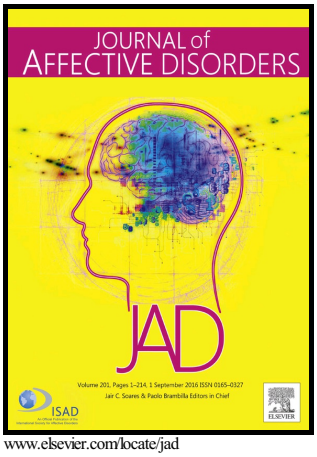

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Efficacy of Curcumin, and a Saffron/ Curcumin Combination for the Treatment of Major Depression: A Randomised, Double-Blind, Placebo-Controlled Study

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Keywords

Depression, Curcumin, Saffron, Antidepressant, Turmeric, Clinical Trial

ABSTRACT

Background:
Several studies have supported the antidepressant effects of curcumin (from the spice turmeric) and saffron for people with major depressive disorder. However, these studies have been hampered by poor designs, small sample sizes, short treatment duration, and similar intervention dosages. Furthermore, the antidepressant effects of combined curcumin and saffron administration are unknown.

Methods:
In a randomised, double-blind, placebo-controlled study, 123 individuals with major depressive disorder were allocated to one of four treatment conditions, comprising placebo, low-dose curcumin extract (250mg b.i.d.), high-dose curcumin extract (500mg b.i.d.), or combined low-dose curcumin extract plus saffron (15mg b.i.d.) for 12 weeks. The outcome measures were the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) and Spielberger State-Trait Anxiety Inventory (STAI).

Results:
The active drug treatments (combined) were associated with significantly greater improvements in depressive symptoms compared to placebo ($p=.031$), and superior improvements in STAI-state ($p<.001$) and STAI-trait scores ($p=.001$). Active drug treatments also had greater efficacy in people with atypical depression compared to the remainder of patients (response rates of 65% versus 35% respectively, $p=.012$). No differences were found between the differing doses of curcumin or the curcumin/saffron combination.

Limitations: Investigations with larger sample sizes are required to examine the efficacy of differing doses of curcumin and saffron/curcumin combination. Its effects in people with atypical depression also require examination in larger scale studies.

Conclusions: Active drug treatments comprising differing doses of curcumin and combined curcumin/saffron were effective in reducing depressive and anxiolytic symptoms in people with major depressive disorder.

INTRODUCTION

Major depressive disorder affects 6 to 8 percent of adults every year, and has a lifetime prevalence of 15 to 20 percent (Gelenberg, 2010; Richards, 2011). It is a disabling condition that has adverse effects on personal, social, occupational, and educational function. Depression is also associated with significant medical difficulties as there is a greater risk of mortality from all causes in people with depression compared to their non-depressed counterparts (Kozela et al., 2016). In fact, according to the World Health Organization (WHO, 2008), depression is the leading cause of disability as measured by Years Lived with a Disability and the fourth leading contributor to the global burden of disease. In a recent examination of a cohort of Danish adults, depression was associated with a reduced life expectancy of 14 years in men and 10 years in women (Laursen et al., 2016).

Major depressive disorder is primarily treated with psychological and/or pharmacological therapies, with research suggesting similar rates of efficacy (Sinyor et al., 2010). Unfortunately, these rates are far from ideal as approximately 60 to 80 percent of people do not obtain full symptom remission (Sinyor et al., 2010; Warden et al., 2007). Pharmacological interventions are also associated with several adverse effects that contribute to their early discontinuation (Goethe et al., 2007).

Interest in alternative and complementary therapies is high, as evidenced by a 2007 study confirming almost 50 percent of women with depression used complementary and alternative medicine over a one year period (Wu et al., 2007). In a more recent study of adults with bipolar disorder, 29 percent had used a dietary supplement for at least 7 days, and 20 percent used a supplement long term (Bauer et al., 2015). A commonly cited reason for their use relates to their perceived safety profile. Unfortunately, high-quality research on many herbal and nutraceutical therapies for depression is limited, reinforcing the need for ongoing research.

Curcumin, derived from the spice turmeric, and saffron (*Crocus Sativus L.*), are two commonly used spices that have been increasingly investigated for their antidepressant effects. In recent meta-analyses and systematic reviews, it was concluded that curcumin (Al-Karawi et al., 2015) and saffron (Hausenblas et al., 2013; Lopresti and Drummond, 2014) were more effective than placebo for the treatment of major depressive disorder. In several studies, saffron's antidepressant effects were also found to be similar to the antidepressant medications fluoxetine (Akhondzadeh Basti et al., 2007; Noorbala et al., 2005; Shahmansouri et al., 2014) and imipramine (Akhondzadeh et al., 2004). However, further research is warranted, particularly in determining optimal treatment dosages and length of treatment. Thus far, no study has been longer than 8 weeks, and investigated doses have often been similar across studies.

In previous studies on the antidepressant effects of curcumin extracts, a daily dose of 500mg b.i.d. has most commonly been used. We sought to determine whether a lower dose comprising 250mg b.i.d. would have similar antidepressant and anxiolytic efficacy. In addition, our aim was to investigate whether saffron augmented the antidepressant effect of curcumin. Both of these compounds appear to have similar antidepressant biological mechanisms of action, namely through their anti-inflammatory, antioxidant, monaminergic, hypothalamus-pituitary-adrenal (HPA) modulating, and neuroprotective effects (Lopresti and Drummond, 2014; Lopresti et al., 2012). However, saffron also contains four major bioactive compounds, crocins, crocetin,

picrocrocin and safranal, which are believed to contribute to its antidepressant activity. We hypothesized that the combination of saffron and curcumin, with its broader profile of active constituents, would lead to enhanced antidepressant and anxiolytic effects.

Our aim was also to investigate the symptomatic effects and safety profile of these spices over a 12-week period, making it the longest study to date on these ingredients for the treatment of major depression. As curcumin has shown particular promise in adults with atypical depression (Lopresti et al., 2014), its effects in participants with this subtype of depression were also examined.

MATERIALS AND METHODS

Study design

This was a 12-week, randomised, double-blind, placebo-controlled clinical trial, with a 1-week, placebo run-in phase (Figure 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 (Trial ID. ACTRN12615000791538) and participants were recruited through social and print media advertisements between August 2015 and February 2016, across the Perth, Western Australia metropolitan region.

Participants were randomly and equally allocated into four groups (placebo, high-dose curcumin, low-dose curcumin, and low-dose curcumin/ saffron combination) using a randomisation calculator (http://www.randomization.com). The randomisation structure comprised 8 randomly permuted blocks, containing 20 subjects per block. All capsules were packed in identical containers labelled by participant code numbers and were allocated according to order of participant enrolment in the study.

An a priori power analysis was undertaken to estimate required sample size. We predicted a moderate effect size of 0.7 for the treatment groups. Assuming a power of 80% and a type one error rate (alpha) of 5%, the number of participants per group to find an effect was estimated as 34.

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 ≥ 18. The diagnosis of major depression and atypical depression subtype 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, herbal/vitamin supplements, the use of the contraceptive pill and no more than once a week use of analgesics were permissible. If participants were on pharmaceutical antidepressants or supplements, the drug dosage or type must have been stable for the past 4 weeks and throughout the duration of the study. 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. Participants were asked about drug use in the initial interview but a drug screen was not conducted. Volunteers were also excluded if they suffered from self-reported 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 or 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.

Interventions

Placebo (cellulose), curcumin, and curcumin/saffron capsules were supplied by Dolcas-Biotech LLT. (New Jersey, USA), and were identical in appearance. All participants were commenced on a one-week, placebo run-in phase, where they were instructed to take one capsule, twice daily. After this blinded, one-week phase, they were then randomly allocated to one of four treatment conditions comprising twice-daily intake of the following capsules: (1) placebo, (2) low-dose curcumin containing 250mg of the patent curcumin, BCM-95® (LDC), (3) high-dose curcumin containing 500mg of BCM-95® (HDC), and (4) low-dose curcumin/ saffron combination, containing 250mg of BCM-95® and 15mg of saffron (LDC+S). Participants were directed to take capsules with or without food for 12 weeks.

Curcumin used in the capsules was derived from BCM-95® which contains total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of *Curcuma longa* Linn. Saffron (affron®), was derived from the stigmas of *Crocus sativus L.* and is standardised to contain >3.5% Lepticrosalides® (a measure of bioactive compounds present in saffron, including safranal and crocin). Medication compliance was measured by volunteer-reported pill count at weeks 4 and 8, and 12. Efficacy of participant treatment blinding was measured by asking participants to predict group allocation (placebo vs real drug treatment) at the completion of the study.

Outcomes

Self-report questionnaires

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; Rush et al., 1996). Respondents were 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; Rush et al., 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; Rush et al., 1996).

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

Statistical analysis

Treatment condition on mood measures

Two successive analyses were conducted. The first used data from all eligible participants, while a second planned analysis compared data from participants diagnosed with atypical depression to participants with other depression.

A one-way ANOVA was used to compare demographic variables across the treatment groups for continuous variables, and Pearson's Chi-square was used to compare categorical data.

Individual mood measures (IDS-SR_{30}, STAI) were assessed for differences between baseline and the three other time points (weeks 4, 8 and 12) using a mixed repeated-measures analysis of variance (ANOVA). Analyses for time (baseline, week 4, week 8 and week 12) within each treatment condition, and treatment (LDC, HDC, LDC+S, and placebo) x time effects were conducted. Planned contrasts were conducted to investigate treatment x time interactions between combined drug treatments (LDC, HDC, & LDC+S) and placebo (to determine whether, overall, curcumin was associated with anti-depressant effects); HDC and LDC (to investigate dose-response effects of curcumin); and LDC and LDC+S (to determine whether saffron augmented the anti-depressant effects of curcumin). There were no significant outliers in data as assessed by the visual inspection of Q-Q plots. Although questionnaire data were not normalised, repeated measures ANOVA was considered appropriate for statistical analyses as it is relatively robust to violations of normality (Tabachnick and Fidell, 2007). Where necessary, degrees of freedom were adjusted using the Greenhouse-Geisser approach to correct for violations of the sphericity assumption.

A further analysis was undertaken to compare response rates across treatment conditions. Greater than 50 percent reduction in IDS score was defined as a responder and was used for statistical comparisons across treatment conditions.

Participants' questionnaire data were used if they experienced less than a 30% change in IDS-SR_{30} score following the 1-week placebo run-in phase. This was done in an attempt to reduce the impact of placebo-effects, and/or to exclude participants with volatile depressive symptoms. Questionnaire scores following the one-week, placebo run-in phase were used as baseline data. Data from participants were included in analyses if questionnaire data were obtained at week 4 (intention to treat, with last observation carried forward for missing values).

For all the tests, statistical significance was set at $P< 0.05$ (two-tailed). All data were analysed using SPSS (version 22; IBM, Armonk, NY).

RESULTS

Study Population

Baseline questionnaire and demographic information

309 people were screened for participation in the study and 160 met inclusion/ exclusion criteria and were enrolled to participate. All 160 participants were placed on placebo for one-week prior to randomisation into treatment conditions. Seven people failed to take capsules and/or complete repeat questionnaires after the first week, and 30 people experienced greater than a 30 percent change in IDS score following the 1-week, placebo, run-in phase, leaving data from 123 participants available for analysis. Sample sizes for each treatment condition comprised 36 in the placebo, 33 in HDC, 28 in LDC, and 26 in LDC+S conditions.

111 participants complied with all necessary treatment requirements (i.e., consumed >70% of capsules and completed all self-report inventories) over the 12-week trial. Five dropped out of the placebo condition, 3 in the HDC condition, 2 in the LDC condition, and 2 in the LDC+S condition. There were no significant differences between the dropout rates across groups. Reasons for withdrawal included medication change, no response/ lost to follow up, and inconsistent capsule intake. No participants withdrew from the study due to reported adverse effects from capsule intake.

As shown in Table 1, there were no significant differences between the groups on any baseline mood questionnaire score or demographic variable.

Exploratory analyses were conducted on 80 participants placed on active drug treatments based on depressive subtype (atypical depression, n =34; other depression, n=46). There were no

significant differences in baseline mood questionnaires or demographic variables based on these depressive subtypes.

Outcome Measures

Treatment effects on mood measures

IDS – Depression measures

Changes in IDS scores across all treatment groups and repeated measures ANOVA significance levels are listed in Table 2. There was a significant reduction in IDS scores across all groups over time although IDS scores decreased in the placebo condition only in the first 4 weeks of treatment. In contrast, IDS scores decreased in the active drug conditions at several additional time points.

A direct comparison between all active drug treatments combined and placebo revealed a significant time x group interaction for IDS from baseline to week 12 ($F_{2.56,279} = 3.181$, $p = .031$). Comparisons between HDC and LDC ($F_{2.28,121} = 0.444$, $p = .675$), and LDC and LDC+S ($F_{2.49,120} = 0.329$, $p = .766$) revealed non-significant time x group interactions for IDS. Changes in depressive symptoms are detailed in Figure 2.

An analysis of IDS response rates revealed the following; 13% in placebo, 28% in active treatments combined, 28% in HDC, 27% in LDC, and 31% in LDC+S. The difference in response rates between placebo and active treatments combined approached but did not achieve statistical significance ($\chi 2(1) = 3.187$, $p = .074$).

STAI – Anxiety measures

Changes in STAI-state (STAI-S) and STAI-trait (STAI-T) scores across all treatment groups and repeated measures ANOVA significance values are listed in Table 2. Both STAI sub-scale scores

decreased significantly across all active drug treatment conditions. STAI-T also decreased significantly in the placebo group whereas STAI-S remained stable.

A direct comparison between all active drug treatments combined and placebo revealed a significant time x group interaction for STAI-S ($F_{2.75,300} = 7.201$, $p < .001$) and STAI-T ($F_{2.42,264} = 6.162$, $p = .001$) from baseline to week 12, favouring active drug treatments. A repeated measures ANOVA comparing (1) HDC and LDC, and (2) LDC and LDC+S revealed no significant group x time interactions for any STAI subscale scores. Changes in anxiety symptoms are detailed in Figure 2.

Atypical Depression Sub-group

A comparison between the effectiveness of combined drug treatments in participants diagnosed with atypical depression, compared to other depressed participants revealed greater efficacy in people with atypical depression in all of the measures used. When using data from all the active drug treatments combined, several significant time x group interactions were identified. Active drug treatments were significantly more effective for people with atypical depression compared to other depressed participants for IDS ($F_{2.64,206} = 4.471$, $p = .007$), STAI-S ($F_{2.84,222} = 7.569$, $p < .001$), STAI-T ($F_{2.42,189} = 4.394$, $p = .009$) (figure 3).

A response rate of 65% was identified in people with atypical depression compared to 35% in participants with other depression ($\chi 2(1) = 6.34$, $p = .012$).

Adverse events

Details of adverse events reported by participants are listed in Table 3. All reported adverse events were of minor severity. There were no significant differences between reported adverse events between placebo and active drug treatment groups, although there was a trend suggesting increased diarrhoea/ loose bowels in the HDC group, and spicy aftertaste in the HDC and LDC group.

Participant Blinding

In order to evaluate the efficacy of condition concealment over the study, participants were asked at the completion of the study to predict his/her condition allocation (i.e., placebo vs real drug treatment). Efficacy of group concealment was shown to be high as the following correct predictions were obtained from participants: 55% in LDC, 56% in HDC, 65% in LDC+S, and 68% placebo.

DISCUSSION

The results of this study add to the existing evidence on the beneficial antidepressant and anxiolytic effects of curcumin in people suffering from major depressive disorder. The addition of saffron to low-dose curcumin did not enhance treatment efficacy.

Compared to a placebo, the 12-week administration of active drug treatments comprising HDC, LDC, or LDC+S was associated with significantly greater improvements in depressive symptoms. A response rate (reduction of greater than 50% in depressive symptoms) of 28% was achieved in people on active treatments combined compared to 13% in people on placebo. However, this difference did not reach statistical significance. Improvements in depressive symptoms were found across each measured 4-week time interval in people taking the active drug treatments. In contrast, depressive symptoms improved only in the first 4 weeks of treatment in people placed on placebo. Interestingly, this pattern was also observed in a previous study by our research group (Lopresti et al., 2014) where placebo effects were identified only in the first 4 weeks of treatment. We attempted to minimise this placebo effect by including a one-week, placebo run-in phase; however, placebo benefits apparently persisted for longer than this one-week period.

The positive antidepressant effects of curcumin in people with major depressive disorder have now been verified in four clinical trials. In a study by Sanmukhani and colleagues (2014), the 6-week administration of curcumin (1,000mg of BCM-95®, daily) was as effective as the antidepressant, fluoxetine. However, this study was flawed by its single-blinded design (researcher masked). In a randomised, double-blind study, conducted by our research group, there was partial support for the antidepressant effects of a patented curcumin extract (500mg b.i.d.) as evidenced by significantly greater improvements in depressive symptoms from weeks 4 to 8 compared to placebo (Lopresti et al., 2014). In a 6-week, double-blind, placebo controlled study, Yu and colleagues (2015) demonstrated greater antidepressant effects of curcumin (1,000mg/day of a standard curcumin extract) compared to placebo. In another study, the adjunct administration of 1,000mg of curcumin to antidepressant treatment enhanced treatment gains compared to antidepressant treatment alone (Panahi et al., 2015). However, this study was flawed by its open-label design.

In addition to the beneficial antidepressant effects of curcumin, our findings suggest beneficial anxiolytic effects in people with major depressive disorder. Volunteers on the active drug treatments experienced significantly greater improvements in anxiety compared to placebo over the 12-week intervention. This was evidenced by improvements in both the State and Trait scores of the STAI. This anxiolytic benefit was also observed in our previous study of curcumin in depression (Lopresti et al., 2014). Interestingly, a study on the effects of curcumin in obese individuals demonstrated no significant changes in depressive symptoms compared to a placebo, although there were significant improvements in anxiety symptoms (Esmaily et al., 2015). However, this sample did not comprise adults with diagnosed major depressive disorder.

Findings from several animal studies suggest that curcumin has anxiolytic effects, potentially via its HPA-modulating, monaminergic, and neuroprotective effects (Benammi et al., 2014; Haider et al., 2015). In a recent study, saffron was also found to be beneficial in reducing anxiety

symptoms in people with depression and anxiety (Mazidi et al., 2016). This observation is promising as anxiety has been reported as an adverse effect following saffron administration (Lopresti and Drummond, 2014).

Our findings indicate that the active drug treatments were associated with improvements in both State and Trait anxiety. State anxiety is a measure of present state anxiety/ tension, whereas trait anxiety is considered a measure of relatively stable anxiety. In the STAI, trait anxiety is measured with the specifier 'how you generally feel' (Spielberger, 1983). The improvement in trait anxiety over the 12-week intervention suggests that the active drug treatments have relatively enduring effects on anxiety symptoms. Mechanisms require further investigation but could involve curcumin's potential neuroprotective and HPA-modulating effects.

A comparison of the antidepressant and anxiolytic effects of two different dosages of curcumin did not reveal any significant differences in overall efficacy. These non-significant differences suggest that therapeutic/ optimal dosages are realised at the lower daily dose of 500mg of BCM-95® (approx. 440mg of curcuminoids) or, alternatively, that there was insufficient power to detect the magnitude of differing efficacies. A similar statistically non-significant finding was also observed when comparing LDC with the LDC+S combination. Again, this may reflect an insufficiently powered study to detect subtle differences, or that optimal benefits can be obtained from stand-alone curcumin treatment. Conclusions about the antidepressant efficacy of saffron alone cannot be made as this was not examined in our study.

In a previous study conducted by our research group, curcumin had stronger antidepressant efficacy in people with atypical depression (Lopresti et al., 2014). Atypical depression represents approximately 40 percent of adults with depression and comprises the following symptoms: mood reactivity as evidenced by mood improvement following positive events, plus at least two symptoms comprising hypersomnia, increased appetite or weight gain, increased sensitivity to rejection, leaden paralysis, or a long-standing pattern of interpersonal sensitivity to rejection

(Singh and Williams, 2006). The present findings provide further support for the enhanced benefits of curcumin in adults with atypical depression. The 12-week administration of the active drug treatments was significantly more effective in people with atypical depression compared to other depressed participants (response rates of 65% and 35%, respectively). Greater improvements state and trait anxiety were also observed in people with atypical depression compared to the other depressed participants.

Superior improvements of curcumin treatment in people with atypical depression could be due to elevated inflammation in this subgroup. Compared to healthy individuals, and people with melancholic or non-atypical depression, atypical depression is 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). Curcumin is traditionally considered a potent natural anti-inflammatory with a meta-analysis on clinical trials confirming that it 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).

A comparison of the reported adverse effects across different treatment conditions suggest that curcumin and the curcumin/saffron combination were well tolerated over a 12-week period. There were no statistically significant differences in reported adverse effects compared to placebo, despite a trend toward greater incidence of diarrhoea/ loose bowels in the HDC group, and spicy aftertaste in the HDC and LDC group. However, these symptoms were not severe enough to result in any withdrawals from treatment.

Limitations and Directions for Future Research

The population of individuals recruited for this study comprised approximately 70 percent suffering from chronic or recurring episodes of depression. Over 50 percent of individuals reported struggling with depression for more than 10 years, while another 20 percent reported

suffering depression for 6 to 10 years. Approximately 50 percent of participants were also using antidepressant medications, and 15% were receiving psychological therapy. Although curcumin was effective in reducing depressive and anxiety-related symptoms, it is likely that the benefits of treatment were smaller in this population of depressed adults than in others with more recent onset of depression. Thus, investigations into the efficacy of curcumin and saffron in individuals with early onset depression may produce stronger findings.

Although an overall sample size of 160 participants was used in the study, data from participants experiencing significant depressive changes over the 1-week, placebo run-in phase were excluded in analysis. This resulted in a sample size of 123 individuals distributed over four treatment conditions. This negatively impacted on the power of the study to detect differing efficacies across conditions, particularly between the differing active treatments. Although several significant findings were obtained in this study, the capacity to detect small differences across groups was compromised. This increased the potential for type II errors (i.e., failing to reject the null hypothesis when it was false). Based on estimates using an effect size of 0.4 between active treatments, future studies with sample sizes over 100 per group will be necessary, particularly when examining the efficacies of differing dosages and combination ingredients. Moreover, the multiple statistical comparisons undertaken in our analyses increased the potential for type I errors (i.e., rejecting the null hypothesis when it was true). However, as analyses were based on planned rather than post hoc comparisons, no adjustment to p-values was made. We acknowledge that this increases the risk for type I error, so replication of the findings in future adequately-powered studies will be required to confirm the validity of our findings.

Assessment of symptomatic changes relied on two self-report instruments. Although these questionnaires have satisfactory reliability and validity, the use of additional measures and clinician-rated instruments would have been desirable.

Two doses of curcumin were compared in this study, along with a curcumin/saffron combination. The findings from this study suggest that the addition of saffron did not enhance the efficacy of low-dose curcumin. In addition, an increased dose of curcumin did not enhance treatment outcomes. These findings suggest that there was insufficient power in the study to detect group differences, or that there was a ceiling antidepressant effect of these natural spices. This ceiling may have been achieved with the administration of the low-dose curcumin alone. The inclusion of a stand-alone saffron condition would be desirable in future studies.

Future examination of these compounds should also take into consideration quality and bioavailability. We used a patented curcumin extract (BCM-95®), demonstrated to have increased bioavailability compared to standard curcumin, and a curcumin/piperine combination (Antony et al., 2008). Whether similar antidepressant efficacy can be achieved with other curcumin extracts requires investigation. There should be similar considerations when evaluating the efficacy of saffron. In previous studies the stigma and petal of *Crocus Sativus L* have been used. Although a 30mg daily dose of dried saffron extracts has most commonly been evaluated, the quality of such extracts is likely to be variable. In some studies, saffron was standardised for crocin and/or safranal, while in others no standardisations were reported (Lopresti and Drummond, 2014). In the present study we used a patented saffron extract (affron®) standardised for Lepticrosalides (a measure of bioactive compounds present in saffron, including safranal and crocin). Quality of saffron extracts may influence antidepressant and anxiolytic efficacy.

Finally, it would be valuable to examine the efficacy of curcumin and saffron as an adjunct to antidepressant medication. In a recent study by Talaei and colleagues (2015) it was demonstrated that crocin, the active constituent in saffron, augmented pharmaceutical antidepressant outcomes. Inconsistent findings have been reported with the adjunct use of curcumin and antidepressants, as evidenced by one positive (Panahi et al., 2015) and two negative studies

(Bergman et al., 2013; Sanmukhani et al., 2014). However, these studies contained significant study design flaws.

In conclusion, the present findings provide support for the antidepressant and anxiolytic effects of curcumin in people with major depressive disorder, although no significant differences in efficacy between high and low-doses (500mg versus 1,000mg of BCM-95®, daily) were detected. The addition of saffron to low-dose curcumin also did not enhance treatment efficacy. This study also provides confirmation of the enhanced potency of curcumin in people with atypical depression compared to other depressed counterparts. However, this requires further validation using more strongly-powered studies.

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Highlights

- Curcumin and saffron effective for the treatment of depression
- Curcumin and saffron effective in reducing anxiety in depressed adults
- Varying doses had no effect on outcome
- Curcumin and saffron have greater efficacy for atypical depression

Table 1: Baseline & Demographic Details of Participants

	LDC	HDC	LDC+S	Placebo	P-value

Sample Size		28	33	26	36	
Age (mean) SE		40.39 2.15	46.53 2.34	41.12 2.30	42.11 1.86	.183[a]
BMI (mean) SE		25.97 1.20	25.21 0.94	27.51 1.37	26.68 1.03	.523[a]
Female		85%	95%	85%	90%	.431[b]
IDS Total Score, Baseline (mean) SE		35.29 2.40	34.15 1.67	34.65 1.74	35.39 2.00	.965[a]
STAI State, Baseline (mean) SE		53.54 2.30	54.73 1.79	55.77 1.83	52.25 2.01	.713[a]
STAI Trait, Baseline (mean) SE		58.00 1.85	56.12 1.59	59.04 1.43	59.67 1.68	.628[a]
Depression History	Depressed < 1 year	0%	0%	0%	0%	.647[b]
	Depressed 1 to 5 years	35%	23%	23%	35%	
	Depressed 6 to 10 years	9%	19%	27%	12%	
	Depressed > 10	57%	58%	50%	54%	
Marital Status	Single	44%	52%	38%	28%	.304[b]
	Married	26%	27%	27%	42%	
	Defacto	22%	12%	19%	28%	
	Divorced	7%	9%	15%	0%	
	Widowed	0%	0%	0%	3%	
Smoking Status	Non Smoker	82%	88%	77%	89%	.556[b]
Educational Status	Secondary	61%	70%	54%	58%	.506[b]
	Tertiary	39%	24%	35%	31%	
	Postgraduate	0%	6%	12%	11%	
Exercise Status	Never/Rarely	41%	16%	32%	39%	.305[b]
	1-2 times a week	15%	25%	20%	21%	
	3-5 times a week	41%	34%	36%	27%	
	>5 times a week	4%	25%	12%	12%	
Antidepressant Use	Yes	64%	48%	50%	42%	.347[b]
Antidepressant Use	SSRI only	44%	32%	35%	32%	.248[b]
	Other (incl. combined SSRI and other)	20%	16%	15%	10%	
Psychological Therapy	Yes	15%	21%	17%	16%	.783[b]

SE= standard error; SSRI= selective serotonin reuptake inhibitor

Table 2: Change in Self-Report Scores Over Time, By Treatment Condition

		Week 0	Week 4	Week 8	Week 12	P-value[a]
IDS Total Score						
Actives Combined	Mean	34.67	28.98[d]	26.67[c]	23.21[d]	<.001
	SE	1.11	1.22	1.33	1.28	
Curcumin extract 500mg (LDC)	Mean	35.29	28.74[d]	27.44	23.04[b]	<.001
	SE	2.40	2.24	2.32	2.21	
Curcumin extract 1000mg (HDC)	Mean	34.15	29.20[c]	24.97[c]	22.43[b]	<.001
	SE	1.67	1.98	2.29	2.08	
Curcumin extract 500mg + Saffron 30mg (LDC+S)	Mean	34.65	28.96[c]	27.88	24.38	<.001
	SE	1.74	2.22	2.32	2.44	
Placebo	Mean	35.39	26.61[d]	27.38	26.48	<.001
	SE	2.00	2.29	2.26	2.49	
STAI State Score						
Actives Combined	Mean	54.66	49.51[d]	47.52	44.40[c]	<.001
	SE	1.13	1.29	1.30	1.48	
Curcumin extract 500mg (LDC)	Mean	53.54	48.93[b]	46.85	42.73[b]	<.001
	SE	2.30	2.19	2.06	2.30	
Curcumin extract 1000mg (HDC)	Mean	54.73	49.30[b]	46.03	44.07	<.001
	SE	1.79	2.14	2.50	2.69	
Curcumin extract 500mg + Saffron 30mg (LDC+S)	Mean	54.73	49.30[b]	46.03	44.07	.002
	SE	1.79	2.14	2.50	2.69	
Placebo	Mean	52.25	46.52[b]	48.06	49.94	.113
	SE	2.01	2.45	2.40	2.40	
STAI Trait Score						
Actives Combined	Mean	57.60	53.77[d]	51.57[b]	48.10[d]	<.001
	SE	0.95	1.04	1.22	1.39	
Curcumin extract 500mg (LDC)	Mean	58.00	54.07[d]	51.37	47.46	<.001
	SE	1.85	1.91	1.94	2.34	
Curcumin extract 1000mg (HDC)	Mean	56.12	52.70	49.63[b]	46.90[c]	.001
	SE	1.59	1.74	2.32	2.51	
Curcumin extract 500mg + Saffron 30mg (LDC+S)	Mean	59.04	54.72[c]	54.21	50.29[b]	<.001
	SE	1.43	1.80	1.94	2.37	
Placebo	Mean	59.67	53.33[d]	53.38	55.00	<.001
	SE	1.68	2.13	1.93	2.24	

a = repeated measures p-value based on all time points
b = significant reductions over previous 4 weeks (p-value < .05)
c = significant reductions over previous 4 weeks (p-value < .01)
d = significant reductions over previous 4 weeks (p-value < .001)
LDC= low-dose curcumin; HDC= high-dose curcumin; LDC+S= low-dose curcumin plus saffron

Table 3: Frequency of Reported Adverse Events

	HDC	LDC	LDC+S	PLACEBO
Diarrhoea/ loose bowels	7	2	2	1
Headache/ migraines	2	3	0	1
Hot flush	1	0	0	0
Stomach ache/ digestive problems	2	0	0	2
Spicy aftertaste	5	4	2	1
Constipation	0	1	0	1
Nausea	0	1	1	1
Vivid dreams	0	0	1	3
Dizziness	0	0	2	3
Dry eyes	0	0	0	1
Weight gain/ increased appetite	2	0	2	2
Total Adverse Events	19	11	10	16

LDC= low-dose curcumin; HDC= high-dose curcumin; LDC+S= low-dose curcumin plus saffron

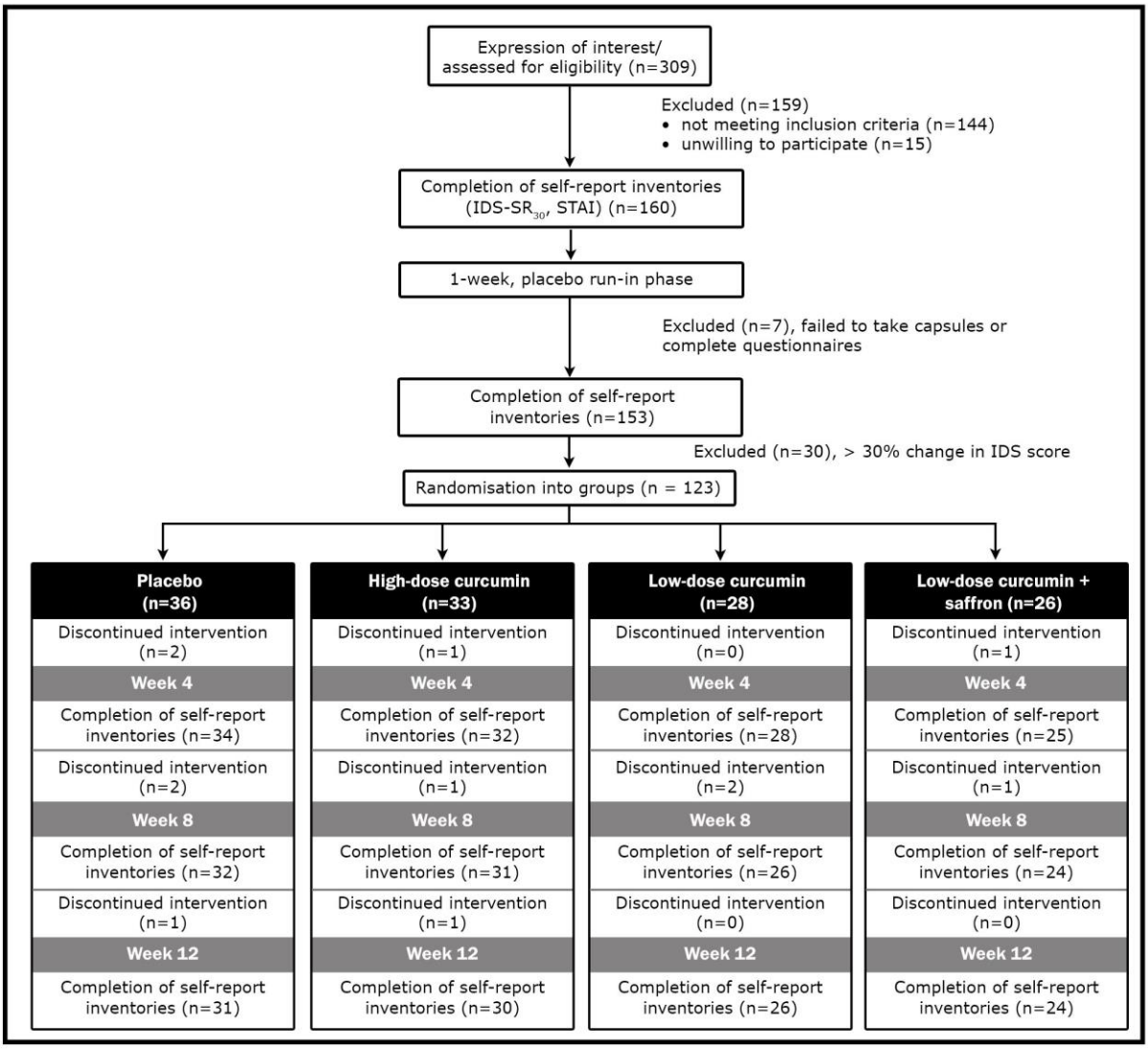

Figure 1: Systemic illustration of study design

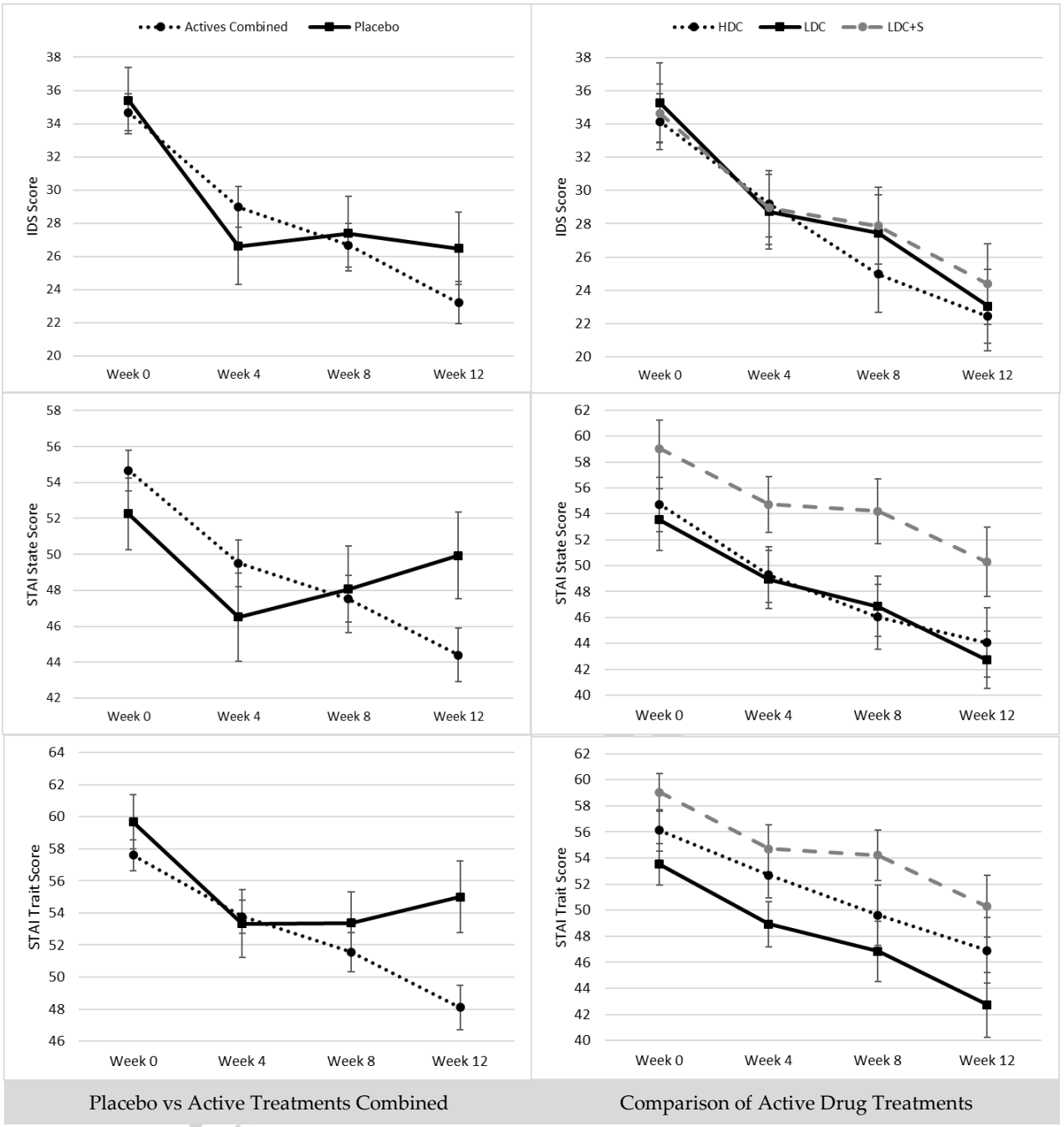

Figure 2: Change in questionnaire scores over 12-week intervention

HDC = High-dose curcumin; LDC = Low-dose curcumin; LDC+S = Low-dose curcumin plus saffron
Vertical bars depict standard errors

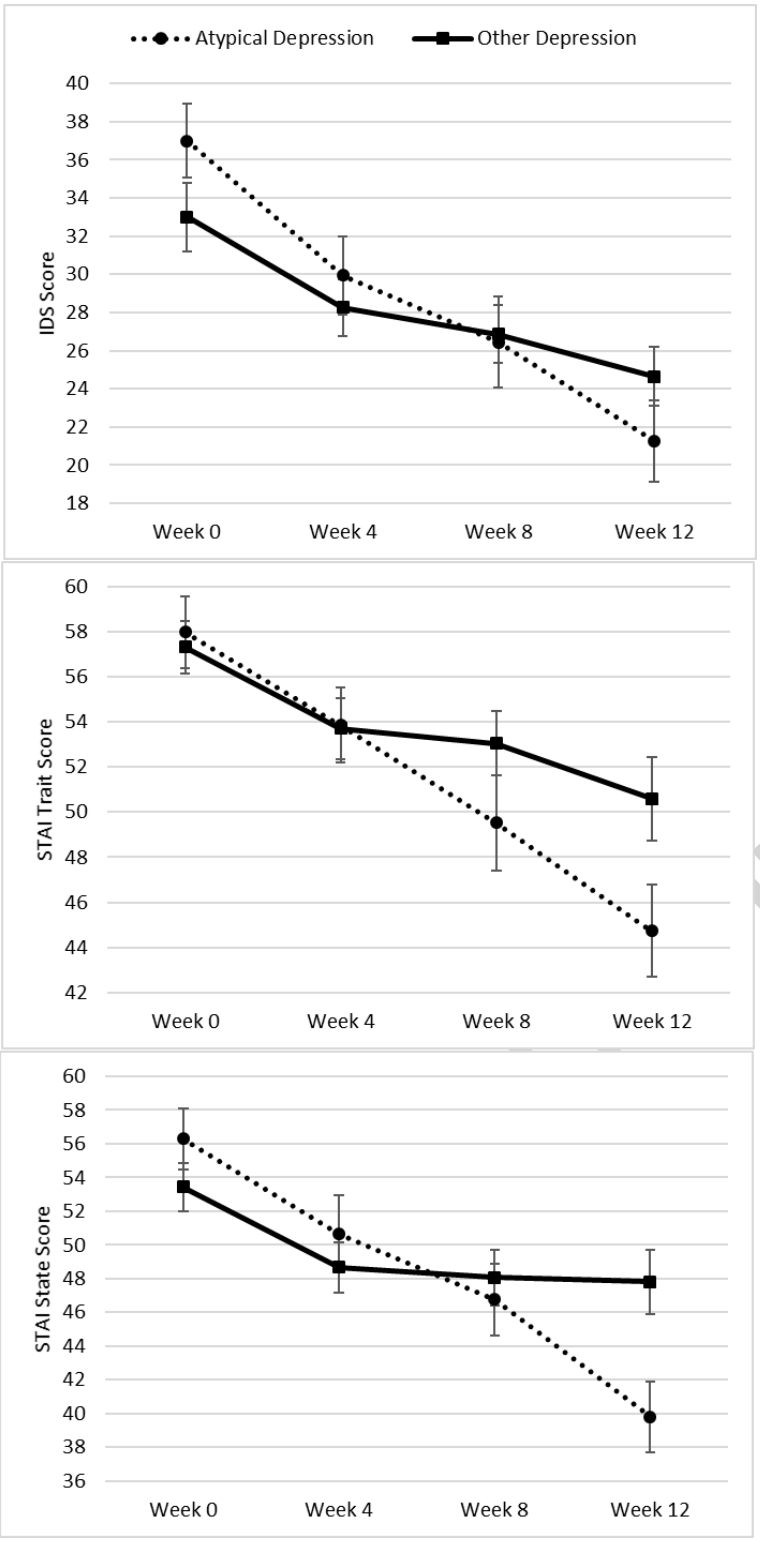

Figure 3: A comparison of change in questionnaire scores over the 12-week intervention in participants receiving active treatments (34 with Atypical depression versus 46 with other depression)

Vertical bars depict standard errors