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Modulation of 6-Gingerolin Antidepressant-like Effects in Mice Model

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ABSTRACT

Aims It has been reported that ginger is involved in serotonergic system. It seems that ginger effect could be attributed to its active compound or gingerol. The present study was conducted to evaluate the effects of gingerol on antidepressant-like effects by investigation of serotonergic system in mice model.

Materials & Methods In an experimental design, following pilot study and selection of doses, mice were divided into 4 groups. Receptor antagonists were injected, gingerol was administrated and a trial suspension test was conducted.

Findings Gingerol could induce antidepressant-like effect ($p<0.001$), without induction of changes in spontaneous locomotor activity in the open-field test. Pretreatment of mice with pCPA (preventor of serotonin synthesis), WAY100135 (receptor antagonist), ketanserin (5HT2A receptor antagonist), and cyproheptadine (5HT2 receptor antagonist) prevented the antidepressant-like effect induced by the gingerol ($p<0.05$).

Conclusion Carvacrol decrease the negative effects of diabetes on inflammation and antioxidant status. Gingerol is involved in antidepressant-like effects through serotonergic system in mice model.

Keywords Antidepressant-like; Gingerol; Mouse Model; Serotonin Pathway

CITATION LINKS

[1] Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey ... [2] The epidemiology of depression across ... [3] The effects of probiotics on depressive symptoms ... [4] Human disease, free radicals, and the oxidant/antioxidant ... [5] Oxidative stress andanxiety relationship and cellular ... [6] Oxidative stress in anxiety and comorbid ... [7] Oxidative stress and neurodegeneration ... [8] Glutathione: Anovel treatment target in ... [9] A reviewon the oxidative and nitrosative stress (O&NS) pathways ... [10] Antioxidants as antidepressants: Fact or ... [11] A novel automated direct measurement method for total ... [12] Increased oxidative stress in submitochondrial particles into the brain ... [13] Zingiber officinale improves cognitive function of the ... [14] The effect of ginger extract ingestion and swimming ... [15] Molecular mechanisms of chemopreventive effects of selected ... [16] Gastrointestinal motility enhancing effect of ginger and ... [17] Reversal of cisplatin-induced delay in gastric emptying ... [18] A new approach to practical ... [19] Wound-Healing Activity of Onosma hispidum (Ratanjot) in Normal ... [20] The tail suspension test: A new method for screening ... [21] Evidence for the involvement of the noradrenergic ... [22] Impact of maternal melatonin suppression on forced swim and tail suspension ... [23] Serotonergic mediation of the antidepressant-like effects of nitric oxide synthase ... [24] Involvement of serotonin receptor subtypes in the antidepressant-like effect of beta receptor ... [25] Role for monoaminergic systems in the antidepressant-like effect of ethanol ... [26] Antidepressant-like effects of flavonoids extracted from Apocynum Venetum leaves in mice: The involvement of monoaminergic ... [27] Differences in measures of exploration and fear in MHC-congenic ... [28] "Behavioural despair" in rats and mice: Strain differences and the effects ... [29] New approaches to antidepressant drug discovery: Beyond ... [30] Antidepressant-like effect of trans-resveratrol: Involvement of serotonin and ... [31] Neurochemical alterations of serotonergic neuronal systems in ... [32] Enhanced serotonergic neurotransmission in the hippocampus following ... [33] The therapeutic role of 5-HT 1A and 5-HT 2A receptors ... [34] Serotonin-1A receptors in major depression quantified using PET: Controversies, confounds ... [35] Antidepressant-like effect of the extract of Rosmarinus officinalis in mice ...

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Introduction

Major depressive disorder has been known a complex psychiatric disorder with unknown cause which will involve up to 20% of the individuals during their lifetime [1] and it causes disability in people [2]. It has been known to have some symptoms including adverse effects on mood, interest, feeling, hope, appetite, sleep, performance and social relationships [3].

Oxidative stress is result of excessive formation offree radicals and it is also attributed to antioxidant defense mechanism which maintains the cells removing free radicals [4]. Oxidative stress is involved in some psychiatric disorders [5, 6] which could be attributed to excessive oxygen consumption and lipid-rich compounds of the brain [7, 8]. Studies have related depression with faulted antioxidative enzyme activities [9-11].

The faulted antioxidant system could reduce the protection against reactive oxygen species (ROS) [9]. Elevated ROS in depression has been related with increased levels of malondialdehyde and arachidonic acid [9]. It has been reported increased oxidative stress in the rats exposed to stress [12]. These evidences suggest therapeutic activity of antioxidant compounds for treatment of depression [10]. 6-Gingerol is known as one phenolic compound which is found in some plants in Zingiberaceae family including ginger, cardamom and grain of paradise. It has been known to have some properties such as cognitive enhancer [13], anti-apoptotic [14], antioxidant and anti-inflammatory [15]. It has been reported effect of ginger on gastric similar to metoclopramide, a 5-HT4 receptor agonist with antagonist properties at 5-HT3 receptors through a selective 5-HT3 receptor antagonist [16, 17].

This study was thus conducted to evaluate the antidepressant-like activity of gingerol in mice model.

Materials and Methods

Materials

Gingerol powder and DMSO (Dimethyl sulphoxide) were purchased from Chromadex (Santa Ana, CA, USA) and Scharlo (Spain), respectively.

Animals

A number of 24 male NMRI mice, 4wk of age with 28±2g weight, were purchased from Pasteur Institute (Tehran, Iran). Those were maintained under lighting/darking program (12h:12h). Animals had free access to water and feed. Commercial feed was purchased from Razi Vaccine and Serum Research Institute (Karaj-Iran). All the used procedures were approved by National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

Acute toxicity test

Previous procedures [18] were used to evaluate the acute toxicity test. Following 24 h food restriction, 24 mice were divided into 4 groups and intrapritoeanally received 200, 400, 800 and 1200mg/kg gingerol dissolved in DMSO. Following treatment, animals were considered for some toxicity signs and behavioral symptoms including locomotor activity, changes in physical appearancerespiratory distress, coma, and mortality for 72h. This action was conducted for 10 days and to be healthiness and mortality were recorded [19]. We did not observe any mortality and only dizziness was observed in levels of 800-1200mg/kg. Thus, we selected levels of 100 and 300mg/kg for future studies.

Tail suspension test

Tail suspension test was conducted as reported by previous studies and total period of immobility was considered as reported by previous studies [20]. Animals were divided into 4 groups with 6 mice and treated by follow protocol:

1) Vehicle group: mice intra pritoeanally received normal saline (10ml/kg);
2) G-100 mice intrapritoeanally received 100mg/kg gingerol;
3) G-200 mice intrapritoeanally received 200mg/kg gingerol; and
4) Fluoxetine: mice intra pritoeanally received 20 mg/kgfluoxetine.

To evaluate the tail suspension test, total period of immobility time was registered by using a chronometer. Decreased immobility time was considered as a criteria for antidepressant activity [21, 22].

Serotonergic system in the antidepressant-like effect of gingerol

To investigate the serotonergic system, pre-treatment with PCPA, blocker of 5HT synthesis, was conducted (once/d for 3consecutive days). Since the best responses were observed in 300mg/kg gingerol, same dose was used in future trials. Following pre-treatment with PCPA, animals were treated with 300mg/kg gingerol, 15min after last administration of PCPA. Animals were submitted to tail suspension test after administration of gingerol [23]. To evaluate the involvement of 5HT1 receptor, mice were pre-treated withWAY100135 (10mg/kg), treated with 300mg/kg gingerol60 min after pre-treatment and exposed to tail suspension test after administration of gingerol [24]. To assess the involvement the 5HT2 receptor, animals were pre-treated with ketanserin and cyproheptadine, treated with 300mg/kg gingerol 60 min after pre-treatment and finally submitted to ail suspension test [25, 26].

Open field test

To evaluate the psychomotor stimulant activity, OFT was conducted as reported by others [28]. Each mouse was grouped in Plexiglas boxes (40×60×50cm). All the crossings and rearing were registered. We considered crossing as locomotors activity and rearing as exploratory behavior.

Statistical analysis

The data were reported as mean± standard deviation (Mean±SD) and analyzed by one-way analysis of variance (ANOVA). Tukey post-hoc test was used to comparethe groups. A level of $p<0.05$ was considered assignificant. The figures were illustrated by Prism 7 (GraphPad Software, Inc., San Diego, CA, USA).

Findings

Administration of gingerol could significantly decrease immobility time ($p<0.05$). Immobility was decreased with increasing dose, so that lowest immobility time was observed in mice administrated with 300mg gingerol. There was no significant difference between fluoextine with 300mg gingerol (Figure 1).

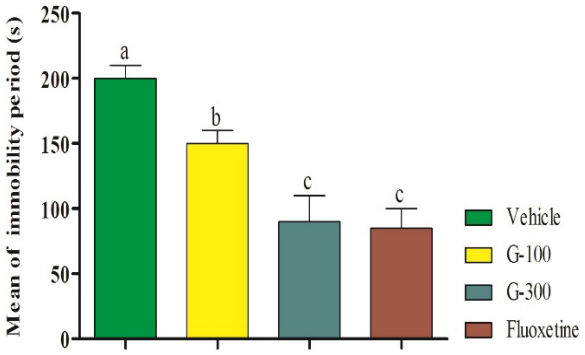

Figure 1. Effect of intra-pritoeanal administration of 6-gingerol in tail suspension test. The data are shown in mean±SD. Superscripts (a-c) show significant difference among groups. The data were analyzed by one-way ANOVA

Number of OFT was not different among different groups ($p>0.05$; Figure 2).

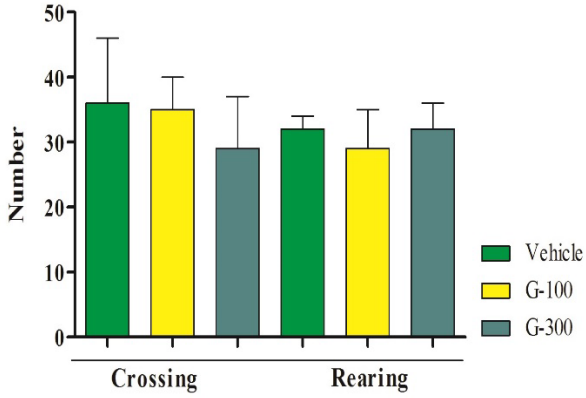

Figure 2. Effect of gingerol in OFT in mice.The data are shown in mean±SD. Superscripts (a-c) show significant difference among groups. The data were analyzed by one-way ANOVA

Pretreatments of mice with pCPA (preventer of serotonin synthesis), WAY100135 (receptor antagonist), ketanserin (5HT2A receptor antagonist), and cyproheptadine (5HT2 receptor antagonist) significantly prevented the antidepressant-like effect induced by the gingerol (Figure 3).

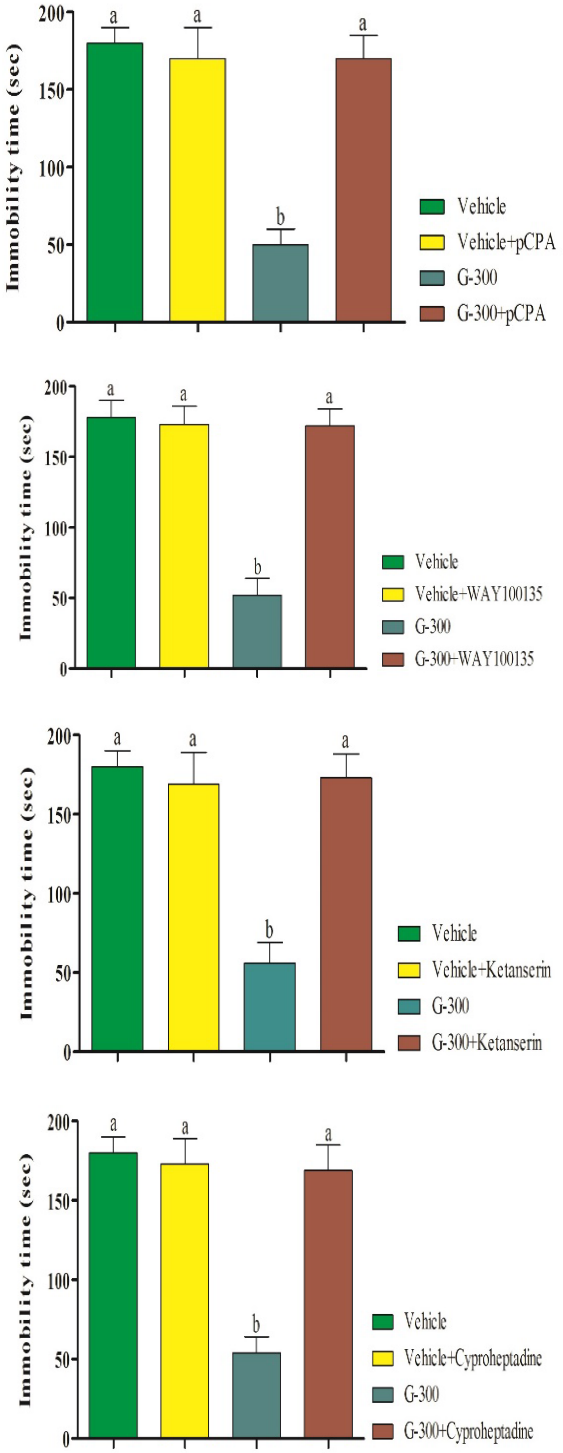

Figure 3. Pretreatment of mice with pCPA (preventorof serotonin synthesis), WAY100135 (receptor antagonist), ketanserin (5HT2A receptor antagonist), and cyproheptadine (5HT2 receptor antagonist) in antidepressant-like effect induced by gingerolin tail suspension test. Superscripts (a-c) show significant difference among groups. The data were analyzed by two-way ANOVA

Discussion

The present results showed that use of the gingerol as an antidepressant agent could express antidepressant-like activity in tail suspension test in mice. Tail suspension test has been known as one behavioral model for detection of antidepressant activity. In the model, decreased immobility time were considered as an indicator for antidepressant-like action [20]. Tail suspension test has been used to evaluate the depressive-like behaviors in mice because it could imitate helpless behaviors that frequently seen in patients with depression [28]. We did not observe differences for immobility time. Increased locomotor activity could be considered as false response. We could not find in the published literature any study to show antidepressant activity of gingerol.

With regards to our findings, it showed antidepressant-like effect of gingerol by modulation in serotonin system. The data for acute mechanism of antidepressant drugs caused to be considered by monoaminergic system [29]. The monoamine pathways such as serotonergic transmission have been known as target site for antidepressant drugs [30].

It has been accepted more or less that most of the drugs administrated for treatment of depression is involved in monoamine neurotransmitters [31]. However, pre-treatment with pCPA (preventer of serotonin synthesis), WAY100135 (receptor antagonist), ketanserin (5HT2A receptor antagonist), and cyproheptadine (5HT2 receptor antagonist) could prevent decreased immobility period induced by gingerol. It means that serotonergic system is involved in the antidepressant effects of gingerol in the tail suspension test in the mice. Previous studies have shown the role of 5HT as one neurotransmitter in depression, because it is involved in some symptoms of major depression [32]. Other reason is that 5HT1A receptors clearly modulate in the clinical effect of antidepressants [33] due to its position in the soma and dendrites of 5HT neurons in the dorsal raphe which inhibit to release 5HT [34]. Previous studies have also reported that ketanserin could prevent antidepressant activity in some herbal medicines in the tail suspension test in the animal model [31, 35]. It has been known tryptophan as substrate for synthesis of serotonin. We believed that gingerol could partly prevent oxidation of tryptophandue to its antioxidant properties. Unfortunately, we could not find any published study in the literature which showing effects of gingerol on serotonergic system.

Conclusion

Gingerol involves in serotonergic system and show antidepressant-like effect. We suggest touse the gingerol for treatment of depression as a novel agent in commercial preparation and prescribed as a drug for therapeutic reasons.

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