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RESEARCH ARTICLE

Nanocurcumine Ameliorates Lipopolysaccharide-induced Depressive-like Behavior in Mice

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ABSTRACT

Objective(s): Curcumin, a plant alkaloid from Curcuma longa, possess antioxidant and anti-inflammatory properties. Recently, the antidepressant activities of curcumin were reported. Nevertheless, bioavailability of curcumin limits its therapeutic utility. Nanotechnology is a developing field that potentially enhances bioavailability and the plasma concentration of curcumin. This study investigates effect of acute intraperitoneal (i.p.) curcumin C3 complex nanoparticles on lipopolysaccharide (LPS)-induced depressive-like behavior in a mouse model.

Methods: Depression-like behavior was induced by LPS (0.83 mg/kg, i.p.). Twenty four hrs later, immobility time in forced-swimming test (FST) and tail suspension test (TST) was recorded as depression-like index. Locomotor activity also was evaluated in open field test (OFT). Curcumin and nanocurcumin were administered 75 min prior to the behavioral assessments.

Results: LPS-treated mice remained considerably more immobile in FST and TST ($P<0.01$). On the other hand, nanocurcumin at doses 40 and 80 mg/kg, i.p., $P<0.05$ and $P<0.01$, respectively and curcumin at dose 80 mg/kg, i.p., $P<0.05$, markedly lowered the immobility in FST. Further, curcumin at dose 80 mg/kg, i.p. and nanocurcumin at doses 40 and 80 mg/kg, i.p. significantly lowered the immobility measure in TST, $P<0.05$, $P<0.01$ and $P<0.001$, respectively.

Conclusions: Acute administration of nanocurcumin and curcumin reduced the index of immobility in FST and TST without influencing the general locomotor activity in OFT. Notably, nanocurcumin at lower doses compared with curcumin decreased the immobility figure in a dose-dependent manner. This neuroprotive effect of nanocurcumin would be related to its anti-inflammatory and anti-oxidant properties as well as modulation of neurotransmitter levels in the brain.

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INTRODUCTION

Depression is a serious disorder, it can have various consequences on an individual's quality of life, and it has included among the most prevalent kinds of mental illnesses [1]. Depressive-like behavior in rodents models is triggered through exogenous pro-inflammatory cytokines or a cytokine inducer such as lipopolysaccharide (LPS), resulting increased immobility time in the forced swimming (FST) and tail suspension (TST) tests, reducing consumption of a sweetened solution and suppressing sexual behavior, which antidepressants

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can diminished these depressive behaviors [2, 3]. Regarding the neuroinflammation in depression, LPS-received mice are extensively under evaluation to clarify the underlying mechanisms [4, 5].

Curcumin, a yellow pigment extracted from rhizomes of the plant *Curcuma longa* (turmeric), has been extensively consumed as food additive and herbal medicine all over the Asia. Curcumin possess antioxidant [6], anti-inflammatory [7], hepato- and nephro-protective [8], anti-microbial [9], and anti-carcinogenic [10] characteristics. Besides, antidepressant activity of curcumin have recently reported [11, 12]. In a recent review article, several antidepressant potential approaches were stated for curcumin include anti-inflammatory, monoaminergic, antioxidant, immune-modulating and neuroprotective [13]. Many preclinical trials have also highlighted curcumin's potential antidepressant-like effects in rats [12] and mice [11] depression models such as FST, olfactory bulbectomy [11, 12], with comparable effects to conventional antidepressants [14].

Using curcumin in depression was extensively demonstrated in a meta-analysis [15] and the existing clinical trials mostly support its antidepressant effects. The substantial curcumin efficacy in improvement of depressive symptoms was demonstrated clinically. Also, curcumin exerted significant anti-anxiety effects in some of the conducted trials [16-18]. Various mechanisms of action for curcumin antidepressant activity have been suggested such as inhibition of monoamine oxidase A and B enzymes [19], modulation of neurotransmitter levels in the brain [19, 20], increase of brain-derived neurotrophic factor (BDNF) [21] and anti-inflammatory [22, 23].

Nevertheless, curcumin bioavailability is still a major concern which can limit its therapeutic effectiveness. Curcumin goes through extensive reduction, most most likely through alcohol dehydrogenase, followed by conjugations like sulfation and glucuronidation at different tissue spots mainly in the liver and the intestine [24, 25]. Numerous approaches have been suggested to improve curcumin effectiveness for example encapsulation of curcumin in liposomes and polymeric micelles, inclusion complex formation with cyclodextrin, formation of polymer–curcumin conjugates etc. [26]. Laboratory studies have also demonstrated that a curcumin-phospholipid combination can extend the systemic retention time in rat serum [27], and curcumin encapsulated poly nanoparticles were maintained almost twice as long in the cerebral cortex and the hippocampus of rats [28]. Encapsulation of curcumin in a nanoparticle platform is a credible and advantageous means enabling its delivery. In view of their small size and high surface-to-volume ratio, nanoparticles can pass through the skin barrier [29]. Liposomal curcumin nanoparticles have better permeability and stronger resistance to metabolic processes [30]. Curcumin nano-formulations have been developed for preclinical studies on cancer, inflammation, wound healing, etc. [29-31], for instance, dendrosomal curcumin had a chemoprotective effect on breast cancer metastasis [32].

Combination of curcumin with piperine, a bioavailability enhancer, increased antidepressant-like effect in chronic unpredictable stress-induced depression in rats [20]. In a more recent study, mice were treated with curcumin (100, 200, and 400 mg/kg, p.o.) and piperine (20 mg/kg, p.o.) for 7 days followed by LPS (0.83 mg/kg, i.p.). Additionally, co-administration of curcumin with piperine significantly potentiated curcumin neuroprotective effect on LPS-induced neurobehavioral and neurochemical deficits [33].

Recently, we showed a dose-dependent anticonvulsant property of curcumin C3 complex acute intraperitoneal administration (i.p.) at the doses 20, 40 and 80 mg/kg, on pentylenetetrazole-induced seizure in mice [34]. This study aims to demonstrate effect of curcumin C3 complex acute i.p. administration on LPS-induced depressive-like behavior in male mice employing behavioral paradigms FST and TST.

MATERIALS AND METHODS

Chemicals

LPS from *Escherichia coli*, serotype 0127:B8 was purchased from Sigma-Aldrich, St. Louis, MO, USA. Nanocurcumin (curcumin C3 complex-loaded nanoparticles) and native curcumin were prepared from Exir Nano Sina Co.,Tehran, Iran.

Animals and Experimental groups

Male NMRI mice weighing 25 ± 5 g (Tehran University of Medical Sciences, Tehran, Iran) were used all over the study. The animals had access to food and water. All the experiments were conducted between 9:00 and 12:00 A.M. with normal room light (12 h regular light/dark cycle) and temperature (23 ± 1 °C). The mice were

handled according to the criteria proposed by the Guide for the Care and Use of Laboratory Animals (NIH US publication, no. 23-86, revised 1985).

All the pharmacological chemicals were dissolved in sterile saline solution (0.9%), except for curcumin, which was dissolved in olive oil. The chemicals were administered intraperitoneally (i.p.) in a volume of 10 ml/kg of the mice body weight.

The mice were divided into 11 groups of 6-8. To induce depression- like behavior, they were injected with LPS (0.83 mg/kg, i.p.) [35] and 24 h later other treatments were done and behavioral tests carried out. Curcumin at doses 40 and 80 (mg/kg, i.p) and nanocurcumin at doses 20,40 and 80 (mg/kg, i.p) were administered 75 min prior to the behavioral tests according to our recent publication [34].

Behavioral tests

Open-field test (OFT)

To confirm that alterations in the immobility duration do not arise from the unusual changes in motor activity, the locomotor behavior was evaluated in an open-field box [36, 37]. The apparatus consisted of a Plexiglass box 40 × 60 × 50 cm. The box floor was divided into twelve equal squares. The animals were gently placed in the one corner and the number of squares crossed with all paws counted manually during six min.

Forced swimming test (FST)

When the animals are exposed to the FST, they normally represent an immobile posture, which is assumed to display a state of behavioral despair or helplessness [38] and the decrease in immobility time is used as an index of antidepressant activity [39]. Immediately after OFT, mouse was placed in an open cylindrical container (diameter 10 cm, height 26 cm) containing 20 cm of water at 23 ± 1 °C. The mouse was permitted to swim for 6 min and the total immobility duration was recorded manually using stopwatches during the last 4 min of the total 6 min [36, 40]. Each mouse was judged to be immobile when stopped climbing and remained floating motionless, making only those movements essential to keep its head above the water.

Tail suspension test (TST)

The total duration of immobility was measured according to the method described by Steru *et al*., [41]. Briefly, acoustically and visually isolated mice suspended 50 cm above the floor by adhesive tapes and placed around 1 cm from the tip of the tail. Immobility time was recorded manually using a stopwatch during a 6 min-period [42].

Statistical Analysis

All data were analyzed with one-way ANOVA followed by Tukey's post-hoc test (GraphPad Prism software, version 5). Totally, a value of $P<0.05$ was considered to be significant change.

RESULTS AND DISCUSSION

Fig. 1 illustrates effects of curcumin (C) and nanocurcumin (NC) on duration of immobility (sec.) in forced-swimming test (FST) on lipopolysaccharide (LPS)-induced depression-like behavior. It is clear that LPS-treated mice remained considerably more immobile in comparison to saline-treated animals ($P<0.01$). On the other hand, nanocurcumin at doses 40 and 80 mg/kg, i.p. significantly lowered the immobility measure in LPS-treated mice in comparison with vehicle (olive oil)-treated animals $P<0.05$ and $P<0.01$, respectively (Fig. 1a). As can be understood, LPS-treated mice remained considerably more immobile in comparison to saline-treated animals ($P<0.01$). On the other hand, curcumin at dose 80 mg/kg, i.p. significantly lowered the immobility measure in LPS-treated mice in comparison with vehicle (olive oil)-treated animals $P<0.05$ (Fig. 1b). Notably, curcumin and nanocurcumin at dose 80 mg/kg, i.p. significantly lowered the immobility measure in LPS-treated mice in comparison with vehicle (olive oil)-treated animals $P<0.05$ and $P<0.01$, respectively. However, curcumin and nanocurcumin did not affect immobility time in saline-treated normal animals (Fig. 1c). Fig. 1d shows open field test (OFT) outcomes. It is clear that LPS, curcumin and nanocurcumin at dose 80 mg/kg did not profoundly influence the general locomotor activity of mice.

Fig. 2 illustrates effects of curcumin (C) and nanocurcumin (NC) on duration of immobility (sec.) in tail suspension test (TST) on lipopolysaccharide (LPS)-induced depression-like behavior. As can be observed, LPS-treated mice remained considerably more immobile in comparison to saline-treated animals ($P<0.01$). On the other hand, curcumin at dose 80 mg/kg, i.p. ($P<0.05$) and nanocurcumin at doses 40 ($P<0.01$) and 80 mg/kg, i.p. ($P<0.001$) significantly lowered the immobility measure in LPS-treated mice in comparison with vehicle (olive oil)-treated animals,

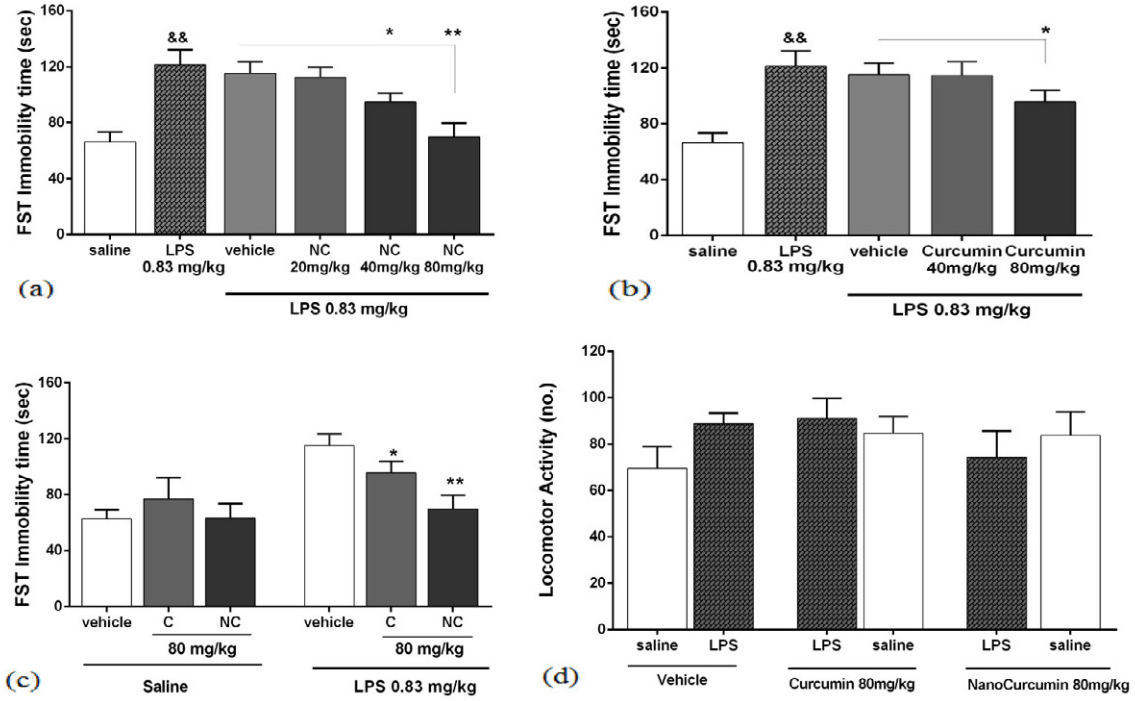

Fig. 1. Effect of curcumin (C) and nanocurcumin (NC) 40 and 80 mg/kg, i.p. on duration of immobility (sec.) in forced-swimming test (FST) on lipopolysaccharide (LPS)-treated mice. && P<0.01 significantly different from saline group. * P<0.05 and ** P<0.01 significantly different from LPS + vehicle (olive oil) group (n= 6-8).

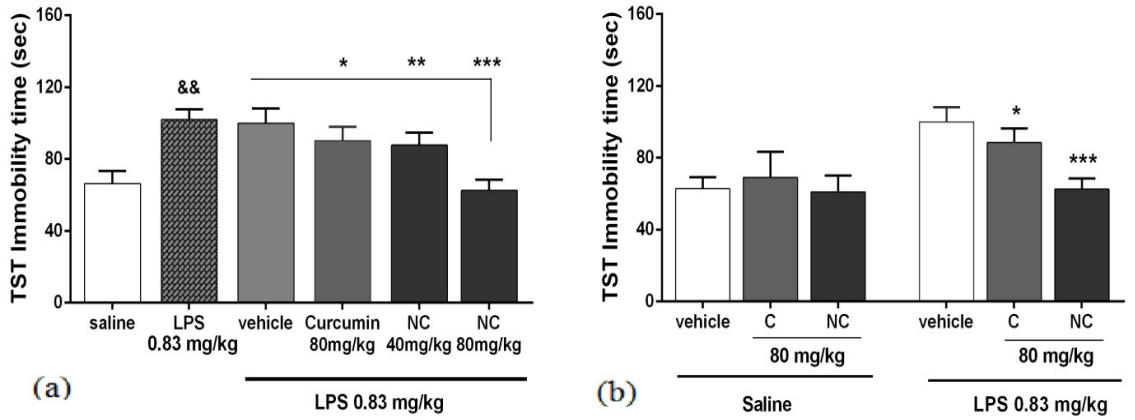

Fig. 2. Effect of curcumin (C) 80 mg/kg, i.p. and nanocurcumin (NC) 40 and 80 mg/kg, i.p. on duration of immobility (sec.) in tail suspension test (TST) on saline- and lipopolysaccharide (LPS)-treated mice. && P<0.01 significantly different from saline group. *P<0.05, ** P<0.01 and *** P<0.001 significantly different from LPS + vehicle group (n= 6-8).

(Fig. 2a). However, curcumin and nanocurcumin did not affect immobility time in saline-treated normal animals (Fig. 2b).

In the current study, effects of acute intraperitoneal (i.p.) administration of curcumin C3 complex nanoparticles and curcumin on LPS-induced depression-like behavior were investigated in a mouse model. Immobility times in FST and TST were recorded as depression-like indices, measure of helplessness. Nanocurcumin and curcumin reduced the immobility in FST and TST without influencing the general locomotor activity of the animals in OFT. It is notable that nanocurcumin at lower doses compared with curcumin decreased the immobility figure in the behavioral trails and its effect was in a dose-dependent manner.

In spite of the fact that no animal model is capable to cover all features of humans depressive symptoms, FST is a trustworthy tool in screening the antidepressant properties [43]. Animals typically rats and mice are forced to swim in an inescapable cylinder filled with water and the time animals spend immobile offers a measure of despair, and has been shown to be reduced by antidepressants [43]. TST is another animal depression model having reliability and predictive validity [44]. In the TST, animals are faced to a short-term, inescapable stress of being suspended of their tail, and the time spent in an immobile pose provides a measure of depressive behavior. A number of antidepressant medications have been revealed to lower the immobility and stimulate escape-related behavior [41].

Consistent with our study, the antidepressant properties of curcumin have been tested through FST and TST in various studies. These studies have consistently established that both acute [45, 46] and chronic [14, 47, 48] administration of curcumin reduce immobility time in rats and mice. Notably, the effects of curcumin were comparable to those of fluoxetine and imipramine [48]. Moreover, curcumin reduced corticosterone-induced depressive-like behaviors in rats, demonstrated by an increase in sucrose consumption in sucrose preference test and a reduction in immobility time in FST [47].

In line with our study, curcumin effects on LPS-induced depressive-like behavior and inflammation were investigated in male mice. A single injection of LPS (0.83 mg/kg, i.p.) raised the immobility time in FST and TST, reduced consumption of sucrose without affecting spontaneous locomotor activity. Curcumin pretreatment (50 mg/kg, i.p.) for seven sequential days reversed LPS-induced alterations in the experimental tests. The results made evident that curcumin may be an effective therapeutic agent for LPS-induced depressive-like behavior, in part due to its anti-inflammatory capacity [49].

A more specific targeting approach is to improve nanotechnology-based drug delivery systems. The dual-drug nanoparticles Cur/SLNs-HU-211, solid lipid nanoparticles (SLNs) to encapsulate HU-211 and curcumin (Cur), significantly lowered the immobility time in FST and increased latency of falling in rotarod test in corticosterone-induced major depression in mice. Cur/SLNs-HU-211 may deliver more curcumin to the brain and thus produce a marked neurotransmitters increase in the brain, especially in the hippocampus and the striatum [50]. Further, the ability of an effective neuroprotective agent, curcumin encapsulated in nano-sized PLGA, in attenuating neuro-inflammation subsequent to experimental subarachnoid hemorrhage in a rat model was reported [51].

CONCLUSIONS

Acute administration of nanocurcumin and curcumin reduced the index of immobility in FST and TST without influencing the general locomotor activity. It is notable that nanocurcumin at lower doses compared with curcumin decreased the immobility figure in the behavioral trails and its effect was in a dose-dependent manner. This neuroprotive effect of nanocurcumin would be related to its anti-inflammatory and anti-oxidant properties as well as modulation of neurotransmitter levels in the brain. Nonetheless, more specific investigations are needed to clarify the exact underlying mechanisms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this study.

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