34; 95% confidence interval (CI) = −0.56, −0.13; p = 0.002], Subgroup analyses showed that curcumin had the highest effect when given to middle-aged patients [SMD = −0.36; 95% CI = −0.59; −0.13; p = 0.002], for longer duration of administration (SMD = −0.40; 95% CI = −0.64, −0.16; p = 0.001), and at higher doses (SMD = −0.36; 95% CI = −0.59, −0.13; p = 0.002). The administration of new formulation of curcumin (BCM-95) had non-significantly higher effect on depression as compared with the conventional curcumin–piperine formula. We conclude that there is supporting evidence that curcumin administration reduces depressive symptoms in patients with major depression. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: curcumin; major depressive disorders.

INTRODUCTION

Major depressive disorders (MDDs) are common and disabling conditions that negatively affect the quality of life and increase the risk of mortality (Sivertsen et al., 2015). It is estimated that depression affects almost 16% of the population on a lifetime basis (Kessler et al., 2005), with a recurrence rate of at least 45% among these patients (Kruisjhaar et al., 2005). Therefore, depression can perhaps be defined as a profoundly recurrent chronic condition, with the recurrent nature of the disorder being the main burden for its treatment (Judd, 1997).

According to the recommended guidelines, depression is usually treated in episodic fashion during the acute phase of the disease (Davidson, 2010), which helps to improve the symptoms in the short term only. Long-term treatment or maintenance of treatment for at least 6 months after remission to prevent relapses was recommended by the National Institute for Health and Clinical Excellence. These recommendations are still under debate concerning the optimal duration of maintenance, which has not yet been thoroughly investigated (Kaymaz et al., 2008). From a clinical perspective, non-adherence to antidepressant medications continues to be high for several reasons (Sansone and Sansone, 2012). The adverse effects of antidepressant medications were cited as a major cause of poor compliance to treatment and a limiting factor to the long-term maintenance of antidepressants, which is necessary to prevent recurrences (van Geffen et al., 2007). It was reported that up to 50% of patients with MDD discontinued antidepressant treatment because of the side effects alone (van Geffen et al., 2007), which necessitates an exploration of more tolerable treatment options.

Curcumin (diferuloylmethane), a yellowish pigment present as a component of turmeric (Curcuma longa), was discovered a century ago (Aggarwal and Harikumar, 2009). It is a natural phenol that is widely used in South Asian countries as a food coloring and additive. Previous studies showed that curcumin possesses antioxidant (Ruby et al., 1995; Sandur et al., 2007; Sahebkar et al., 2013; Sahebkar et al., 2015), antiinflammatory (Jurenka, 2009), and antidepressant (Xu et al., 2005; Kulkarni et al., 2008) qualities. Previous epidemiological studies examined the neuroprotective effect of curcumin and demonstrated that its regular consumption is associated with reduced cognitive function diseases such as Alzheimer disease (Chandra et al., 2001), dementia (Vas et al., 2001), and cognitive deficits in elderly (Ng et al., 2006). Previous review suggests that the neuroprotective effect of curcumin is synergistically boosted by the other components of turmeric, demethoxycurcumin, and bisdemethoxycurcumin, in patients with Alzheimer disease (Ahmed and Gilani, 2014). The same evidence suggested that each

* Correspondence to: Dalia Al-Karawi, Al-Kadhimiya Teaching Hospital, Kadhimiya, Baghdad, Iraq 10006.
E-mail: Daliaalkarawi@gmail.com

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component of turmeric acts through multiple pathways such as decreasing inflammatory stress and attenuation of stress-inducing cytokines that slow down the disease process and improve cognitive function (Ahmed and Gilani, 2014).

Several clinical trials attempted to examine the antidepressant effect of curcumin administration in patients with depression. However, the results from these human trials were controversial in regard to whether curcumin can reduce depressive symptoms and enhance the antidepressant effect (Andrade, 2014). The present meta-analysis assesses whether curcumin administration can alleviate depression and reduce its symptoms. An investigation of its effect can be an important step to improving depression treatment outcomes and guide future research effort to further assess its clinical effect and application in the treatment of major depression.

METHODS

Literature search. The review protocol has been registered at Prospero International Prospective Register of Systematic Reviews (registration ID=CRD42015025203). The following databases have been systematically searched for relevant studies during the past 30 years: Pubmed, Scopus, Psychinfo, Evidence Based Medicine Guidelines, DynaMed, JAMA evidence, and the Cochrane Library. A combination of the following key words was employed to locate relevant studies: curcumin AND depression OR MDD AND efficacy OR effect. The search was restricted to studies published in English only. In addition, reference lists of the identified papers were also searched for relevant studies. We followed the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-analysis, the PRISMA statement, to search the literature and present the results (Moher et al., 2009). The identified articles were imported into the EndNote reference management software to remove any duplicates. The titles and abstracts were initially screened for relevance. The full text of the relevant articles was retrieved for further reading and assessment.

Inclusion criteria. At the initial stage of the search, six criteria were used to filter the search results – Criterion A: only human studies were included; Criterion B: it must be quantitative; Criterion C: studies must have intervention and control groups; Criterion D: studies that addressed curcumin as a key independent intervention were included; Criterion E: only studies that addressed MDDs as an outcome were included; and Criterion F: only studies that measured depression utilizing standardized measurement scales were included. Two independent reviewers screened for potentially relevant articles independently, according to the previously specified criteria. A summary of the review is presented in the PRISMA flow chart (Fig. 1).

Data abstraction and quality assessment. The abstraction of data and subsequent quality assessment were conducted by two reviewers (Dalia A and Doaa A) independently. A pre-piloted data form was used to extract data from the selected studies. Relevant demographic information such as age, gender, body mass index, the use of antidepressant medication, and antidepressant class were extracted. Information regarding study design, settings, location, sample size, diagnostic criteria of depression, duration of intervention, dosage of curcumin, addition of absorption enhancers, the type of measurement scale of depression, and major findings were also extracted. The assessment of the abstracted articles was discussed during a consensus meeting. Moreover, the corresponding authors were contacted to obtain missing data.

The Quality Assessment Tool for Quantitative Studies (by the Effective Public Health Project) was utilized to assess the quality of the abstracted articles (Supporting Information) (Quality Assessment Tool for Quantitative Studies, 2008). This tool provides standardized means to appraise study quality that leads to an overall methodological rating of strong, moderate, or weak in eight sections: (1) selection bias, (2) study design, (3) confounders, (4) blinding, (5) data collection methods, (6) withdrawals, and dropouts, (7) intervention integrity, and (8) analysis appropriate to question. The final global rating classifies studies into either strong (no weak ratings), moderate (with one weak rating), or weak (two, or more weak ratings) (Quality Assessment Tool for Quantitative Studies, 2008). Discrepancies in quality assessment were resolved by discussion, reference to Cochrane guidelines, or inviting an expert opinion.

Quantification of depression outcome. In order to ascertain the assumption that differences in standard deviations (SDs) among studies do not reflect the differences in depression measurement scales, all studies with inconsistent scales were converted into Hamilton Depression Rating Scale, the 17-item version (HAM-D 17). To convert total scores from the Inventory of Depressive Symptomatology self-rated version scale to equivalent HAM-D 17 scores, the Rush et al. (2003) method, which is based on item response theory analysis, was utilized (Rush et al., 2003). Similarly, to convert depression total scores from the Beck Depression Inventory II scale to equivalent HAM-D 17 scores, the factor-analytic method was used (Vittengl et al., 2005). Because this meta-analysis included some studies with small sample size, Hedge’s adjusted g formulation of standardized difference in means was implemented to adjust for small sample bias (Higgins and Green, 2011).

Statistical analysis. Because the included studies are different in their characteristics, the random-effects model and generic inverse variance method were used to combine the results. This model assumes that the inter-study variations are due to both random variation and differences in individual studies as well (DerSimonian and Laird, 1986). The individual and combined standardized mean difference (SMD) and the corresponding 95% confidence interval (CI) were calculated. The SD of the SMD was calculated according to this formula: SD = square root [(SD_{pre-treatment})^2 + (SD_{post-treatment})^2 - (2R \times SD_{pre-treatment} \times SD_{post-treatment})]. Because the correlation coefficient (R) value was not reported by the included trials, we assumed that R value is equal to 0.5. In order to ascertain that the
assumption of $R$ value did not confound the results of this meta-analysis, a sensitivity analysis was further conducted by repeating the analysis with different $R$ values ranging from 0.1 to 0.9. Standard error (SE) was converted to SD by the following formula: $SD = S.E. \times \sqrt{\text{number of subjects}}$. In addition, the individual influence of each study was estimated by conducting sensitivity analysis using the leave-one-out method to ascertain the robustness of the results (Higgins, 2008), by excluding one study each time and re-examining the changes in the effect size.

Subgroup analyses were also performed subdividing studies according to age group (middle versus old age groups), duration of intervention (6 weeks or more versus less than 6 weeks), dosage of curcumin (1 g/day versus less than 1 g/day), addition of absorption enhancers (curcumin plus piperine versus curcumin with no enhancers), presence of other comorbidities (no comorbidities versus comorbidities) and study design/quality of evidence [randomized controlled trial (RCT) versus open-label studies], and the effect sizes were recalculated.

Because the number of included studies is small, the heterogeneity between studies was assessed by calculating the $I^2$ index that describes the percentage of the variability in effect estimates that is due to inconsistency rather than chance. We assumed that heterogeneity is low, moderate, or high when $I^2$ is less than 30%, 30–50%, or more than 50%, respectively. In addition, publication bias was examined by visual inspection of funnel plot asymmetry. Data were analyzed using the REVIEW MANAGER software (version 5.3.0) from Cochrane Collaboration.

### RESULTS

#### Description of the included studies

Of the 1757 studies identified during the initial search, 34 articles were fully retrieved. The full text was assessed according to the previously stated selection criteria. Of the total, 28 studies were excluded because of either the lack of control or being non-human studies. Six studies met all inclusion criteria. Fig. 1 depicts the selection process of the included studies. Data were pooled from four RCTs (Bergman et al., 2013; Lopresti et al., 2014; Sanmukhani et al., 2014; Yu et al., 2015), one cross-over (Esmaily et al., 2015), and one open-label study (Panahi et al., 2015). In total, 342 patients were enrolled and completed these studies, with 177 patients in the intervention arm and 165 patients in the control arm. The included studies were published between 2013 and 2015. All these studies enrolled patients diagnosed with major depression who were diagnosed

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart of the literature search. RCT, randomized controlled trial.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Design; location</th>
<th>Participants (no. I/C)</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Medication</th>
<th>Diagnostic criteria</th>
<th>Treatment duration (weeks)</th>
<th>Curcumin dosage</th>
<th>Addition of absorption enhancer</th>
<th>Outcome measurement scale</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman et al., 2013</td>
<td>RCT DB; Israel</td>
<td>20/20</td>
<td>65.8 (10.7)/61.3 (15.2)</td>
<td>17/23</td>
<td>Escitalopram or venlafaxine</td>
<td>CGI-S ≥ 4, HAM-D17 &gt; 21 MADRS &gt; 22</td>
<td>5</td>
<td>500 mg/day</td>
<td>50 mg of piperine per day</td>
<td>HAM-D17, MADRS, CGI-S</td>
<td>Non-significant reduction, curcumin group had more rapid relief of depressive symptoms</td>
</tr>
<tr>
<td>Esmaily et al., 2015</td>
<td>DB cross-over; Iran</td>
<td>Obese 15/15</td>
<td>38.84 (11.12)/37.81 (12.31)</td>
<td>6/24</td>
<td>ND</td>
<td>BDI; BAI</td>
<td>4; 2 (wash-out); 4</td>
<td>1 g/day</td>
<td>10 mg of piperine per day</td>
<td>BDI, BAI</td>
<td>Non-significant difference in BDI scores</td>
</tr>
<tr>
<td>Lopresti et al., 2014</td>
<td>DB RCT; Australia</td>
<td>28/28</td>
<td>44.04 (11.94)/48.54 (11.73)</td>
<td>16/40</td>
<td>Antidepressant</td>
<td>DSM-IV, IDS-SR30 ≥ 14</td>
<td>8</td>
<td>1 g/day</td>
<td>None, BCM-95</td>
<td>IDS-SR30, STAI</td>
<td>Significant reduction of IDS-SR30 scores for curcumin group</td>
</tr>
<tr>
<td>Panahi et al., 2015</td>
<td>Open-label; Iran</td>
<td>61/50</td>
<td>40.69 (10.04)/40.40 (9.56)</td>
<td>51/60</td>
<td>Antidepressant</td>
<td>DSM-IV</td>
<td>6</td>
<td>1 g/day</td>
<td>10 mg of piperine per day</td>
<td>HADS, BDI</td>
<td>Significant reduction in both HADS and BDI scores among curcumin group</td>
</tr>
<tr>
<td>Sanmukhani et al., 2014</td>
<td>SB RCT; India</td>
<td>20/20</td>
<td>40.4 (34.1−46.7)/33.6 (28.9−38.3) *</td>
<td>16/24</td>
<td>Fluoxetine</td>
<td>HAM-D17 &gt; 7</td>
<td>6</td>
<td>1 g/day</td>
<td>None, BCM-95</td>
<td>HAM-D17, CGI-S</td>
<td>Non-significant reduction in HAM-D17 scores</td>
</tr>
<tr>
<td>Yu et al., 2015</td>
<td>DB RCT; China</td>
<td>50/50</td>
<td>44.14 (8.02)/45.22 (7.68)</td>
<td>100/0</td>
<td>Antidepressants</td>
<td>HAM-D17 &gt; 10 MADRS &gt; 14</td>
<td>6</td>
<td>1 g/day</td>
<td>None</td>
<td>HAM-D17, MADRS</td>
<td>Significant reduction of depressive symptoms among curcumin group, and reduction in inflammatory cytokines</td>
</tr>
</tbody>
</table>

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory II; CGI-S, Clinical Global Impression Severity Scale; CI, confidence interval; DB, double blind; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HADS, hospital anxiety and depression scale; HAM-D17, Hamilton Depression Rating Scale, 17-item version; I/C, intervention/control; IDS-SR30, Inventory of Depressive Symptomatology self-rated version; MADRS, Montgomery–Asberg Depression Rating Scale; ND, not determined; RCT, randomized controlled trial; SB, single blind; STAI, Spielberger State-Trait Anxiety Inventory.

*Data are presented as (95% CI).
according to standardized tools described earlier. Both intervention and control groups in these studies had antidepressant treatment, while the intervention group also had curcumin, and the control group had a placebo. All selected trials quantified major depression as the primary outcome and estimated the effect of intervention utilizing standardized tools. The characteristics of the included trials are summarized in Table 1.

**Risk of bias assessment**

The included studies were appraised according to the Quality Assessment Tool for Quantitative Studies guidelines (Quality Assessment Tool for Quantitative Studies, 2008), (Supporting Information). The results showed that all included studies had a ‘strong’ global final rating, except Panahi et al. (2015) which was classified as having a ‘moderate’ rating (Panahi et al., 2015). The later study did not blind the assessors to which participants where in the intervention or control groups and the patients were aware about the treatment received. Therefore, this study received a ‘weak’ rating in the blinding section and an overall ‘moderate’ quality of evidence. The difference in effect size between ‘strong’ and ‘moderate’ quality studies was further explored by subgroup analysis, and the effect size was recalculated.

**Clinical effect of curcumin on depressive symptoms.** This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

**Table 2. Subgroup analysis of the effect of curcumin on depressive symptoms**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No</th>
<th>I² (%)</th>
<th>Mean difference [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle age</td>
<td>5</td>
<td>0</td>
<td>-0.36 [-0.59, -0.13]</td>
<td>0.002</td>
</tr>
<tr>
<td>Old age</td>
<td>1</td>
<td>N/A</td>
<td>-0.21 [-0.84, 0.42]</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Duration of intervention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks or more</td>
<td>4</td>
<td>0</td>
<td>-0.40 [-0.64, -0.16]</td>
<td>0.001</td>
</tr>
<tr>
<td>Less than 6 weeks</td>
<td>2</td>
<td>12</td>
<td>-0.10 [-0.58, 0.37]</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Dosage of curcumin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 g/day</td>
<td>5</td>
<td>0</td>
<td>-0.36 [-0.59, -0.13]</td>
<td>0.002</td>
</tr>
<tr>
<td>Less than 1 g/day</td>
<td>1</td>
<td>N/A</td>
<td>-0.21 [-0.84, 0.42]</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Addition of absorption enhancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curcumin plus piperine</td>
<td>3</td>
<td>6</td>
<td>-0.33 [-0.65, -0.01]</td>
<td>0.05</td>
</tr>
<tr>
<td>Curcumin without enhancers</td>
<td>3</td>
<td>0</td>
<td>-0.35 [-0.64, -0.06]</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Presence of other comorbidities in addition to depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities</td>
<td>5</td>
<td>4</td>
<td>-0.38 [-0.60, -0.15]</td>
<td>0.001</td>
</tr>
<tr>
<td>Comorbidity (obesity)</td>
<td>1</td>
<td>N/A</td>
<td>0.03 [-0.68, 0.75]</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Study design and quality of evidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT (strong quality)</td>
<td>5</td>
<td>0</td>
<td>-0.28 [-0.53, -0.04]</td>
<td>0.02</td>
</tr>
<tr>
<td>Open label (moderate quality)</td>
<td>1</td>
<td>N/A</td>
<td>-0.53 [-0.97, -0.08]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI, confidence interval; N/A, not applicable; RCT, randomized controlled trial.

2013). Subgroup analysis showed that there was a more significant reduction in depression symptoms when the higher dose of curcumin was administered (SMD = -0.36; 95% CI = -0.59, -0.13; p = 0.002), while the low dose administration of curcumin yielded non-significant results (SMD = -0.21; 95% CI = -0.84, 0.42; p = 0.51). Further stratification of the pooled data was carried out according to the addition of the absorption-enhancer piperine, the active ingredient in black pepper. Although not significantly different, trials that administered curcumin with piperine had less effect (SMD = -0.33; 95% CI = -0.65, -0.01; p = 0.05) as compared with the administration of curcumin without absorption enhancers (SMD = -0.35; 95% CI = -0.64, -0.06; p = 0.02). Additionally, the analysis was also stratified according to the presence of other comorbidities in addition to depression. The Esmaily et al. (2015) trial only enrolled obese patients (body mass index >30) with an abnormal low density lipoprotein cholesterol level and risk factors for cardiovascular disease (Esmaily et al., 2015). The results revealed that curcumin administration had more a profound effect on depression among patients with major depression (SMD = -0.38; 95% CI = -0.60, -0.15; p = 0.001) in comparison with patients with depression and other comorbidities (SMD = 0.03; 95% CI = -0.68, 0.75; p = 0.93).

Interestingly, trials with either a ‘strong’ or ‘moderate’ quality rating demonstrated an equally significant effect in reducing symptoms among patients with depression. Data stratification based on the quality of evidence (strong; RCT design versus moderate; open-label design) revealed that clinical trials with a ‘strong’ rating significantly reduced depressive symptoms (SMD = -0.28; 95% CI = -0.53, -0.04; p = 0.02). Similarly, trials with a ‘moderate’ rating had a significant effect in reducing total depression score (SMD = -0.53; 95% CI = -0.97, -0.08; p = 0.02).

Inter-study heterogeneity was assessed utilizing the $I^2$ index. The results revealed that the pooled data had minimal heterogeneity, which is evident by a non-significant heterogeneity index ($I^2=0\%$, p = 0.73). The test for subgroup differences showed that there was a minimal heterogeneity between subgroups, with subgroup difference between middle-age versus old-age groups ($I^2=6\%$, p = 0.43); long duration (≥6 weeks) versus short duration of intervention (<6 weeks) ($I^2=17.7\%$, p = 0.27); 1 g/day versus less than 1 g/day ($I^2=0\%$, p = 0.73); presence of other comorbidities versus no associated comorbidities ($I^2=13.8\%$, p = 0.28), and ‘strong’ quality rating versus ‘moderate’ quality rating of evidence ($I^2=9\%$, p = 0.53).

Adverse events

However, non-significant adverse effects of curcumin administration were reported among some of the included studies. Lopresti et al. (2014) reported one case of digestive complaints after administration of curcumin. Similarly, Panahi et al. (2015) reported three cases of gastrointestinal complications and two cases of tachycardia and flushing. Gastrointestinal adverse events also seem to be present in the Sanmukhani et al. (2014) trial, where gastritis, nausea, and giddiness were also reported. Nausea was the only adverse event reported after administration of curcumin in the clinical trial of Yu et al. (2015), and both Bergman et al. (2013) and Esmaily et al. (2015) reported no adverse events.

**Publication bias**

Visual inspection of the funnel plot (inverse SE) by effect size (standardized mean difference) showed no evidence of publication bias. In addition, Egger’s linear regression did not reveal any statistically significant evidence of publication bias for the assessed outcome (intercept = 0.98; SE = 1.97; 95% CI = -2.79, 3.65; t = 0.52; p = 0.418).

**DISCUSSION**

**Main findings**

We identified six clinical trials, with a total of 342 patients diagnosed with major depression, examining the effect of curcumin administration on depressive symptoms. We hypothesized (H1) that the administration of curcumin can enhance the action of antidepressants and alleviate depressive symptoms among patients with MDD. Indeed, the meta-analysis of the included trials demonstrated that the administration of curcumin significantly reduced depressive symptoms (SMD = -0.34; 95% CI = -0.56, -0.13; p = 0.002; $I^2=0\%$). Our results were robust and not sensitive to the influence of any single study, as demonstrated by leave-one-out sensitivity analysis. Several mechanisms were proposed in an attempt to explain how curcumin may improve the outcome in depression (Tizabi et al., 2014; Kulkarni and Dhir, 2010). Hence, the pathophysiology of depression involves over-activation of the inflammatory response that may result in severe detrimental consequences including precipitation of depressive-like behavior (Hayley et al., 2005; Khaireva et al., 2009). The well-documented anti-inflammatory properties of curcumin are implicated as a mechanism explaining curcumin’s effect in reducing depressive symptoms (Qualls et al., 2014; Aggarwal et al., 2013). Previous meta-analysis suggests that the supplementation with curcumin can reduce circulating C-reactive protein – a reliable biomarker of systemic inflammation (Sahebkar, 2014). Curcumin is believed to have anti-inflammatory effect by suppressing nuclear factor kappa B transcription signaling pathway, which is essential for production of pro-inflammatory cytokines (such as interleukin-6 and 1β), which are important for the expression of C-reactive protein and other acute phase reactants (Mackiewicz et al., 1991). The anti-inflammatory properties of curcumin were also demonstrated by suppressing systemic inflammatory mediators when given as adjuvant therapy in cancer patients (Panahi et al., 2014).

It is well documented that major depression is associated with alterations in serotonergic neuronal function in central nervous system that is characterized by reduction in the concentration of active metabolite of serotonin (Owens and Nemeroff, 1994). Similarly, dopamine deficiency has also been implicated in the pathophysiology of depression (Kapur and Mann, 1992). Previous evidence showed that when curcumin is combined with conventional and newly discovered antidepressants, it
enhanced the antimobility effect of several antidepressants through enhancing the serotonergic and dopaminergic systems in animal models (Kulkarni et al., 2008).

Several other mechanisms were also suggested to explain the antidepressant effect of curcumin (Lopresti et al., 2012). Several reviews confirmed that major depression is associated with decreased total antioxidant status and activation of oxidative and nitrosative pathways (Black et al., 2015; Michel et al., 2012; Palta et al., 2014). The findings from many studies demonstrated that curcumin possesses a potent anti-oxidant quality (Menon and Sudheer, 2007; Meng et al., 2013; Du et al., 2012), and it is at least ten folds more potent as an antioxidant compared with vitamin E (Toda et al., 1985). Therefore, the antioxidant properties of curcumin may also be implicated as an explanation of its antidepressant effect. Other antidepressant modes of action of curcumin were also suggested such as its influence on a range of hormones and neurotransmitters commonly disturbed in depression, its neuroprotective properties, and its effect against stress-induced neurotoxicity (Lopresti et al., 2012).

While the evidence remains weak, the subgroup analyses showed that curcumin administration had the highest effect when administrated to middle-aged patients. Late life depression may have different etiology and risk factors in comparison with depression at a younger age (Fiske et al., 2009). The pathological processes of the development of late-onset depression also involve cardiovascular and neurological changes that occur with normal aging, which seem to increase the vulnerability to depression (Fiske et al., 2009). This may explain why the response to curcumin was poor among older patients. These patients may also be more sensitive to the adverse effects of antidepressants (Unützer and Park, 2012), which may also implicate non-adherence as a reason for poor response to curcumin administration.

Furthermore, the subgroup analyses revealed that longer duration of curcumin administration (6 weeks or more) and higher dosage (1 g/day) had the greatest effect at reducing depressive symptoms. Previous evidence suggests that curcumin can up-regulate the expression of synapse-associated proteins such as brain-derived neurotrophic factor, PSD-95, and Synaptophysin in the Lateral Amygdala in rat model (Zhang et al., 2014). These neurotrophins are essential to protect and maintain the functional integrity of neurons and play a key role in preventing depression (Huang and Reichardt, 2001). These neuronal changes induced by curcumin administration may require longer period of time to manifest a significant antidepressant effect. Although dose–response assessment was not undertaken in any of the included trials, previous study demonstrated that curcumin can be given up to 8 g/day without serious side effects or toxicity (Cheng et al., 2001). Considering the fact that the health benefits of curcumin are restricted by its low solubility, low absorption in the intestine, rapid metabolism, and systemic elimination (Wahlstrom and Blennow, 1978), the appropriate dose of curcumin to achieve the highest benefits should be assessed and adjusted.

Three trials in this meta-analysis added piperine to enhance the intestinal absorption of curcumin (Bergman et al., 2013; Esmaily et al., 2015; Panahi et al., 2015). Intriguingly, the subgroup analysis revealed that there is no statistically significant difference in curcumin’s effect on depression with or without the addition of piperine. In contrast, those trials that did not administer piperine had a non-significantly higher effect on depression at the same curcumin dosage. It is noteworthy that a patented formulation of curcumin (BCM-95) was administered instead of the conventional curcumin plus piperine in two trials (Lopresti et al., 2014; Sanmukhani et al., 2014). With this formulation, the relative bioavailability of curcumin was assumed to be superior as compared with curcumin–piperine formula (Antony et al., 2008). Moreover, two trials used a low dosage of piperine (10 mg/day), which may not be enough to enhance the bioavailability of curcumin (Panahi et al., 2015; Esmaily et al., 2015). Only one study used a high dose of piperine (50 mg/day), but it also administered a low dose of curcumin (500 mg/day), which may explain why it had no significant effect on depression (Bergman et al., 2013).

Stratification of data based on the presence of other comorbidities showed that curcumin administration had the highest effect when given to depressed patients with no other comorbidities. The results were not significant when curcumin was administrated to obese patients with risk factors of cardiovascular disease and abnormal low density lipoprotein cholesterol level (Esmaily et al., 2015). It is well documented that obesity and abnormal lipid profile are associated with over-activation of the inflammatory response and oxidative stress (Monteiro and Azvedo, 2010). These stress reactions may influence body response to curcumin and reduce its efficacy.

Curcumin administration was associated with few gastrointestinal adverse events such as nausea, maldigestion, and giddiness. This is consistent with previous studies that showed curcumin is generally well-tolerable with no significant side effects, even at higher doses and longer duration (Vadhan-Raj et al., 2007). This is essentially important, considering the fact that the side effects of antidepressants were cited as a major contributing factor for medication non-adherence among depressed patients (Sansone and Sansone, 2012).

Strengths, limitations, and implications

This is the first meta-analysis that has reported on the effect of curcumin in patients with MDDs. The quality of the evidence is high; all the included trials described the placebo-controlled design, selection process, randomization, patient's allocation, blinding, and dropouts with reasons, except Panahi et al. (2015), which was rated as ‘moderate’ because of non-blinding. Moreover, the overall and subgroup heterogeneity was very low. However, there are some noteworthy limitations that should be considered when examining the results of our study. First, the number of studies included is small because of limited data, especially for subgroup analyses. Owing to the scarcity of data, the results should be interpreted with caution. Further studies on the effect of curcumin administration in patients with major depression are needed. Second, the dosage of curcumin was limited to 500–1000 mg/day, which may not be the most optimal to show the actual effect of curcumin on depression. Future studies addressing the dose–response assessment of curcumin’s effect on depression are needed. This is also true regarding the dosage of piperine and which dose is optimal to enhance curcumin’s absorption and bioavailability. Third, the duration of
intervention seemed short for some included studies. Because depression is a chronic disease, we will also be interested to observe the long-term effect of curcumin, and whether the observed positive outcome of curcumin administration is sustained. In addition, different measurement scales of depression were used in the included trials and were converted to corresponding HAM-D17 scores utilizing published methods. It is acknowledged that these methods were criticized regarding scale translation at the idiographic level (Hawley et al., 2013). Another limitation is acknowledged regarding the language restriction of the search. Studies published in languages other than English were not included, so it is unknown whether the results from these studies would have modified the reported findings.

Conclusions

The findings of this study suggest that curcumin administration is effective in reducing depressive symptoms among patients with MDD. Curcumin is more effective when administrated to middle-aged patients at higher doses and for longer period of time. The administration of a new formulation of curcumin (BCM-95) had a better effect on depression as compared with the conventional curcumin plus low doses of piperine. In addition, curcumin is well tolerable, with few adverse events reported. Given its high safety and tolerability profile, together with its demonstrated effect, the role of curcumin administration as a new avenue in the treatment of major depression is worth exploring.

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Conflict of Interest

The authors declare no conflict of interest.

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