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Protective effect of mangiferin against lipopolysaccharide-induced depressive and anxiety-like behaviour in mice

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ABSTRACT

Numerous studies have demonstrated that inflammation, oxidative stress and altered level of neurotrophins are involved in the pathogenesis of depressive illness. Mangiferin, a C-glucosylxanthone is abundant in the stem and bark of *Mangifera indica* L. The compound has been shown to possess antioxidant, anti-inflammatory and immunomodulatory activities. The present study was performed to investigate the effect of mangiferin pretreatment on lipopolysaccharide-induced increased proinflammatory cytokines, oxidative stress and neurobehavioural abnormalities. Mice were challenged with lipopolysaccharide (0.83 mg/kg, i.p.) after 14 days of mangiferin (20 and 40 mg/kg, p.o.) pretreatment. Mangiferin pretreatment significantly ameliorated the anxiety-like behaviour as evident from the results of an elevated plus maze, light-dark box and open field test. Mangiferin pretreatment also improved the anhedonic behaviour as revealed by sucrose preference test and increased social interaction time. It also prevented the lipopolysaccharide-evoked depressive-like effect by reducing the immobility time in forced swim and tail suspension test. Lipopolysaccharide-induced elevated oxidative stress was decreased with mangiferin pretreatment due to its potential to increase reduced glutathione concentration, Superoxide dismutase and catalase activity and decrease lipid peroxidation and nitrite level in the hippocampus as well as in the prefrontal cortex. Mangiferin pretreatment also attenuated neuroinflammation by reducing the interleukin-1 beta (IL-1β) level in hippocampus and prefrontal cortex. In conclusion, our results demonstrated that mangiferin possessed antidepressant and anti-anxiety properties due to its ability to attenuate IL-1β level and oxidative stress evoked by intraperitoneal administration of lipopolysaccharide. Mangiferin may be a potential therapeutic agent for the treatment of depressive and anxiety illness.

1. Introduction

Depression is a common, recurring and sometimes lethal psychiatric disorder resulting in personal suffering and suicides, in addition to social and economic burden. World health organization estimated 350 million people suffering from depression worldwide, and reported depression as a major contributor to the global burden of disease (World Health Organization, 2012). Core symptoms of major depressive disorder include loss of interest, loss of energy, dysfunctional thoughts, self guilt, suicidal ideation, disturbed sleep and appetite, and sexual dysfunction. Currently, various drug therapies are available for the treatment of depression. However, lower efficacy, delayed action and more side effects of the current medications warrant a requirement of a novel antidepressant, which is more efficacious and shows a promising approach for the treatment of depression. Several experimental studies have shown that oxido-nitrosative stress is involved in the pathophysiology of depression and anxiety. The observed effects include lipid peroxidation, reduced glutathione level, DNA damage and reduction in the level of antioxidant enzymes (De Oliveira et al., 2007; Gibson et al., 2012; Maes et al., 2008, 2011; Salim et al., 2010; Suzuki et al., 2001). Therefore, targeting oxidative and nitrosative stress with strong antioxidants can be a beneficial approach to provide protection against depression.

Patients with major depressive disorder show marked rise in inflammatory markers, including pro-inflammatory cytokines (IL-1,

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IL-6, TNF-α) and their soluble receptors, both peripherally as well as centrally (Raison et al., 2006). Inflammatory challenge by peripheral administration of lipopolysacchride (LPS) exhibits both depressive-like and anxiety-like behaviour in animal model by causing a systemic inflammation through increase in the production of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF-α), interferon-gamma (IF-γ), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β). Furthermore, these pro-inflammatory cytokines produce sickness behaviour syndrome such as hyperthermia, anorexia, sleepiness, reduction of locomotor activity, exploration, libido, loss of body weight and anhedonia (Godbout et al., 2005; Huang et al., 2008; Kelley et al., 2003; Qin et al., 2007; Swiergiel et al., 1997). Moreover, LPS-induced inflammation leads to significant reduction in the neurotrophic factors like brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin-3 (NT-3) levels in different regions of the brain (Guan and Fang, 2006).

Mangiferin (2-C-β-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone), a natural C-glucosylxanthone is an active phytochemical present in the leaves, bark and root of *Mangifera indica* (Singh et al., 2009). It has been reported to exhibit antioxidant (Rao et al., 2012), analgesic, anti-inflammatory (Garrido et al., 2001), antitumor, immunomodulatory (Guha et al., 1996), antidiabetic (Aderibigbe et al., 2001), cardioprotective (Hou et al., 2013), hepatoprotective (Das et al., 2012) and monoamine oxidase inhibition properties (Bhattacharya et al., 1972). Mangiferin inhibits LPS-induced chronic inflammation by regulating MAPK (Mitogen-Activated Protein Kinase) signalling pathway through alteration in the expressions of ERK (Extracellular signal-regulated kinase) and JNK (c-Jun N-terminal kinase) (Wei et al., 2011). It also shows neuroprotective action by preventing neuroinflammation and oxidative damage in brain induced by restraint stress exposure (Márquez et al., 2012).

The anti-depressant and anti-anxiety activities of mangiferin in LPS induced depressive-like behaviour model has not been studied so far. Thus, in the present study, we investigated the possible anti-depressant and anxiolytic effects of mangiferin through its effect on oxidative stress and inflammation. Furthermore, we assessed the effects of mangiferin pre-treatment on oxidative stress, pro-inflammatory cytokines and BDNF level in the brain following an immune challenge with LPS in mice.

2. Materials and methods

2.1. Chemicals

Lipopolysaccharide from *Escherichia coli*, serotype 0127:B8 and mangiferin were purchased from Sigma-Aldrich, St. Louis, MO, USA. Lipopolysaccharide and mangiferin were prepared freshly for the study. All other chemicals used were of analytical grade.

2.2. Animals

The experiments were performed in male Swiss mice (weight: 22–30 g) from 8.00 to 14.00 h in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) Government of India guidelines. The study was approved by the Institutional Animal Ethics Committee (IAEC) (Approval no. MC/32/2012/40), Gauhati Medical College & Hospital (CPCSEA Registration no. 351, 3/1/2001). The animals were kept at room temperature (24 ± 1 °C), with 65 ± 10% humidity, 12 h light and dark cycles. Standard laboratory animal feed (Pranav Agro Industries Ltd. Pune, India) and water were provided ad libitum. Animals were acclimatized under the experimental conditions for a period of 1 week prior to the commencement of the experiment.

2.3. Preparation of doses

Different doses of mangiferin (20 and 40 mg/kg) were selected based on the previous experimental study (Biradar et al., 2012). Mangiferin was dissolved in 30% dimethyl sulfoxide (DMSO) and administered daily by oral route at the dose volume of 10 ml/kg. Lipopolysaccharide (0.83 mg/kg) serotype 0127:B8 was dissolved in endotoxin free normal saline and administered intraperitoneally (i.p.) at the dose volume of 10 ml/kg.

2.4. Experimental design

At the beginning of the experiment, mice were randomly divided into six experimental groups, each group consisting of 8 mice (Fig. 1):

- Group I was treated with vehicle (30% DMSO) of mangiferin for 14 days and then challenged with saline on the 15th day. This group served as the control group.
- Group II was treated with vehicle (30% DMSO) of mangiferin for 14 days and then challenged with LPS (0.83 mg/kg, i.p.) on the 15th day. This group served as the LPS control group.
- Group III was treated with mangiferin (20 mg/kg, p.o.) for 14 days and then challenged with LPS (0.83 mg/kg, i.p.) on the 15th day.
- Group IV was treated with mangiferin (40 mg/kg, p.o.) for 14 days and then challenged with LPS (0.83 mg/kg, i.p.) on the 15th day.
- Group V was treated with mangiferin (20 mg/kg, p.o.) for 14 days.

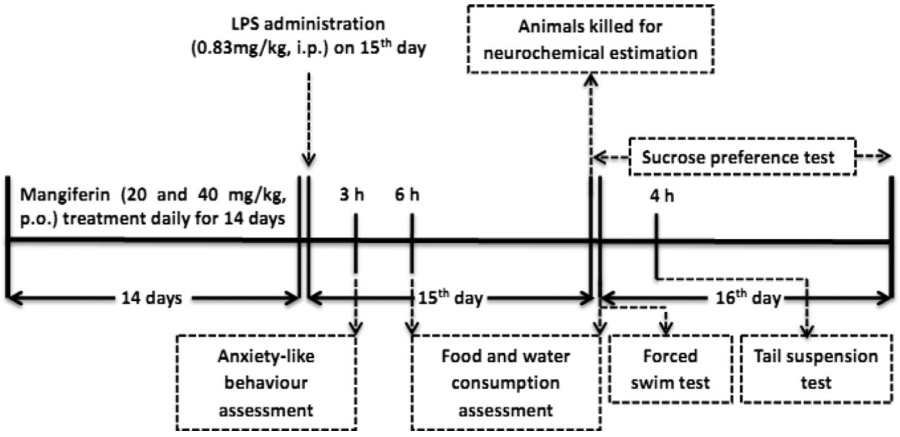

Fig. 1. Illustration of experimental timeline and study plan.