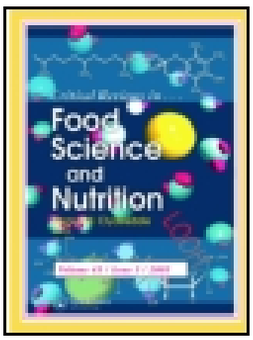

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REVIEW

Curcumin for depression: a meta-analysis

Laura Fusar-Poli, Lucia Vozza, Alberto Gabbiadini, Antonio Vanella, Ilaria Concas, Silvia Tinacci, Antonino Petralia, Maria Salvina Signorelli, and Eugenio Aguglia

Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania, Italy

ABSTRACT

Curcumin is the principal curcuminoid found in turmeric (*Curcuma longa*), a spice frequently used in Asian countries. Given its anti-inflammatory and antioxidant properties, it has been hypothesized that curcumin might be effective in treating symptoms of a variety of neuropsychiatric disorders, such as depression. We conducted a systematic review following the PRISMA guidelines. In August 2019, we screened 930 articles, of which 9 were eligible for the meta-analysis. In 7 articles, participants were affected by major depressive disorder (MDD), while in other two they suffered from depression secondary to a medical condition. We found an overall significant effect of curcumin on depressive (10 studies, 531 participants, Hedge's $g = -0.75$, 95% CI -1.11 to -0.39, $p < 0.001$) and anxiety symptoms (5 studies, 284 participants, Hedge's $g = -2.62$, 95% CI -4.06 to -1.17, $p < 0.001$), with large effect size. Curcumin was generally well-tolerated by patients. Our findings suggest that curcumin, if added to standard care, might improve depressive and anxiety symptoms in people with depression. However, given the small sample size, our results should be cautiously interpreted. Further trials should be implemented, particularly in Western countries, where curcumin does not represent a usual component of dietary regimens.

KEYWORDS

Curcumin; curcuma; depression; anxiety; meta-analysis; review; psychiatry; turmeric

Introduction

Major depressive disorder (MDD) is the most common mental health condition among the general population (Sinyor, Rezmovitz, and Zaretsky 2016) and impacts about 322 million of people worldwide. Notably, the total estimated number of people living with depression increased by 18.4% between 2005 and 2015 (World Health Organization 2017). According to the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013), MDD is characterized by sadness, hopeless, loss of energy, feels of worthlessness and excessive or inappropriate guilt, insomnia or hypersomnia, significant weight loss, diminished ability to concentrate and recurrent thoughts of death. Moreover, depression might be a consequence of other medical or psychiatric conditions (American Psychiatric Association 2013). Depression is often associated with significant medical difficulties and to a greater risk of mortality from all causes compared to non-depressed individuals (Kozela et al. 2016). Additionally, at least half of patients with depressive disorders show comorbid anxiety symptoms (Weitz et al. 2018). Individuals with this comorbidity usually present greater levels of functional impairment, a reduced life quality and poorer treatment outcomes compared to patients affected only by depression (Weitz et al. 2018).

Guidelines suggest a combination of psychological and pharmacological therapies for the management of depression, depending also on its level of severity (National Collaborating Centre for Mental Health 2010). For instance, antidepressants should be cautiously used in patients with mild depression, while stronger evidence supports the benefit of medications for patients with severe depression; a combination of psychotherapy and pharmacotherapy seems particularly effective in patients with persistent depression and more severe symptomatology (Olfson, Blanco, and Marcus 2016). However, lack of adherence to antidepressant medications is frequent (Sansone and Sansone 2012), and the presence of adverse effects seems to be one of the main causes (Goethe et al. 2007). Consequently, the interest in complementary and alternative medicine (CAM), combining efficacy and tolerability in depressed patients, is growing (Lopresti 2019). Notably, the Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines recently inserted some types of CAM (acetyl-L-carnitine, saffron, folate and *Lavandula*) among third-line monotherapies or adjunctive treatments for the management of MDD in adults (Ravindran et al. 2016).

Curcumin, or diferuloylmethane, is the principal curcuminoid present in turmeric (*Curcuma longa*), a rhizomatous plant belonging to the ginger family *Zingiberaceae*. Because of its brilliant yellow color, turmeric is also known as "Indian saffron". It has been used for over 4000 years in Southern Asian countries, both as a culinary spice and as a component in religious ceremonies (Prasad and Aggarwal

CONTACT Laura Fusar-Poli laura.fusarpoli@gmail.com Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Via Santa Sofia 78, 95123, Catania, Italy.

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2011). Given its anti-oxidant and anti-inflammatory properties, it has also been used for the treatment of several physical chronic diseases, such as arthritis, diabetes, inflammatory bowel disease, or cancer (Kunnumakkara et al. 2017). Toxicity studies showed that it is quite safe also in high doses (up to 12 g in humans) (Lao et al. 2006). Curcumin has been extensively studied for its potential benefits in the prevention or as complementary therapy in some neuropsychiatric conditions, such as cognitive impairment (Brondino et al. 2014; Brondino, Fusar-Poli, et al. 2017; Tang and Taghibiglou 2017). In fact, this compound seems to be involved in serotonin and dopamine release, in the inhibition of monoamine oxidase (MAO) and in the regulation of hypothalamus-pituitary-adrenal (HPA) axis (Kaufmann et al. 2016). Given the capacity of modulating neurobiological substrates strongly associated with depression, such as inflammation, it has been hypothesized that curcumin might have beneficial effects also in MDD. Notably, the antidepressant properties of curcumin have been reported by many preclinical trials conducted on rat models, thus supporting the use of curcumin's derivatives to treat depression also in humans (Kulkarni, Dhir, and Akula 2009). Curcumin also showed anxiolytic-like effects on biochemical and behavioral symptoms associated with anxiety (Lee and Lee 2018).

Several clinical trials about the potential effectiveness of curcumin in MDD or secondary forms of depression have been recently conducted. Two meta-analyses, published, respectively, in 2016 (Al-Karawi, Al Mamoori, and Tayyar 2016) and 2017 (Ng et al. 2017), concluded that curcumin may improve depressive symptoms when compared with control or placebo. Given the growing interest towards alternative and complementary therapies, and the global burden of depression, we sought to provide an up-to-date summary regarding the efficacy on depressive disorders. Therefore, the primary aim of the present review was to evaluate the efficacy of curcumin as an add-on therapy in people affected by depression in comparison to placebo or standard care alone. Secondly, we aimed to evaluate the efficacy of curcumin on anxiety symptoms, which are frequently present in comorbidity with depression, and on clinical global impression.

Materials and methods

We followed the PRISMA Statement guidelines to perform a systematic search (Moher et al. 2009). The protocol has been published on Figshare, an online repository for research data sharing (doi:10.6084/m9.figshare.9114422).

The following databases were searched from inception to 1st August 2019: Web of Science^{SM} (including Web of Science, MEDLINE®, KCI – Korean Journal Database, Russian Science Citation Index and SciELO Citation Index), CINAHL, Embase, PsycINFO, and ClinicalTrials.gov. There were no restrictions of language, year of publication or reference type. We adopted the following search strategy: (curcumin OR curcuma OR diferloymethane OR turmeric OR "E100") AND (depression OR depressive OR "mood disorder*"). Additionally, we hand-searched the reference lists of all included systematic reviews and meta-analyses to identify additional articles.

Selection procedure

All records were extracted to EndNote reference management software. Duplicates were detected and deleted. Two researchers (AG and LV), working independently and in duplicate, screened titles and abstracts to identify potentially relevant studies and assessed full-texts to determine eligible studies. Any doubt was solved through consultation with a third reviewer (LF).

We included all original articles written in English which met the following criteria:

1. Participants: individuals with a diagnosis of major depressive disorder (MDD), according to international valid diagnostic criteria or measured by a validated scale. We have also included individuals with depressive symptoms unrelated to a specific depressive syndrome, but secondary to other psychiatric or medical conditions. We excluded studies in which participants did not have clinically significant levels of depression at baseline.
2. Intervention: curcumin, administered at any dosage and in any form.
3. Comparison: placebo plus standard care or standard care alone.
4. Outcomes: Our primary outcome was represented by depressive symptoms, evaluated with standard measures. Secondary outcomes were represented by anxiety symptoms and clinical global impression.
5. Study design: randomized or controlled clinical trials, both parallel and crossover.

Data extraction

Two review authors (LV and ST), working independently and in duplicate, extracted data. Any doubt was solved through consultation with a third reviewer (LF). A standardized form was used to extract data from the included studies. We extracted information about study characteristics, sample characteristics, type and duration of the intervention and outcome measures. Moreover, pre- and post- treatment means, standard deviations, and number of participants, or pre-post mean differences and standard deviations were extracted from the studies for meta-analytic purposes. Study authors were contacted via e-mail to request missing data or for clarification, providing an individualized data table for reporting the requested information.

Risk of bias assessment

Two review authors (AV and IC) assessed the quality of the included studies following the Cochrane risk of bias tool (Higgins et al. 2011). Any doubt was solved after consultation with a third reviewer (LF). The following items were considered: random sequence generation, allocation

concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other source of bias (e.g. potential conflict of interest).

According to Cochrane's tool (Higgins et al. 2011), we defined a study as having an overall high risk of bias, if it was judged as having a high risk in at least one out of six domains (we did not consider the item "other source of bias"). Low risk of bias was assigned if a study scored as low risk in all the six domains. Otherwise, we considered the study at unclear risk of bias.

Statistical analysis

A random-effects model was used for calculation of the effect size. For continuous outcomes, we pooled the Hedge's *g* to correct the effect size for small sample sizes. According to Rosenthal and Rosnow (1991), we adopted a conservative pre-post correlation coefficient of 0.7, if not reported in the original article. We interpreted effect sizes in line with common guidelines (i.e. 0.2, small; 0.5, medium; 0.8 large) (Higgins and Green 2017). We calculated 95% confidence intervals and two-sided *p*-values for each outcome. Heterogeneity between studies was assessed using the Cochrane Q and I^2 statistics. Thresholds for the interpretation of heterogeneity were consistent with those of the Cochrane Collaboration (I^2 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity) (Higgins and Green 2017).

When more than one scale was used to measure the same cluster of symptoms, the scale with the best psychometric and clinical reliability was inserted in the meta-analysis. When studies had multiple treatment groups (as in Sanmukhani et al. 2014), we chose the group with curcumin plus standard care as active treatment, and standard care alone or placebo plus standard care as comparison group, as stated in inclusion criteria. If more two active treatment groups were present (Lopresti et al. 2014), the sample size of the comparison group was halved in the meta-analysis, following standard Cochrane methodology. For cross-over RCTs (Esmaily et al. 2015), we used data only of the first part of the trial, as they had a parallel design, following Cochrane's guidelines.

Sensitivity and subgroup analyses were used to evaluate the impact of moderators on pooled effect sizes. First, we performed an influence plot analysis by removing each study to identify possible outliers. Second, subgroups analyses for the primary outcome (depressive symptoms) were performed according to the following variables: curcumin daily dosage ($\leq$500 mg or $>$500 mg), duration of treatment ($\leq$6 weeks or $>$6 weeks), type of depression (MDD or depression secondary to a medical condition), risk of bias (at high risk or not at high risk of bias), depression status at baseline (mild, moderate or severe). Meta-analyses were conducted using Comprehensive Meta-Analysis Version 2.0 (CMA).

Results

Search results

Our literature search identified a total of 930 publications, while five further potentially relevant publications were obtained from references lists of included reviews and meta-analyses and other sources. After removing duplicates, 713 titles and abstracts were screened. Full-texts of 13 articles were read for a detailed evaluation. Finally, 9 articles were included in the systematic review and meta-analysis, for a total of 10 studies included in the meta-analysis. Reasons for exclusion have been explained in the PRISMA flow-chart (Fig. 1).

Characteristics of included studies

We included 9 articles, among which 8 were double-blind RCTs and one was open-label (Panahi et al. 2015). Of note, Lopresti and Drummond 's study (2017) had four arms of treatment, and we included two active treatment groups in the meta-analysis, for a total of 10 studies. Also, Sanmukhani et al. (2014) implemented a three-arm group trial. All studies had a parallel group design, apart from Esmaily et al. (2015) which had a crossover design. Duration of active treatment varied from 4 (Esmaily et al. 2015) to 12 weeks (Kanchanatawan et al. 2018; Lopresti and Drummond 2017). Studies were principally conducted in Eastern countries (China, India, Indonesia, Iran, Israel, and Thailand), while two studies were conducted in Australia (Lopresti et al. 2014; Lopresti and Drummond 2017). Of note, none of the included trials were conducted in Europe or in the United States.

Randomized samples varied from 14 (Setiawati, Ikawati, and Kertia 2017) to 123 (Lopresti and Drummond 2017) participants. Most of the articles included individuals with a principal diagnosis of MDD, while in two studies depressive symptoms were secondary to a medical condition. In particular, one study (Esmaily et al. 2015) recruited patients with obesity, while another one (Setiawati, Ikawati, and Kertia 2017) included patients affected by systemic lupus erythematosus (SLE). Depression levels at baseline varied from mild (Esmaily et al. 2015) to severe (Bergman et al. 2013; Sanmukhani et al. 2014). All studies included adult participants, with mean ages ranging from 33 (Setiawati, Ikawati, and Kertia 2017) to 63 years (Bergman et al. 2013).

In eight studies the active treatment was represented by curcumin (extracted from *Curcuma longa*), administered at different dosages, which ranged from 150 mg daily (Setiawati, Ikawati, and Kertia 2017) to 1500 mg daily (Kanchanatawan et al. 2018). In one study (Setiawati, Ikawati, and Kertia 2017), a different type of curcuma (*Curcuma xanthorriza*) was administered. In some studies, formulations contained also other compounds, typically used to increase curcumin bioavailability, such as piperine (Bergman et al. 2013; Esmaily et al. 2015; Panahi et al. 2015) or volatile oils (Lopresti et al. 2014; Lopresti and Drummond 2017). In studies were MDD was the primary diagnosis, curcumin was administered in association with

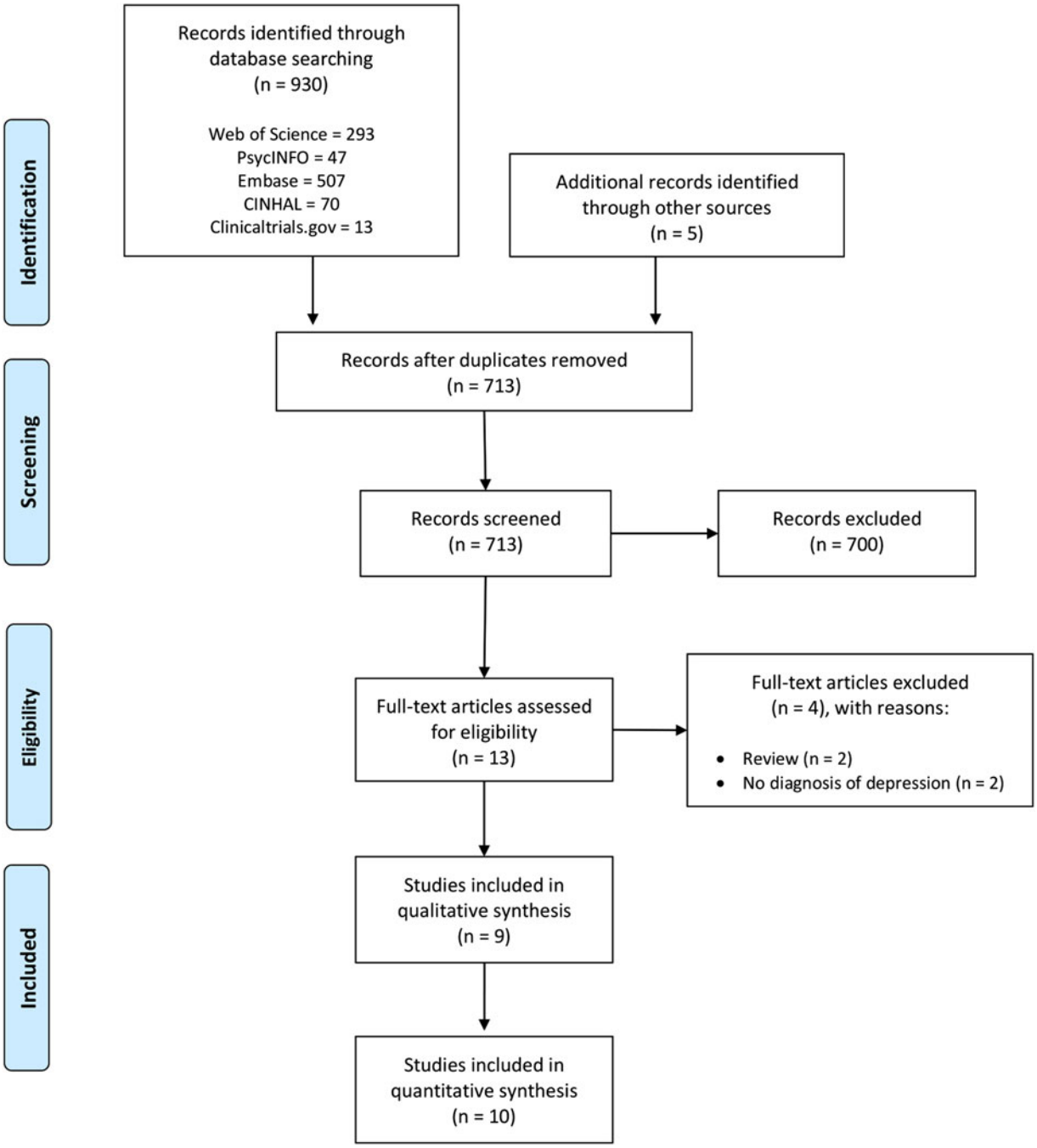

Figure 1. Prisma flow diagram of study selection process.

other pharmacological therapies, mainly antidepressants. Comparisons were represented by placebo plus standard care, except for Sanmukhani et al. (2014), in which only fluoxetine was administered as comparison treatment. Characteristics of included studies are reported in Table 1.

Risk of bias assessment

Random sequence generation was rated at low risk of bias for all studies, apart from Esmaily et al. (2015) and Panahi et al. (2015), an open-label study, which were judged at high risk of bias; in Setiawati, Ikawati, and Kertia (2017), random sequence generation was unclear. Allocation concealment was considered at low risk in four studies (Bergman et al. 2013; Kanchanatawan et al. 2018; Lopresti et al. 2014; Lopresti and Drummond 2017), at unclear risk in four studies (Esmaily et al. 2015; Sanmukhani et al. 2014; Setiawati, Ikawati, and Kertia 2017; Yu et al. 2015), and at high risk of bias in one study (Panahi et al. 2015). Participants were blind in all studies, apart from Panahi et al. (2015) and Sanmukhani et al. (2014). Outcome assessors were blind in six studies. Additionally, blinding of outcome assessors was unclear in Esmaily et al. (2015) and Yu et al. (2015), and assessors were unblinded in one study (Panahi et al. 2015). Incomplete outcome data were at high risk of bias in two studies (Bergman et al. 2013; Panahi et al. 2015), while selective reporting was considered at low risk of bias in all studies. Concerning other potential sources of bias, we

Table 1. Characteristics of the included studies.

Study ID	Design	Country	N randomized subjects (curcumin, comparison)	Mean age (range)	Gender (M/F)	Main diagnosis (diagnostic tool)	Depression at baseline	Curcumin administration form	Daily dosage	Other compounds	Concomitant psychotropic medication	Duration of active treatment (weeks)	Outcome (measures)
Bergman et al. (2013)	Double-blind RCT, parallel	Israel	40 (20, 20 placebo)	63.55 (21–81)	17/23	MDD (DSM-IV)	Severe	Curcumin Forte Balance	500 mg	50 mg piperine, 120 mg ellagic acid extracted from pomegranate peel	Escitalopram, venlafaxine	5	Depression (HAM-D*, MADRS), clinical global impression (CGI-S)
Esmaily et al. (2015)	Double-blind RCT, cross- over	Iran	30 (15, 15 placebo)	38.32 (17–80)	6/24	Obesity	Mild	C3 Complex®	1000 mg	5 mg bioperine®	Not reported	4	Depression (BDI), anxiety (BAI)
Kanchanatawan et al. (2018)	Double-blind RCT, parallel	Thailand	65 (33, 32 placebo)	44.37 (18–63)	19/49	MDD (DSM-IV)	Moderate	Not reported	500 up to 1500 mg	None	Fluoxetine, SSRI, trazodone, lamotrigine, sodium valproate, mianserin	12	Depression (MADRS), anxiety (HAM-A)
Lopresti et al. (2014)	Double-blind RCT, parallel	Australia	56 (28, 28 placebo)	46.29 (18–65)	16/40	MDD (DSM-IV)	Moderate	BCM-95®	1000 mg	Volatil oils 7% from rhizomes of Curcuma longa	Antidepressants	8	Depression (IDS-SR30), anxiety (STAI-S*, STAI-T)
Lopresti and Drummond (2017)	Double-blind RCT, parallel	Australia	123 (33 high dosage*, 28 low dosage*, 26 curcumin and saffron, 36 placebo)	43.11 (18–65)	14/109	MDD (DSM-IV)	Moderate	BCM-95®	1000 mg (high dosage), 500 mg (low dosage)	Volatil oils 7% from rhizomes of Curcuma longa	Antidepressants	12	Depression (IDS-SR30), anxiety (STAI-S*, STAI-T)
Panahi et al. (2015)	Open-label, parallel	Iran	111 (61, 50 placebo)	40.55 (18-65)	51/60	MDD (DSM-IV)	Not reported	C3 Complex®	1000 mg	10 mg bioperine®	Tryciclic antidepressants, benzodiazepines, SSRI, SNRI	6	Depression (BDI-II*, HADS-D), anxiety (HADS-A)
Sanmukhani et al. (2014)	Double-blind RCT, parallel	India	60 (20* curcumin plus fluoxetine, 20 curcumin alone, 20 fluoxetine*)	37.27 (not reported)	21/39	MDD (DSM-IV)	Severe	BCM-95®	1000 mg	Volatil oils 7% from rhizomes of Curcuma longa	Fluoxetine	6	Depression (HAM-D17), clinical global impression (CGI-I, CGI-S*)
Setiawati, Ikawati, and Kertia (2017)	Double-blind RCT, parallel	Indonesia	14 (10, 4 placebo)	33.28 (20–59)	0/14	Systemic Lupus Erythematosus	Mild to moderate	Curcuma Xanthorrhiza	150 mg	None	Not reported	4	Depression (BDI)
Yu et al. (2015)	Double-blind RCT, parallel	China	100 (50, 50 placebo)	44.68 (31–59)	100/0	MDD (DSM-IV)	Moderate	Curcumin 70%, demethoxicurcumin 20%, double demetoxicurcumin 10%	1000 mg	None	Escitalopram	6	Depression (HAM-D17*, MADRS)

Legend: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; DSM: Diagnostic and statistical manual of mental disorders; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; IDS-SR30: Self-rated Inventory of Depressive Symptomatology; MADRS: Montgomery–Åsberg Depression Rating Scale; RCT: randomized-controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; STAI-S: State-Trait Anxiety Inventory-State; STAI-T: State-Trait Anxiety Inventory-Trait.
*Data used for meta-analyses.

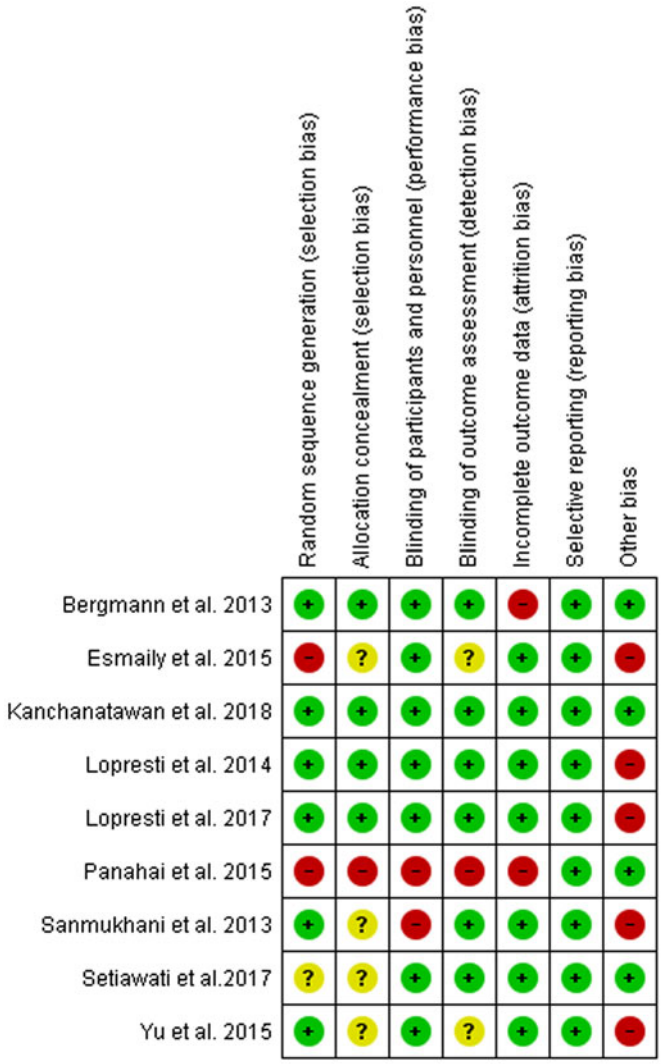

Figure 2. Risk of bias assessment of the included studies. Legend: Green (+) = Low risk of bias; Yellow (?) = Unclear risk of bias; Red (-) = High risk of bias.

considered five out of nine studies (Esmaily et al. 2015; Lopresti et al. 2014; Lopresti and Drummond 2017; Sanmukhani et al. 2014) at high risk of bias, because curcumin was supplemented by a pharmaceutical company. The risk of bias of the included studies are presented in Fig. 2.

Effect of curcumin on depressive symptoms

All 9 studies measured depressive symptoms, which represented the primary outcome of the present systematic review. A total of 10 comparisons were inserted in the meta-analysis, since for Lopresti and Drummond (2017) two groups (high and low dosage curcumin) were considered as active treatment. As reported in Table 1, depression was measured by means of several different scales, such as the Hamilton Depression Rating Scale (HAM-D), full scale (Williams 1988) or 17-items scale (Fleck et al. 1995), the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979), the Beck Depression Inventory (BDI; Beck et al. 1961), the Inventory of Depressive Symptomatology Self-Report (IDS-SR30; Rush et al. 1996) and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983).

Random effects meta-analysis (10 studies, 531 participants, of which 285 in the curcumin group and 246 in the comparison group), showed a significant effect of curcumin on depressive symptoms (Hedge's $g = -0.75$, 95% CI -1.11 to -0.39, $p < 0.001$) with large effect size. Heterogeneity was low ($I^2 = 26.28\%$). By removing each study from the overall effect size, we did not find any significant difference in our results. Forest plot is presented in Fig. 3a.

As *a priori* stated, we decided to explore the effect of five moderators with subgroup analyses. According to random-effects meta-analyses, we did not find any statistically significant difference in people with MDD compared to depression secondary to a medical condition (between-group heterogeneity $Q = 0.12$, df $= 1$, $p = 0.73$). However, while in the subgroup of studies with patients with MDD depression significantly improved for the curcumin group (8 studies, Hedge's $g = -0.74$, 95% CI -1.11 to -0.36, $p < 0.001$), no significant differences were found when considering only the studies which recruited patients with depression secondary to a medical condition (2 studies, Hedge's $g = -1.07$, 95% CI -2.95 to 0.8, $p = 0.26$) (see Table 2).

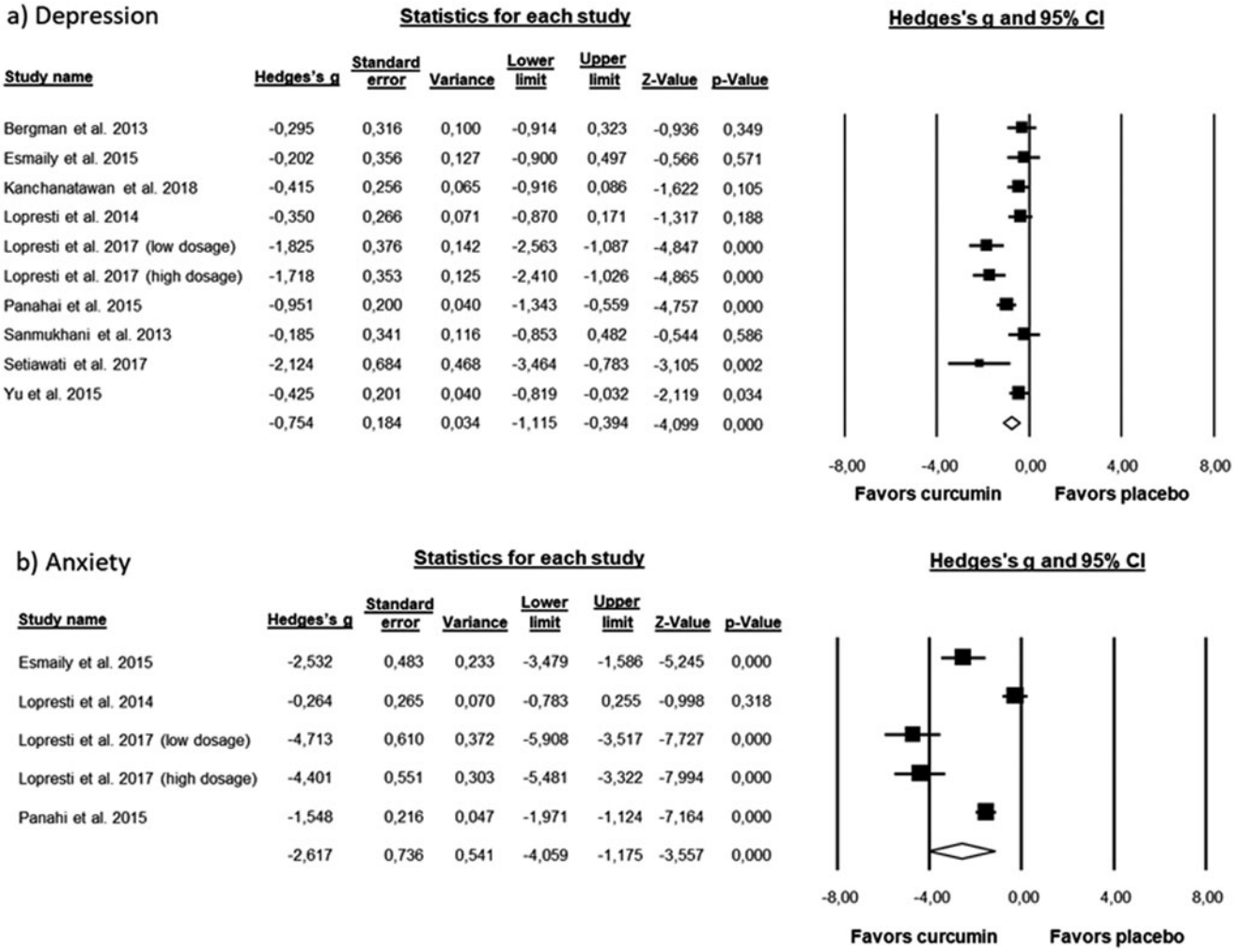

Figure 3. Meta-analyses of the effect of curcumin in people with depressive disorders on the following outcomes: (a) depression; (b) anxiety.

Table 2. Subgroup meta-analyses of the effect of curcumin on depression.

Variable	Subgroup	*N* of studies	Hedge's *g* (95% CI)	*p*-value	*Q*	Q df	I^2 (%)
Daily dosage	≤500 mg/day	3	−1.34 (−2.55 to −0.13)	0.03	1.71	2	0
	>500 mg/day	7	−0.6 (−0.95 to −0.25)	0.001	7.30	6	17.87
Duration	≤6 weeks	6	−0.56 (−0.94 to −0.18)	0.004	6.58	5	23.99
	>6 weeks	4	−1.04 (−1.8 to −0.28)	0.007	3.21	3	6.51
Type of depression	Major depression	8	−0.74 (−1.11 to −0.36)	<0.001	9.15	7	23.49
	Depression secondary to a medical condition	2	−1.07 (−2.95 to 0.8)	0.262	1	1	0
Risk of bias	High risk	6	−1.02 (−1.59 to −0.45)	<0.001	6.23	5	19.75
	Low or unclear risk	4	−0.47 (−0.9 to −0.04)	0.034	2.39	3	0
Depression status at baseline	Mild	2	−1.07 (−2.95 to 0.8)	0.262	1	1	0
	Moderate	5	−0.89 (−1.47 to −0.32)	0.002	5.08	4	21.22
	Severe	2	−0.24 (−0.7 to 0.21)	0.291	0.06	1	0

Moreover, no significant difference was found according to the daily curcumin dosage (≤500 mg or >500 mg/daily, between-group heterogeneity $Q = 1.32$, $df = 1$, $p = 0.25$) and according to the duration of active treatment (≤6 weeks or >6 weeks, between-group heterogeneity $Q = 1.21$, $df = 1$, $p = 0.27$). Also, no differences were found according to the risk of bias (low and unclear or high risk of bias, between-group heterogeneity $Q = 2.24$, $df = 1$, $p = 0.13$). Finally, no significant difference was found while comparing studies with different levels of depression at baseline (mild, moderate, or severe, between-group heterogeneity $Q = 3.36$, $df = 2$, $p = 0.19$). Nevertheless, while examining subgroups separately, a significant effect was found for moderate depression at baseline (Hedge's $g = -0.89$, 95% CI −1.47 to 0.32, $p = 0.002$); on the contrary, no significant effect could be detected in the mild (Hedge's $g = -1.07$, 95% CI −2.95 to 0.8, $p = 0.26$) and in the severe depression (Hedge's $g = -0.24$, 95% CI −0.7 to 0.21, $p = 0.29$) groups. It is worth mentioning that all within-group analyses with no significant effects included only two studies. Subgroup analyses were reported in Table 2.

Effect of curcumin on anxiety symptoms

Anxiety symptoms were measured in four studies, by means of the Hamilton Anxiety Rating Scales (HAM-A; Maier et al. 1988), the Beck Anxiety Inventory (BAI; Beck et al. 1988) or the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983).

Random effects meta-analysis (5 studies, 284 participants, of which 160 in the curcumin group and 124 in comparison group) showed a significant effect of curcumin on anxiety, with large effect size (Hedge's $g = -2.62$, 95% CI -4.06 to -1.17, $p < 0.001$). Heterogeneity between studies was low ($I^2 = 23.89\%$). By removing each study from the overall effect size, we did not find any significant difference in our results. Meta-analysis is presented in Fig. 3b.

Effect of curcumin on clinical global impression

Only two studies (Bergman et al. 2013; Sanmukhani et al. 2014) evaluated the efficacy of curcumin on clinical impression, measured by the Clinical Global Impression-Severity (CGI-S; Busner and Targum 2007), for a total of 74 participants. Due to the small number of studies and participants, we did not perform a meta-analysis. Both studies did not report any significant difference in clinical global impression as measured by the CGI-S.

Discussion

Curcumin is a spice frequently used in dietary regimens of Asian population, such as in India or China. Its anti-oxidant and anti-inflammatory properties have been exploited for centuries for the treatment of several chronic diseases. Also, its usefulness as complementary treatment in several neuropsychiatric diseases has been reported by several authors; the number of trials testing its efficacy in mental health conditions have been constantly increasing over the years, both in animal models and in humans. Given these properties, it has been hypothesized that curcumin might be useful in the treatment of depression, a condition currently affecting millions of people worldwide, which is going to become the most important cause of disability in 2020 (World Health Organization 2017).

Our meta-analysis showed that curcumin might be effective as adjunctive treatment in depressive disorders. Many preclinical trials have highlighted curcumin's potential antidepressant-like effects in animal models, with similar effects to conventional antidepressants like fluoxetine and imipramine (Sanmukhani, Anovadiya, and Tripathi 2011). Curcumin appears also involved in serotonin and dopamine modulation (Kaufmann et al. 2016). However, the most frequently studied mechanisms of action are related to its antioxidant and anti-inflammatory properties (Kaufmann et al. 2016). For instance, curcumin is an inhibitor of monoaminoxidase A and B (Baek et al. 2018), which are widely distributed mitochondrial enzymes, with a major role in the metabolization of released neurotransmitters and in the detoxification of a large variety of endogenous and exogenous amines (Finberg and Rabey 2016). Moreover, it seems to increase the levels of brain-derived neurotrophic factor (BDNF) (Franco-Robles et al. 2014; Hurley et al. 2013), a neurotrophin implicated in the etiopathogenesis of depression (Martinowich, Manji, and Lu 2007). Another potential mechanism of action of curcumin on depressive symptoms is related to the suppression of transcription signaling pathways of some nuclear factors, such as nuclear factor kappa B, which is essential for the production of pro-inflammatory cytokines (such as interleukin-6 and interleukin-1β) and is thus involved in the pathogenesis of inflammation (Bava et al. 2018). Finally, curcuminoids reduces the levels of circulating C-reactive protein, a biomarker of systemic inflammation (Sahebkar 2014). As previously mentioned, a large amount of literature has linked inflammation to the development of depressive symptoms (Kiecolt-Glaser, Derry, and Fagundes 2015), and curcumin properties may help improving inflammatory symptoms in depressed individuals.

Our results also suggest a significant positive effect of curcumin on anxiety symptoms, which are highly prevalent in people with depressive disorders. This finding is in contrast with a recent study (Ceremuga et al. 2017), reporting that curcumin did not demonstrate anxiolytic effects or changes in behavioral despair in a rat model. Moreover, researchers did not observe interactions of curcumin with the benzodiazepine site of the γ- aminobutyric acid (GABA)-A receptor (Ceremuga et al. 2017). Nevertheless, several other mechanisms may explain the beneficial effects of this spice on anxiety levels. First, curcumin seems to increase serotoninergic transmission in rats and interferes with serotonin turnover inhibiting monoamine oxidase (MAO). This mechanism leads to higher serotonin levels in medial prefrontal cortex brain area (Benammi et al. 2014). Other authors reported that curcumin favors the conversion of hepatic α-linoleic acid in docosaesaenoic acid (DHA), an omega-3 fatty acid with anxiolytic-like properties, also favoring its accumulation in the brain (Wu et al. 2015). Third, curcumin has been shown to suppress the synthesis of an isoform of nitric oxide synthase (iNOS), which is increased in brain cortex during stress, thus producing anxiolytic-like effects (Gilhotra and Dhingra 2010). However, it is important to underline that these findings are based only on preclinical studies, and, to our knowledge, no specific trials evaluating the efficacy of curcumin in anxiety disorders have been conducted.

Notably, none of the included studies examined cognition as an outcome. As reported by literature, depressed people frequently show cognitive problems, which may affect several domains, ranging from memory to executive functions, from vigilance to verbal abilities (Ahern and Semkovska 2017; Brondino, Rocchetti, et al. 2017; MacQueen and Memedovich 2017). Nevertheless, previous epidemiological studies examined the neuroprotective effect of curcumin and reported that its regular consumption may be associated with improvements in cognitive functions (Zhu et al. 2019). Moreover, because depression is a risk factor for dementia (Almeida et al. 2017), curcumin's multifaceted neuroprotective effects may further support its use for depressed patients.

To our knowledge, this is the most recent and up-to-date meta-analysis studying the efficacy of curcumin on depression. In addition, this is the first review to specifically analyze the efficacy of curcumin on anxiety symptoms in people with MDD or secondary depressive disorders. However, several limitations should be considered while discussing the results of the present study. First, our meta-analysis included only nine articles, anxiety was evaluated only in four trials (involving five active treatment groups), and clinical global impression in two studies. Further trials are needed to explore the potential role of curcumin as an add-on therapy in depression and anxiety. Another consequent limitation is related to the number of patients. In fact, samples of the studies included in our systematic review are generally small. Since curcumin is easily available and well-tolerated by patients, it would be desirable to enlarge the samples in future studies. Additionally, due to the unavailability of databases of all trials, we could not perform a single patient data analysis which would undoubtedly be more rigorous. Notably, most of the included studies were conducted in Asian countries, where dietary regimes habitually include curcuminoids. In future trials, it would be interesting to test the effects of curcumin also in Western countries, since baseline dietary conditions might be different. Nevertheless, the greater effect in favor of curcumin was shown in the two studies conducted in Australia (Lopresti and Drummond 2017; Lopresti et al. 2014). Also, it is worth mentioning that dietary regimens have not been adequately reported by authors of the trials included in the present review. Finally, only two studies evaluated the efficacy of curcumin on depressive and anxiety symptoms related to a medical condition. Since curcuminoids are largely known for their beneficial effects in chronic diseases (e.g. diabetes, inflammatory bowel disease, cancer, arthritis, etc.), future research should investigate also mood and stress-related disorders while investigating the role played by curcumin efficacy in chronic organic conditions.

In conclusion, our results regarding the efficacy of curcumin in depression in addition to standard care are promising. However, our findings need to be cautiously interpreted since they still rely on a small number of trials and subjects. For this reason, it would be desirable to implement further clinical trials to better understand the mechanisms underlying the efficacy of curcumin in depressed patients.

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ORCID

Laura Fusar-Poli http://orcid.org/0000-0002-5847-6947

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