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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.

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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

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