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Research report

Curcumin for the treatment of major depression: A randomised, double-blind, placebo controlled study

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ABSTRACT

Background: Curcumin, the principal curcuminoid derived from the spice turmeric, influences several biological mechanisms associated with major depression, namely those associated with monoaminergic activity, immune-inflammatory and oxidative and nitrosative stress pathways, hypothalamus-pituitary-adrenal (HPA) axis activity and neuroprogression. We hypothesised that curcumin would be effective for the treatment of depressive symptoms in individuals with major depressive disorder.
Methods: In a randomised, double-blind, placebo-controlled study, 56 individuals with major depressive disorder were treated with curcumin (500 mg twice daily) or placebo for 8 weeks. The primary measure was the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}). Secondary outcomes included IDS-SR_{30} factor scores and the Spielberger State-Trait Anxiety Inventory (STAI).
Results: From baseline to week 4, both curcumin and placebo were associated with improvements in IDS-SR_{30} total score and most secondary outcome measures. From weeks 4 to 8, curcumin was significantly more effective than placebo in improving several mood-related symptoms, demonstrated by a significant group *x* time interaction for IDS-SR_{30} total score ($F_{1, 53}=4.22$, $p=.045$) and IDS-SR_{30} mood score ($F_{1, 53}=6.51$, $p=.014$), and a non-significant trend for STAI trait score ($F_{1, 48}=2.86$, $p=.097$). Greater efficacy from curcumin treatment was identified in a subgroup of individuals with atypical depression.
Conclusions: Partial support is provided for the antidepressant effects of curcumin in people with major depressive disorder, evidenced by benefits occurring 4 to 8 weeks after treatment.
Limitations: Investigations with larger sample sizes, over extended treatment periods, and with varying curcumin dosages are required.

1. Introduction

Disturbances in monoaminergic neurotransmission, particularly around serotonin availability, were originally posited as the primary cause of major depression (Cowen, 2008). However, studies now confirm that major depression is associated with a large array of biological disturbances. These include dysregulation in the hypothalamus-pituitary-adrenal (HPA) axis, activation of immune-inflammatory pathways, increased oxidative and nitrosative stress, neuroprogression, and mitochondrial dysfunction (Leonard and Maes, 2012; Maes et al., 2011). Consequently, this has sparked interest in compounds that target these pathways. Examples include anti-inflammatory treatments influencing immuno-inflammation such as cyclooxygensase-2 (COX-2) inhibitors, aspirin, minocycline and polyunsaturated fatty acids (Berk et al., 2013a; Fond et al., 2014; Muller, 2013) and antioxidant therapies to increase antioxidant defences and lower free radical damage such as n-acetyl cysteine, Ebselen, vitamin E and coenzyme-Q_{10} (Berk et al., 2013b; Scapagnini et al., 2012). Interestingly, despite pharmaceutical antidepressants originally being heralded as targeting monoaminergic actions, there is also evidence that they can modulate immuno-inflammation, reduce oxidative stress, enhance neurotrophic factors and influence HPA activity (Abdel-Wahab and Salama, 2011; Andrade and Rao, 2010; Hannestad et al., 2011; Kocki et al., 2012; Schule, 2007).

Curcumin is the most active compound of the Indian spice turmeric and comprises 2–8% of most turmeric preparations

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(Sharma et al., 2005). Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a low molecular weight polyphenol, first chemically characterised in 1910 by Milobedzka et al. (1910) and influences all of the aforementioned biological mechanisms (Aggarwal and Harikumar, 2009; Lopresti et al., 2012). More specifically, curcumin is a potent antioxidant that can lower markers of oxidative stress (Naik et al., 2011; Rai et al., 2010), modulate immuno-inflammation by acting as a COX-2 inhibitor (Lee et al., 2011; Plummer et al., 1999) and lower pro-inflammatory cytokines (Basnet and Skalko-Basnet, 2011; Belcaro et al., 2010), provide significant neuroprotection (Huang et al., 2011; Xu et al., 2007), modulate HPA activity (Huang et al., 2011; Li et al., 2009) and influence monoamine transmission through its effect on serotonergic and dopaminergic activity (Bhutani et al., 2009; Kulkarni et al., 2008; Xia et al., 2007). In animal studies, antidepressant effects of curcumin have been attributed to its serotonergic, dopaminergic, neuroprotective and HPA-modulating effects (Huang et al., 2011; Kulkarni et al., 2008; Xu et al., 2006). Two clinical trials have also now been completed investigating the antidepressant effects of curcumin in people with major depression. In the first study, curcumin as an add-on to antidepressant therapy did not enhance treatment outcome (Bergman et al., 2013), whereas in the second trial curcumin demonstrated similar antidepressant efficacy to fluoxetine (Sanmukhani et al., 2014). However, the latter study lacked a placebo-control and volunteers were not blinded.

The purpose of this study was to expand investigation into the antidepressant effects of curcumin supplementation in people with major depressive disorder. It was hypothesised that treatment with curcumin would lead to greater antidepressant benefits than a placebo, reflected by reductions in the administered depression and other mood-related self-report questionnaires. Curcumin was also hypothesised to have greater benefits for participants with atypical depression as it is associated with dysregulated immune-inflammatory pathways (Hickman et al., 2013; Lamers et al., 2013).

2. Materials and methods

2.1. Study design

This study was an 8-week, randomised, double-blind, placebo-controlled clinical trial (Fig. 1). The trial protocol was approved by the Human Research Ethics Committee at Murdoch University, Western Australia. The trial was registered with the Australian New Zealand Clinical Trials Registry (no. 12612001260819) and participants were recruited between February and November 2013, across the Perth, Western Australia metropolitan area. Recruitment occurred through advertisements and promotions in community newspapers and a health magazine, and after interviews with local radio media outlets.

Participants were randomly and equally allocated into two groups (placebo and curcumin) using a randomisation calculator (http://www.randomization.com). Both curcumin and placebo capsules were packed in identical containers labelled by participant code numbers and were allocated according to order of participant enrolment in the study.

2.2. Participants

Inclusion criteria: male and female participants aged 18 to 65 years were eligible to participate if they met the DSM-IV criteria for current major depressive disorder and had an Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) score ≥ 14. The diagnosis of major depression was made by the first author, an experienced clinical psychologist, using The Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) (Sheehan et al., 1998). Pharmaceutical antidepressants, the use of the contraceptive pill and no more than once a week use of analgesics were permissible. If participants were on pharmaceutical antidepressants, the drug dosage or type must have been stable for the past 8 weeks and throughout the duration of the study. Only non-smokers were included in the study and volunteers were not currently taking turmeric/curcumin supplements. If volunteers were receiving psychological therapy, the treatment must have commenced at least 8 weeks prior to participating in the study.

Exclusion criteria: participants with a psychotic disorder, bipolar disorder, comorbid obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, or any substance abuse or dependence disorder were excluded, as were participants assessed as having high risk of suicide. Volunteers were also excluded if they suffered from medical illnesses including diabetes, autoimmune diseases, cardiovascular disease, hypertension, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis), chronic fatigue syndrome, fibromyalgia and asthma; were pregnant or intended to fall pregnant; currently breastfeeding; had suffered from an infection or illness over the past month; were currently taking any antiplatelet or anticoagulant medications; or had been diagnosed with any coagulation disorder.

2.3. Interventions

Placebo (cellulose) and curcumin capsules were supplied by Arjuna Natural Extracts Ltd. (Kochi, India), and were identical in appearance. Curcumin was provided in a 500 mg capsule (BCM-95®) containing total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of *Curcuma longa* Linn. Participants were directed to take one capsule, twice daily with or without food for 8 weeks. Curcumin was used at a dose of 1000 mg/day. Medication compliance was measured by volunteer-reported pill count at weeks 4 and 8.

2.4. Outcomes

2.4.1. Self-report questionnaires

2.4.1.1. Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}). The IDS-SR_{30} was used as the primary outcome measure. It contains 30 items measuring depressive symptoms based on the DSM-IV criteria for major depressive episode (Rush et al., 1986, 1996). Respondents are asked to rate the severity and frequency of specific symptoms present over the past 7 days. The IDS-SR_{30} has acceptable psychometric properties in depressed outpatients (Rush et al., 2000, 1996; Trivedi et al., 2004) and correlates highly with common depression inventories such as the $HRSD_{17}$, BDI, and MADRS (Corruble et al., 1999; Rush et al., 2000, 1996).

In a factor analytical study on the IDS-SR_{30}, two dimensions were identified: a 'mood/cognition' factor representing affective and cognitive symptoms (IDSm), and an 'anxiety/arousal' factor indicating arousal and somatic complaints (IDSa) (Wardenaar et al., 2010). In addition, items in the IDS-SR_{30} associated with 'atypical' and 'melancholic' depression have been used for the clinical subtyping of these two subtypes of depression (Gili et al., 2012). This item analysis was used to categorise volunteers into atypical or melancholic depression.

2.4.1.2. The Spielberger State-Trait Anxiety Inventory (STAI). The STAI is a self-report tool for assessing anxiety consisting of two

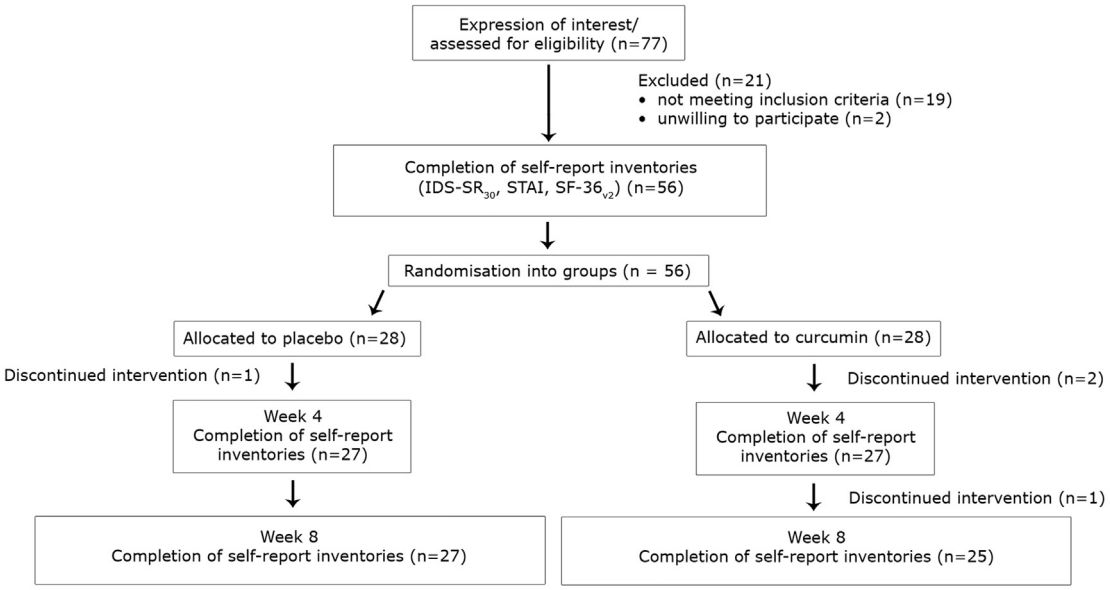

Fig. 1. Systematic illustration of study design.

subscales (state and trait anxiety) each containing 20 items (Spielberger, 1983). The STAI is among the most widely researched and commonly used measures of general anxiety and has good reliability and validity (Metzger, 1976; Okun et al., 1996). The STAI was considered an appropriate measure given its strong correlation with measures of depression (Kennedy et al., 2001).

2.5. Statistical analysis

2.5.1. Treatment condition on mood measures

Two successive analyses were conducted. The first compared curcumin versus placebo groups. Second, as an exploratory analysis, volunteers with atypical depression were compared across treatment groups (curcumin versus placebo). Analysis of volunteers with melancholic depression could not be completed due to limited numbers ($n=3$).

Independent samples t-tests were used to compare demographic variables across the treatment groups for continuous variables, and Pearson Chi-squared tests (or Fisher exact test for low cell counts) were used to compare categorical data. Individual mood measures (IDS-SR_{30}, STAI, and relevant sub-scores) were assessed for differences between baseline, mid-point (week 4) and end-point (week 8) by a mixed repeated-measures analysis of variance (ANOVA).

Analyses for time (baseline, midpoint and post-treatment) within each treatment condition, and treatment (curcumin and placebo) x time (baseline, midpoint and post-treatment) effects were conducted. Planned contrasts were also conducted to compare mood changes at differing time points (i.e., baseline to week 4; week 4 to week 8). There were no significant outliers in data as assessed by the visual inspection of Q–Q plots, although questionnaire data was not normalised. The repeated measures ANOVA were considered appropriate for statistical analyses as it is relatively robust to violations of normality when group sample sizes are equivalent (Tabachnick and Fidell, 2007). Data from all participants were included in analyses (intention to treat, with multiple imputation for missing values).

For all the tests, statistical significance was set at $P< 0.05$ (two-tailed). All data were analysed using SPSS (version 21; IBM, Armonk, NY).

3. Results

3.1. Study population

3.1.1. Baseline questionnaire and demographic information

Seventy-seven people were screened for participation in the study and 56 met inclusion/exclusion criteria and were enrolled to participate. Twenty-eight people were randomised into the placebo group and 28 into the treatment (curcumin) group. Fifty-two participants completed up to week 8. There were 4 drop-outs, one from the placebo group and three from the curcumin group, with no significant difference between the dropout rate in each group. Reasons for withdrawal included an unexpected visit overseas for family purposes (1 in the curcumin group), flare up of digestive complaints (1 in the curcumin group), and inconsistent intake of allocated capsules (1 each in the curcumin and placebo group). As shown in Tables 1 and 2, there were no significant differences between the two groups for any baseline mood questionnaire scores or demographic variables, except for distribution of medical illnesses, with greater reported medical illnesses in the placebo ($n=15$) versus curcumin ($n=5$) group (X^2 (1)=7.78, p-=.011). Medical illness was therefore included as a covariate in the repeated measures ANOVA analyses.

Exploratory analyses were conducted on 18 participants identified as suffering from atypical depression (placebo, $n=8$; curcumin, $n=10$). There were no significant differences between the two treatment groups for any baseline mood questionnaires. Demographic characteristics were also similar across treatment groups, except for differences in mean age (placebo, $x=50.75$; curcumin, $x=40.80$). The difference, 9.95, 95% CI [0.81, 19.09] was significant ($t(16)=2.31$, $p=.035$). Age was therefore included as a covariate in repeated measures ANOVA analyses on the atypical depression sample.

3.2. Outcome measures

3.2.1. Treatment effects on mood measures

3.2.1.1. IDS—depression measures. Changes in IDS scores across both treatment groups and repeated measures ANOVA significance values are listed in Table 3. There was a significant reduction in all IDS scores across both groups for time although there were

Table 1
Demographic characteristics of curcumin and placebo participants.

	Placebo $n=28$	Curcumin $n=28$	p-value
Age, years mean (SD)	48.54 (11.73)	44.04 (11.94)	0.16[b]
BMI (kg/m^2)mean (SD)	27.06 (4.76)	26.12 (5.48)	0.51[b]
Sex *n*			
Female	20	20	1.00[c]
Male	8	8	
Marital status *n*			
Single	7	11	.551[c]
Married	12	11	
De facto[a]	5	4	
Divorced	2	2	
Widowed	2	0	
Educational status *n*			
Secondary	6	9	.658[c]
Tertiary	17	15	
Post-graduate	5	4	
General health *n*			
Great	9	7	.194[c]
Average	19	18	
Poor	0	3	
Medical illness *n*			
Yes	15	5	.011[c]
No	13	23	
Antidepressant medication *n*			
Yes	9	10	1.00[c]
No	19	18	
Antidepressant class *n*			
SSRI	7	6	.628[c]
SNRI	2	4	
Depression episodes *n*			
Single episode	11	7	.391[c]
Recurrent episodes	17	21	
Exercise frequency *n*			
Never/rarely	6	4	.421[c]
1–2 times week	9	10	
3–5 times week	11	14	
6+ times week	2	0	
Injuries causing regular pain *n*			
Yes	14	10	.418[c]
No	14	18	

SSRI=selective serotonin reuptake inhibitor; SNRI=selective serotonin-norepinephrine reuptake inhibitor.

[a] Domestic partner outside marriage.
[b] Independent samples *t*-test.
[c] Chi-square Test.

Table 2
Baseline questionnaire scores between curcumin and placebo participants.

	Placebo $n=28$ Mean (SD)	Curcumin $n=28$ Mean (SD)	p-value[a]
STAI state	50.25 (13.02)	52.00 (13.17)	.62
STAI trait	55.89 (13.24)	56.29 (8.30)	.90
IDS	33.14 (9.39)	33.04 (9.39)	.97
IDS mood	14.64 (5.67)	13.93 (5.37)	.63
IDS arousal	6.68 (2.79)	6.82 (2.40)	.84

Data are shown as mean (SD).

[a] Independent samples *t*-test.

no significant group *x* time interactions for any IDS measure across the full 8 weeks of treatment. However, contrasts revealed a significant group *x* time interaction from week 4 to week 8 for IDSm ($F_{1,\ 53}=6.51$, $p=.014$) and IDS total ($F_{1,\ 53}=4.22$, $p=.045$).

Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in all IDS scores, in both the curcumin and placebo groups. However, there were no significant changes in any IDS scores from week 4 to week 8 in the placebo group. In the curcumin group, there were significant changes in IDS total ($F_{1,\ 27}=5.50$, $p=.026$), and IDSm ($F_{1,\ 27}=6.07$, $p=.020$) over this time. This indicates that in the placebo group, all improvements in IDS depressive scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

3.2.1.2. STAI—anxiety measures. Changes in STAI scores across both treatment groups and repeated measures ANOVA significance values are listed in Table 3. There were significant reductions in STAIs and STAIt scores across both groups for time ($p<0.001$; for all scores across time). There were no significant group *x* time interactions for either STAIs or STAIt across the full 8 weeks of treatment.

Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in both STAIs and STAIt scores, in both the curcumin and placebo groups. However, from week 4 to week 8, in the placebo group, there were no significant changes in either score. In the curcumin group, there was a significant change in STAIt ($F_{1,\ 27}=4.36$, $p=.046$), and non-significant trend for STAIs ($F_{1,\ 27}=3.64$, $p=.067$) over this time. This indicates that in the placebo group, improvements in STAI anxiety scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

3.2.2. Atypical depression sub-group

3.2.2.1. IDS—depression measures. There was a significant reduction in most IDS scores across both groups for time. In the placebo group, there were significant time effects for IDS total ($p<0.05$), IDSm ($p<0.05$), but not IDSa ($p>0.05$). In the curcumin group, there were significant time effects for IDS total ($p<0.01$), IDSm ($p<0.001$), and IDSa ($p<0.01$). There were no significant group *x* time interactions in any IDS measure across the full 8 weeks of treatment (IDSm, $F_{2,\ 32}=2.40$, $p=.110$; IDSa $F_{2,\ 32}=0.62$, $p=.670$) although there was a non-significant trend for IDS total ($F_{2,\ 32}=2.73$, $p=.088$). Contrasts revealed a significant group *x* time interaction from week 4 to week 8 for IDS total ($F_{1,\ 16}=7.78$, $p=.013$) and IDSm ($F_{1,\ 16}=10.61$, $p=.006$).

In Fig. 2, changes in IDS scores are detailed for each treatment condition. Further ANOVA analyses revealed that from baseline to week 4 there were significant changes in IDS total ($F_{1,\ 7}=6.13$, $p=.043$) in the placebo group. In the curcumin group there were significant changes in IDS total ($F_{1,\ 9}=8.74$, $p=.016$), IDSm ($F_{1,\ 9}=10.30$, $p=.011$) and IDSa ($F_{1,\ 9}=9.11$, $p=.015$) over this time period. From week 4 to week 8, there were no further significant changes in any IDS score in the placebo group. However, in the curcumin group there were significant changes in IDS total ($F_{1,\ 9}=8.62$, $p=.017$), IDSm ($F_{1,\ 9}=9.86$, $p=.012$), and IDSa ($F_{1,\ 9}=6.42$, $p=.032$) scores over this time. This indicates that in the placebo group, all improvements in IDS depressive scores occurred in the first 4 weeks of treatment, while improvements continued in the curcumin condition.

3.2.2.2. STAI—anxiety measures. There were significant reductions in STAIs and STAIt scores across both groups for time ($p<0.001$:for all scores across time). There was no significant group *x* time interactions for either STAIs across the full 8 weeks of treatment. However, contrasts revealed a significant group *x* time interaction from week 4 to week 8 for STAIt ($F_{1,\ 15}=6.00$, $p=.027$). In Fig. 2, changes in STAI scores are detailed for each treatment condition. Further ANOVA analyses revealed that from baseline to week

Table 3
Changes in questionnaire scores over time.

	Treatment	Baseline		Week 4		Week 8		Treatment *x* time effect (p-value)		
								Baseline-week 4	week 4- week 8	Baseline - week 8
STAI—state, mean (SD)	Placebo ($n=28$)	50.25	(13.02)	43.14[a]	(13.30)	43.21[e]	(12.94)	.687	.255	.595
	Curcumin ($n=28$)	52.00	(13.17)	45.89[a]	(12.65)	42.29[c,e]	(12.21)			
STAI—trait, mean (SD)	Placebo ($n=28$)	55.89	(13.25)	49.82[a]	(12.79)	50.21[e]	(9.41)	.516	.097	.358
	Curcumin ($n=28$)	56.29	(8.30)	50.75[b]	(9.46)	47.96[c,e]	(11.32)			
IDS—total, mean (SD)	Placebo ($n=28$)	33.14	(11.88)	25.82[b]	(14.55)	25.89[e]	(13.43)	.313	.045*	.189
	Curcumin ($n=28$)	33.04	(9.39)	26.61[b]	(11.87)	22.71[c,e]	(9.36)			
IDS—mood, mean (SD)	Placebo ($n=28$)	14.64	(5.67)	10.50[b]	(6.88)	11.00[e]	(6.60)	.496	.014*	.192
	Curcumin ($n=28$)	13.93	(5.37)	11.00[b]	(5.34)	9.25[c,e]	(4.42)			
IDS—arousal, mean (SD)	Placebo ($n=28$)	6.68	(2.79)	5.64[b]	(3.37)	5.25[d]	(3.12)	.282	.312	.489
	Curcumin ($n=28$)	6.82	(2.40)	5.57[b]	(3.18)	4.71[e]	(2.81)			

Medical illness included as covariate

[a] $p < .01$—within group significant time effects from baseline to week 4.
[b] $p < .001$—within group significant time effects from baseline to week 4.
[c] $p < .05$—within group significant time effects from week 4 to week 8.
[d] $p < .01$—within group significant time effects from baseline to week 8.
[e] $p < .001$—within group significant time effects from baseline to week 8.

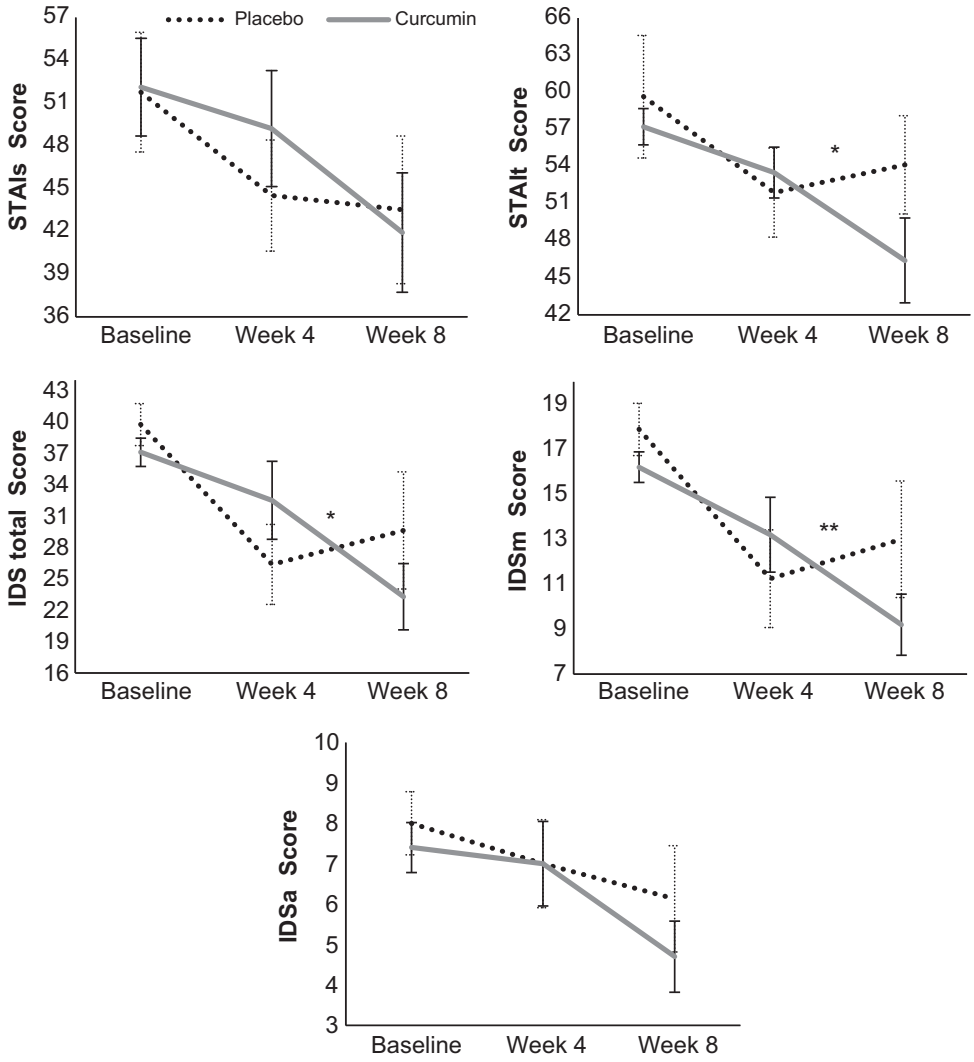

Fig. 2. Atypical depression—change in mood scores over time (± 1 Std. error) across curcumin and placebo groups. *($p < .05$); **($p < .01$) indicates significant group *x* time interaction for specified period.

Table 4
List and frequency of adverse events reported by participants.

Curcumin		Placebo	
Frequency	Reported complaints	Frequency	Reported complaints
16	No adverse events	14	No adverse events
7	Digestive: stomach bloating, nausea, mild diarrhoea	6	Digestive: appetite change, bloating, mild diarrhoea
0	Respiratory: none	1	Respiratory: breathing problems
3	Dermatological: dry skin, flaking skin	2	Dermatological: dry skin, flaking skin, itchy skin
2	Neurological: headaches, dizziness	2	Neurological: memory slower, tingling in hands
2	Pain: joint pain, back pain	4	Pain: joint pain, back pain, neck pain
2	Cardiovascular: racing heart, chest pain	0	Cardiovascular: none
3	Visual: sore eyes, dry eyes, blurry vision	0	Visual: none
1	Auditory: ringing in ears	2	Auditory: ringing in ears
2	Oral: dry mouth, sore gums	2	Oral: dry mouth, mouth ulcers

4 there were significant changes in STAIt scores, in the curcumin group only ($F_{1,\ 9}=11.62$, $p=.008$). Continued significant changes in STAIt occurred from weeks 4 to 8 in the curcumin group only ($F_{1,\ 9}=7.24$, $p=.025$).

3.2.3. Adverse events

Details of adverse events reported by participants are included in Table 4. All reported adverse events were of minor severity and only one participant in the curcumin intervention withdrew from the study as a result of reported side effects. This participant experienced an exacerbation of pre-existing digestive complaints (stomach bloating and pain). There were no significant differences between reported adverse events between placebo and curcumin groups.

4. Discussion

The results of this study provide partial support for the antidepressant and anxiolytic effects of curcumin in people suffering from major depressive disorder. While curcumin and placebo were equally effective in reducing depressive and anxiety symptoms in the first four weeks of treatment, curcumin was significantly more effective than placebo in lowering self-reported depressive and anxiety symptoms from weeks 4 to 8. When examining the effects of curcumin in people with atypical depression, curcumin had even greater antidepressant and anti-anxiety efficacy compared to placebo. Again, equivalent improvements in mood occurred from baseline to week 4 in both placebo and curcumin-treated individuals. However, from weeks 4 to 8, curcumin was significantly more effective in lowering total depressive symptoms (total IDS score), mood/cognitive depressive symptoms (IDSm), arousal-related symptoms (IDSa) and trait anxiety (STAIt).

While greater antidepressant effects of curcumin compared to placebo were observed from weeks 4 to 8, when evaluating the whole treatment period (i.e., baseline to week 8), curcumin was not found to be significantly more effective than placebo in reducing depressive and anxiety symptoms. Several explanations could account for this overall non-significant treatment effect: (1) it may be that curcumin lacks a true antidepressant effect in people with major depressive disorders, at least at the dose prescribed (i.e., 500 mg twice daily). However, this argument is countered by significant and near significant changes in several mood measures in the second half of treatment; (2) it is a reflection of the placebo response, typical in placebo-controlled trials. From a statistical point of view, when performing the analyses on the whole treatment period, the positive placebo response in the first month of treatment masked the positive gains from curcumin over the second study period (weeks 4 to 8). Placebo responses in depression trials are common and it has been suggested that true drug responses are characterised by a 2-week delay, with continued improvement thereafter, whereas placebo effects are characterised by abrupt, transient improvements (Rothschild and Quitkin, 1992). Although assessments were not completed until week 4, this study confirms a similar pattern of change—that is, in placebo-treated individuals, a response in the first month, followed by no change, or even worsening of symptoms thereafter. In contrast, curcumin-treated individuals continued to experience improvements over the course of the study; (3) the antidepressant effects of curcumin may not begin until after 4 weeks of intake, reflecting a slow acting, possibly longer term treatment for depression. It is feasible that specific mechanistic changes need to be set in motion and maintained for a period of time before mood changes prevail. The high portion of recurrent depressed sufferers enrolled in the study (approximately 70 per cent) may also contribute to curcumin's slow action in this trial. These possibilities require exploration through follow-up studies with larger sample sizes, and extended treatment periods.

The antidepressant effects of curcumin in people with major depressive disorder have now been investigated in two additional randomised clinical trials. As an add-on to newly commenced antidepressant medication (escitalopram or venlafaxine XR), curcumin, at a dose of 500 mg/day, did not enhance treatment efficacy compared to a placebo (Bergman et al., 2013). In this double-blind, placebo controlled, 5-week trial, there were significant improvements in depressive symptoms over time in both treatment groups. In the second study, Sanmukhani et al. (2014) compared the antidepressant effects of curcumin alone (500 mg twice daily), fluoxetine alone (20 mg/day) or curcumin plus fluoxetine (500 mg twice daily and 20 mg/day, respectively) in people suffering from major depressive disorder. In this randomised, single-blinded (researcher masked), 6-week trial, all three treatment conditions were associated with significant improvements in depressive symptoms. Group comparisons revealed comparable treatment efficacy across the three conditions. Weaknesses associated with this study include the lack of placebo control, and non-masking of participants from the treatment conditions.

The current study therefore adds to the aforementioned ones as the length of treatment was extended to 8 weeks, double-blind placebo controlled conditions were included, and curcumin was used a standalone treatment or was used in patients undergoing pre-existing, stabilised antidepressant or psychological therapies. Exploratory analyses on people with atypical depression were also conducted, and several questionnaires were used to assess depressive, anxiety and general health changes. Further support for the antidepressant effects of curcumin is provided by consistent findings of protective behavioural effects in animal models of depression and chronic mild stress (Jiang et al., 2013; Sanmukhani et al., 2011; Zhang et al., 2014).

An important finding from this study is the enhanced antidepressant and anxiolytic efficacy of curcumin in people with atypical depression. According to DSM-IV criteria, atypical depression is characterised by mood reactivity to actual or potential positive events, and two or more of the following features: significant weight gain or increased appetite, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity (American Psychiatric Association, 2000). Compared to healthy individuals, and people with melancholic or non-atypical depression, atypical depression is often associated with higher levels of inflammatory markers such as C-reactive protein (CRP) (Hickman et al., 2013; Lamers et al., 2013), IL-6 and tumour necrosis factor-α (TNF-α) (Lamers et al., 2013). Due to the anti-inflammatory effects of curcumin, it is this immuno-inflammatory dysregulation that may account for the increased efficacy of curcumin in people with atypical depression. In a recent meta-analysis on clinical trials it was concluded that curcumin lowers CRP levels (Sahebkar, 2014). It can also lower IL-6 (Belcaro et al., 2010; Zhou et al., 2011) and TNF-α levels (Aggarwal et al., 2013).

5. Limitations and directions for future research

The relatively small samples size used in this study limits the reliability and statistical power associated with the findings. For evaluation of curcumin's antidepressant effects, data from approximately 50 participants was obtained. Sample sizes were even lower when evaluating the effects of curcumin on people with atypical depression. The results from this study therefore require replication with larger sample sizes.

In this study, a high proportion (approximately 70%) of participants reported a history of multiple depressive episodes, thereby reflecting a sample with high chronicity of depression and likely treatment resistance. Comparative evaluations of the efficacy of curcumin with single- and recurrent-episode depressives would be useful, along with an examination of the influence of differing treatment periods and curcumin dosages.

Investigations into the antidepressant effects of curcumin would also be strengthened by studies controlling for important covariates such as medication use, psychological therapies, medical illnesses and BMI. While this 8-week study now represents the longest investigation into effects of curcumin on depression, future investigations with longer follow up periods are certainly warranted. Because the effects of curcumin were not recognised until after week 4, longer treatment duration will be necessary to determine if mood improvements maintain or increase over time.

Self-report instruments were used to monitor changes in mood. While this provides a valid index of clinical progress, the implementation of additional measures, such as reliable and valid clinician-rated instruments, will provide a more robust evaluation of the clinical effectiveness of curcumin.

Other areas of interest include investigations into the optimal curcumin dose for best antidepressant effects and the frequency of intake. In two studies a dose of 500 mg twice daily has been used, and in the other 500 mg once daily was used. Because of problems with bioavailability of curcumin, doses greater than these may be necessary to achieve optimal treatment efficacy. Increasing intake to 3 times a day may also be necessary to combat problems associated with the short half-life of curcumin (Anand et al., 2007).

In conclusion, the present findings provide partial support for the antidepressant effects of curcumin in people with major depressive disorder, and particularly atypical depression. However, replication with larger clinical trials, using variable doses, and conducted over an extended treatment period is required.

Conflict of interest

This study was supported in part by a grant from Arjuna Natural Extracts Limited to Murdoch University.

The authors report no biomedical financial interests or potential conflicts of interest.

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