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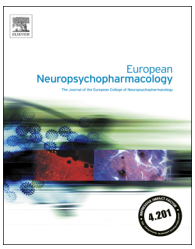

Curcumin and major depression: A randomised, double-blind, placebo-controlled trial investigating the potential of peripheral biomarkers to predict treatment response and antidepressant mechanisms of change

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Abstract
A recent randomised, double-blind, placebo controlled study conducted by our research group, provided partial support for the efficacy of supplementation with a patented curcumin extract (500 mg, twice daily) for 8 weeks in reducing depressive symptoms in people with major depressive disorder. In the present paper, a secondary, exploratory analysis of salivary, urinary and blood biomarkers collected during this study was conducted to identify potential antidepressant mechanisms of action of curcumin. Pre and post-intervention samples were provided by 50 participants diagnosed with major depressive disorder, and the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}) was used as the primary depression outcome measure. Compared to placebo, 8 weeks of curcumin supplementation was associated with elevations in urinary thromboxane B2 ($p<0.05$), and substance P ($p<0.001$); while placebo supplementation was associated with reductions in aldosterone ($p<0.05$) and cortisol ($p<0.05$). Higher baseline plasma endothelin-1 ($rs=-0.587$; $p<0.01$) and leptin ($rs=-0.470$; $p<0.05$) in curcumin-treated individuals was associated with greater reductions in IDS-SR_{30} score after 8 weeks of treatment. Our findings demonstrate that curcumin supplementation influences several biomarkers that may be associated with its antidepressant mechanisms of

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action. Plasma concentrations of leptin and endothelin-1 seem to have particular relevance to treatment outcome. Further investigations using larger samples sizes are required to elucidate these findings, as the multiple statistical comparisons completed in this study increased the risk of type I errors.

1. Introduction

In medical and pharmaceutical practice biomarkers are regularly used to assist in the prediction, diagnosis and evaluation of treatments associated with disease (Biomarkers Definitions Working Group, 2001). However, in psychiatry, biomarkers are utilised primarily for research purposes and are seldom used in clinical practice. Greater understanding of biomarkers in psychiatry has the potential to enhance diagnostic accuracy, improve treatment-matching and evaluate treatment progress. Evaluation of biomarkers can also expand understanding into the mechanisms of change associated with specific treatments for depression (Lopresti et al., 2014b).

Several dysregulated biological pathways have been identified in major depressive disorder including disturbances in monoaminergic activity, immuno-inflammation, oxidative stress, hypothalamus-pituitary-adrenal (HPA) activity and neuroprogression (Leonard and Maes, 2012). Examination of biomarkers is particularly relevant as there are identified differences between depressed and healthy populations in markers of immuno-inflammation, such as C-reactive protein, interleukin-6 and tumour-necrosis factor-α (Howren et al., 2009); markers of oxidative stress such as malondialdehyde (MDA) (Galecki et al., 2009) and 8-Hydroxy-2-deoxyguanosine (8-OHdG) (Maes et al., 2009); and markers of HPA activity such as increased baseline or post-dexamethasone cortisol (Belvederi Murri et al., 2014).

Because of its effects on all of these pathways, interest in curcumin for the treatment of major depression has increased. In animal models of depression, curcumin has demonstrated antidepressant and anxiolytic effects (Lopresti et al., 2012). Three human-based trials on people with major depressive disorder have now been completed. In one study the addition of curcumin to antidepressant treatment provided no additional antidepressant benefit (Bergman et al., 2013), whereas in another study curcumin had similar antidepressant efficacy to fluoxetine (Sanmukhani et al., 2014). However, in this latter study there was no placebo-control or blinding of participants from treatment conditions. A recent randomised, double-blind, placebo controlled study conducted by our research team provided partial support for the efficacy of curcumin in reducing depressive symptoms in people with major depression, particularly in a subset of participants with atypical depression (Lopresti et al., 2014a). In the present paper, exploratory analysis of results from this study is provided with an emphasis on the effects of curcumin on blood, urinary and salivary biomarkers, and on the potential of biomarkers to predict treatment response. The primary goal of this exploratory-driven analysis was to identify potentially important biomarkers that will require validation in future, greater powered studies.

2. Experimental procedures

2.1. Study design

Details of this study have been previously published in Lopresti et al. (2014a). Briefly, this study was an 8-week, randomised, double-blind, placebo-controlled clinical trial (Figure 1). Investigators responsible for study administration, data collection, intervention allocation and data analysis were blinded to treatment conditions until the final collection of all participant data. The trial protocol was approved by the Human Research Ethics Committee at Murdoch University, Western Australia and 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. 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 allocation was assigned by the first author according to order of participant enrolment in the study.

As no previous clinical study has investigated the effect of curcumin on most of the measured biomarkers, data to complete an *a priori* power analysis could not be determined. However, to achieve a power of 0.8, sample size estimates were based on the assumption of a moderate effect size of 0.4 indicating a total sample size of approximately 50 was required for this study.

2.2. Participants

Full details of inclusion and exclusion criteria are outlined in Lopresti et al. (2014a). Briefly, male and female participants aged 18–65 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). Participants with a psychotic disorder, bipolar disorder, comorbid obsessive-compulsive disorder, posttraumatic stress disorder, eating disorder, chronic fatigue syndrome, fibromyalgia, or any substance abuse or dependence disorder were excluded, as were participants assessed as high risk of suicide. Volunteers were also excluded if they suffered from medical illnesses including diabetes, autoimmune diseases, cardiovascular disease, hypertension, chronic fatigue syndrome, or asthma.

2.3. Interventions

Placebo (cellulose) and curcumin capsules were supplied by Arjuna Natural Extracts Ltd. Kochi, Kerala, 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