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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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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 (250 mg b.i.d.), high-dose curcumin extract (500 mg b.i.d.), or combined low-dose curcumin extract plus saffron (15 mg 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.

1. Introduction

Major depressive disorder affects 6–8% of adults every year, and has a lifetime prevalence of 15–20% (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 60–80% 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% 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% had used a dietary supplement for at least 7 days, and 20% 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*

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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 500 mg b.i.d. has most commonly been used. We sought to determine whether a lower dose comprising 250 mg 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.

2. Materials and methods

2.1. Study design

This was a 12-week, randomised, double-blind, placebo-controlled clinical trial, with a 1-week, placebo run-in phase (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 (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.randomisation.com). The randomisation structure

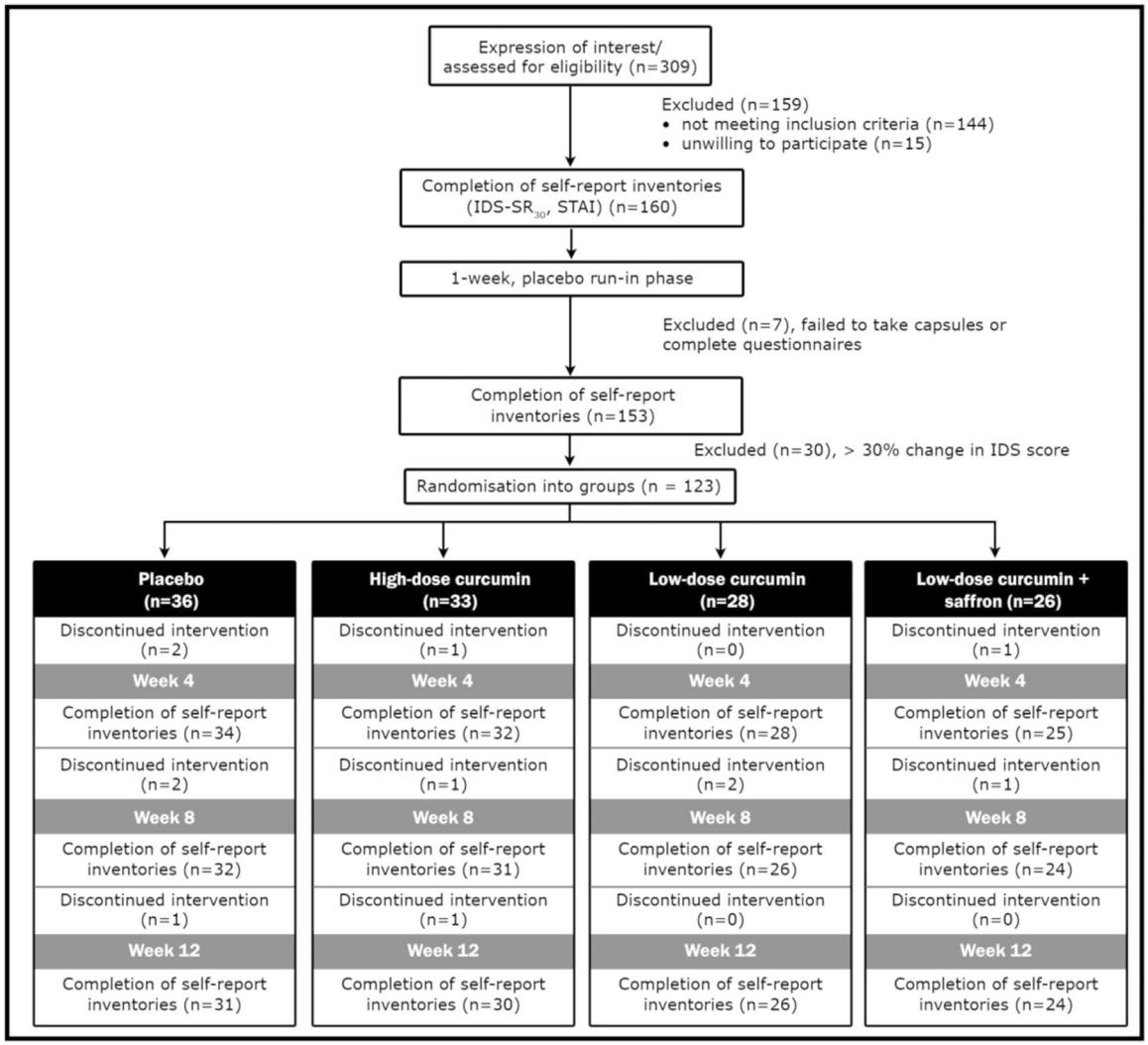

Fig. 1. Systemic illustration of study design.