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Evaluation of Antidepressant Effect of 6-Shogaol in animal models

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Abstract

The objective of the study was therefore to evaluate the role of 6-shogaol in the antidepressant effect *Zingiber officinale* using two different animal models viz., tail suspension test and forced swim test. Ginger rhizomes were extracted using water-methanol (80/20) as the solvent using maceration and 6-shogaol was isolated from the extract using mixture of n-hexane-diethyl ether (70/30, v/v) in column chromatography. The yield of the isolated 6-shogaol after column chromatographic isolation of the aqueous methanolic ginger extract was found to be 1.3%. The isolated 6-shogaol was of pale-yellow color and the texture appeared to be fine and crystalline. The forced swim test revealed that the immobility time was significantly reduced at all the administered doses of 6-shogaol in a dose dependent manner. The swimming time was found to increase in a similar fashion but was not significantly increased at a dose of 30 mg/kg of 6-shogaol. ANOVA analysis of the tail suspension test revealed that the reduction of immobility time was not significant at a dose of 30 mg/kg 6-shogoal whereas at doses of 100 and 300 mg/kg, the reduction was significant as compared to the control group.

Keywords

Shogaol, extract, tail suspension, forced swim, antidepressant, isolation

Introduction

The World Health Organization (WHO) estimates that about 75 % of the world population—primarily those of developing countries—depend on traditional remedies (mainly herbs) for the healthcare of its people (Gilani and Atta ur, 2005). Depression is a common psychiatric disorder characterized by change in mood, lack of interest in the surroundings, and psychosocial and physical impairment (Girish et al., 2012; Nakajima et al., 2010).

Zingiber officinale has been reported to exert anti-oxidant and anti-ulcer, anti-inflammatory, anti-tumor, carminative, diaphrodic and digestive, expectorant, as well as gastro protective activities. It is used in Chinese traditional medicine as a stomachic, antiemetic, antidiarrheal and cardiotonic, for the treatment of several gastrointestinal and respiratory diseases. Powdered ginger is also used for treatment of motion sickness.

6-Shogaol (1-4-hydroxy-3-methoxyphenyl-4-decen-3- one) is one of the major biologically active compounds found in the rhizome of *Zingiber officinale*/ginger (Kota et al, 2008). This compound was previously reported to have antipyretic and analgesic effects in addition to inhibitory effect on lipoxygenase activity (Flynn et al, 1968).

From the literature it was evident that the *Zingiber officinale* hydroalcoholic extract possessed the potential to protect the neurons and exhibit antidepressant effects in animal models. A few reports of the antidepressant effect of *Zingiber officinale* were found but none presented the role of gingerol or 6-shogoal in treatment of depression (Kukula-Koch et al., 2018; Phukan & Adhikari, 2017). The objective of the study was therefore to evaluate the role of 6-shogaol in the antidepressant effect *Zingiber officinale*.

Material and Methods

6-Shogaol was isolated from ginger rhizomes using reported method and was used without analyzing the purity. All other chemicals used in the study were of AR grade and were procured from the local chemical supplier.

Extraction of ginger (Rigane et al, 2018)

Ginger was procured from local market and shade dried. The dried ginger was powdered coarsely and the powder was subject to extraction procedure as follows.

About 20 g of fine powder of the dried ginger rhizome was suspended in a methanol–water mixture, 20/80 (v/v), at room temperature for 72 h under constant stirring. The resulting extract was filtered, the solvent was completely removed using a rotary evaporator, and the extract was stored at 4°C until further use.

Isolation of 6-shogaol (Rigane et al, 2018)

Silica gel column was employed to purify the aqueous methanolic *Zingiber officinale* extract. The extract was directly applied on the Silica gel column, and eluted by a mixture of n-hexane-diethyl ether (70/30, v/v). The fractions were separated and mixed. The mixed fractions were subjected to evaporation of the solvent in order to obtain the crystalline 6-shogaol.

Evaluation of antidepressant action

The *in vivo* antidepressant action of 6-shogaol was carried out in male albino mice weighing between 25–30 g by FST and TST method. The animal were grouped and housed in poly acrylic cages (38x23x10 cm) in the animal house of the institute. Not more than four animals per cage were housed and maintained under standard laboratory conditions with natural dark and light cycle (14 h light/10 h dark) at 27±2°C and relative humidity (RH) 44-56% with free access to standard diet (Golden Feeds, India) and tap water *ad libitum* for one week for acclimatization before and during the experiments.

Animal were divided into 5 groups of 6 animals each for conducting the study. Group I was administered with normal saline and served as control, group II, III & IV were administered 30, 100 & 300 mg/kg (i.p) of 6-shogaol, whereas group V served as positive control and was administered with fluoxetine, 10 mg/kg (i.p).

Forced Swim Test (Ashok Kumar et al, 2014; Malviya et al, 2021)

The isolated 6-shogaol and fluoxetine were dissolved in DMSO and administered in a standard volume of 0.05 mL per 20 g body weight, to each mouse 30 minutes prior to the test. To determine the effect of the test compound mice were individually placed in a glass cylinder (25 cm height, 10 cm diameter) filled with water (22-25°C) up to 10 cm height. Each mouse was allowed to swim for 6 minutes during the test, and the duration of immobility was observed and noted during the final 4 minutes of the test. The time spent by the mouse floating in the water without

struggling and making only those movements necessary to keep its head above water was regarded as the immobility period.

The animals were dried using tower and returned back to their housing conditions.

Tail Suspension Test (Ashok Kumar et al, 2014; Malviya et al, 2021)

The isolated 6-shogaol and fluoxetine were dissolved in DMSO and administered in a standard volume of 0.05 mL per 20 g body weight, to each mouse 30 minutes prior to the test. To determine the effect of the test compound mice were individually suspended by tail using clamp (2 cm from the tip of the tail) in a box (25 × 25 × 30 cm) with the head 5 cm from the bottom. Minimal background noise was maintained and the testing was carried out in dark room. All animals were suspended for total 6 minutes, and the duration of immobility was observed and noted during the final 4 minutes of the test. Mice were considered immobile only when they hung passively and completely motionless.

The animals were used only once for this test.

Statistical Analysis

The results of pharmacological studies were expressed as mean ± S.D. The total variations present in data were evaluated by using Graph Pad Prism 5 project software one way ANOVA (analysis of variance) followed by Dunnett's multiple comparison Test. The result were considered statistically significant when P- value less than 0.05 ($P<0.05$) vs control.

Results and Discussion

Physicochemical characterization of 6-Shogaol

The yield of the isolated 6-shogaol after column chromatographic isolation of the aqueous methanolic ginger extract was found to be 1.3%.

The identity of the isolated shogaol was ascertained by its IR spectra (figure 1). The peak of the functional groups was compared with that of the standard data available at Organic spectroscopy international (https://orgspectroscopyint.blogspot.com/).

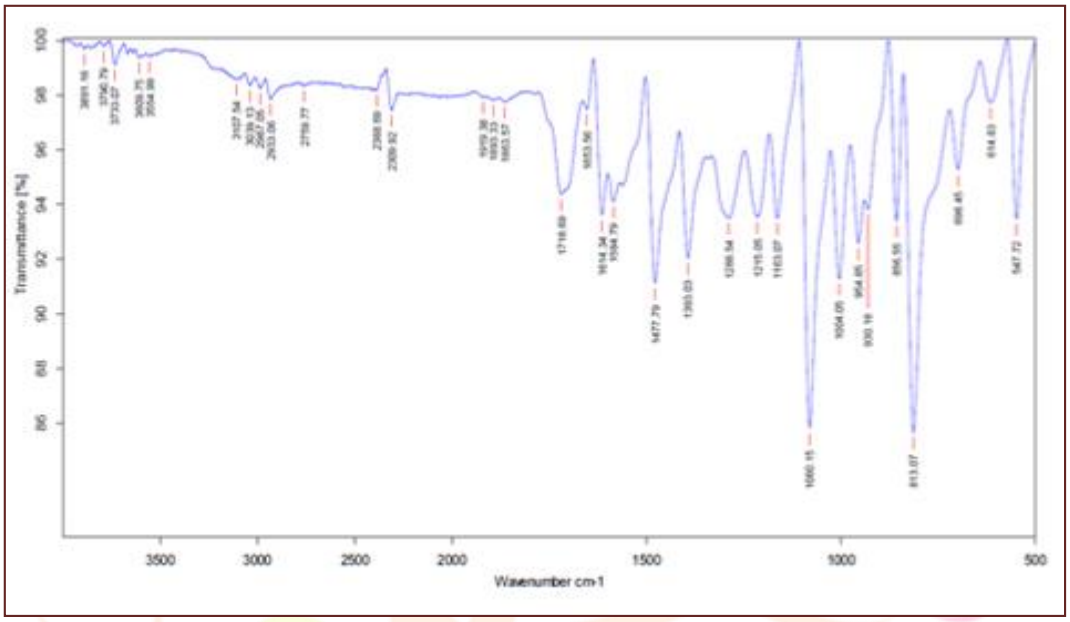

Figure 1 FTIR spectra of 6-Shogaol

The isolated 6-shogaol was of pale-yellow color and the texture appeared to be fine and crystalline. The data from drug bank also confirms the crystalline structure of 6-shogaol.

Solubility of 6-shogaol was observed in different solvents and the isolated 6-shogaol was found to be soluble in ethanol, DMSO and slightly soluble in water.

Forced Swimming Test

The decrease in immobility and increase in swimming time of the test animals was observed to infer the effect of 6-shogaoal as antidepressant. The results obtained are presented in table 1.

Table 1 Immobility and swimming time in FST

	Control	Fluoxetine	S30	S100	S300
Swimming Time (sec)	16.67±1.211	41.33±2.503	20±2.607	23.67±2.503	27.83±3.060
Immobility Time (sec)	29.83±1.471	9.83±1.471	23.33±2.338	20.33±1.211	15.33±1.032

Results are represented as mean ± SD (n = 6); S30-300 represent dose of 6-shogaol

Figure 2 shows the effect of acute administration of 6-Shogaol (30-300 mg/kg, i.p) and the classical antidepressant drug fluoxetine (10 mg/kg, i.p) on immobility behavior of mice during the FST. It was observed that the immobility time was significantly reduced at all the administered doses of 6-shogaol.

The swimming frequency was also observed for the tested animal to ascertain that 6-shogoal was able to avert depression and promote wakefulness in the animals (Yankelevitch-Yahav et al, 2015). Figure 6 shows the swimming frequency of the tested animals and reveals that at dose of 30 mg/kg, 6-shogaol could not significantly evoke wakefulness, nonetheless at 100 and 300 mg/kg dose the swimming frequency was significantly increased as compared to the animals of the untreated group.

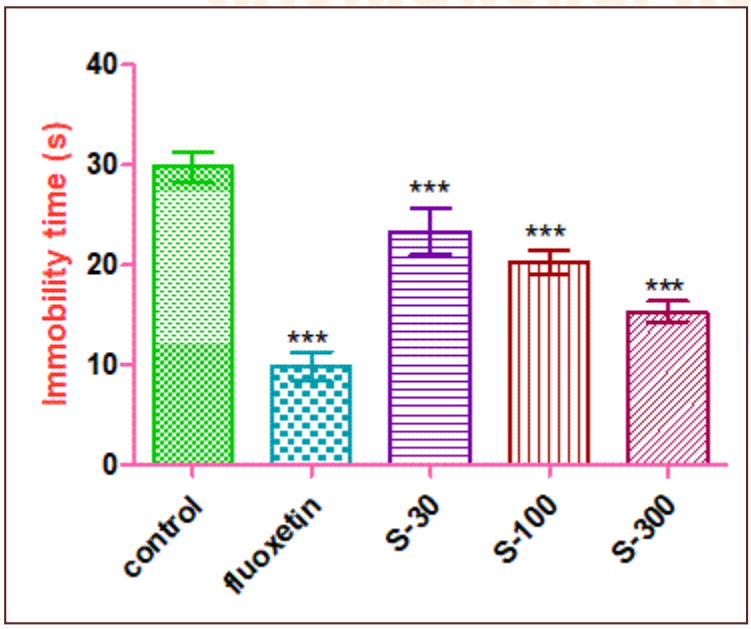

Figure 2 Immobility time exhibited by mice in FST (*P <0.001 (One-way ANOVA followed by Dunnett's multiple comparison test) as compared to control)**

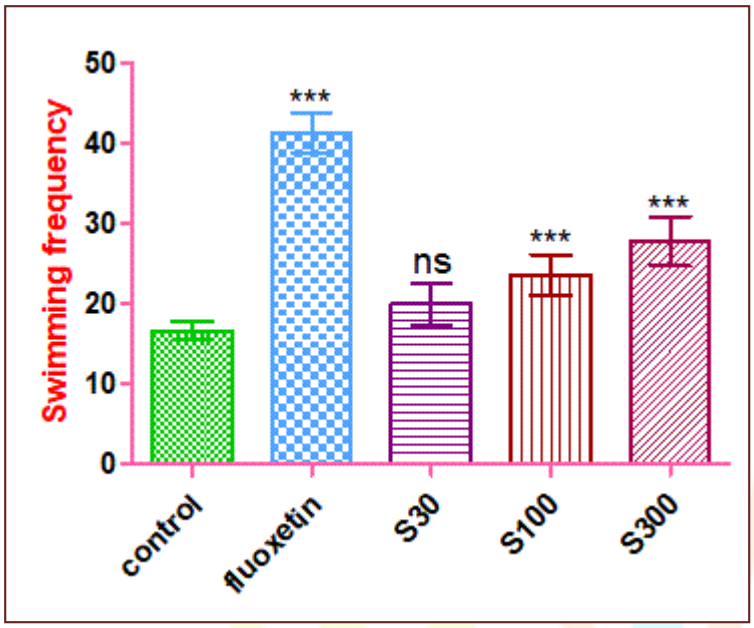

Figure 3 Swimming time exhibited by mice in FST (*P <0.001 (One-way ANOVA followed by Dunnett's multiple comparison test) as compared to control)**

Tail Suspension Test

The tail suspension test (TST) is an experimental method that is used widely to evaluate stress in rodents (Can et al, 2012). It is based on the principle that if rat/mice are given short term unavoidable stress then the rat/mice will become immobile. In order to assess a drugs effect, the reduction or enhancement of the immobility time may be observed. Antidepressant drugs tend to decrease the overall immobility time of the suspended rat/mice.

Table 2 Immobility time in TST

	Control	Fluoxetin	S30	S100	S300
Immolitity time (sec)	185.33±6.470	103.5±5.319	177.16±7.413	133.5±3.987	118.16±4.665

Results are represented as mean ± SD (n = 6); S30-300 represent dose of 6-shogaol

As witnessed from table 2, the time for which the mice remained immobile decreased with an increase in dose of 6-shogaol. ANOVA analysis revealed that the reduction of immobility time was not significant at a dose of 30 mg/kg 6-shogoal whereas at doses of 100 and 300 mg/kg, the reduction was significant as compared to the control group (figure 4).

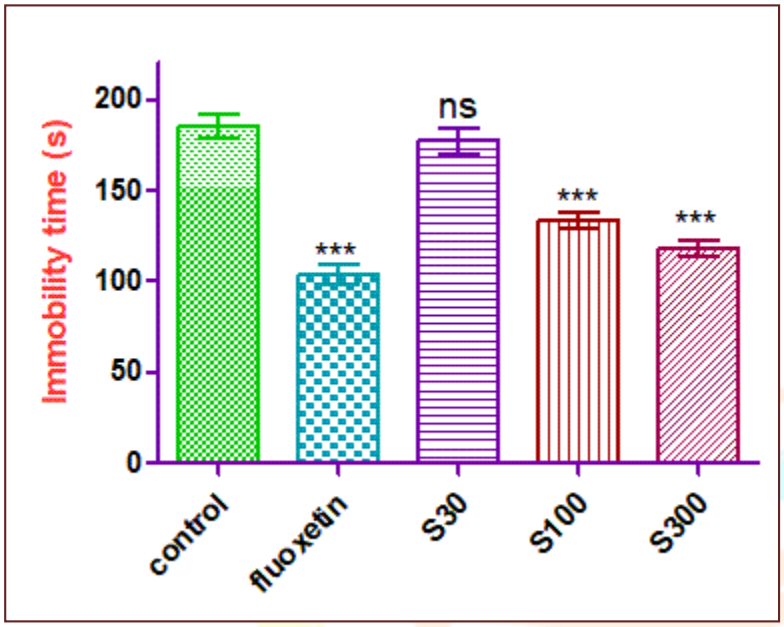

Figure 4 Immobility time exhibited by mice in TST (*P <0.001 (One-way ANOVA followed by Dunnett's multiple comparison test) as compared to control)**

Conclusion

The present investigation was undertaken to confirm the role of 6-shogaol in the antidepressant action exhibited by *Zingiber officinale* extracts. The FST and TST were used as the preliminary protocols to assess the effect of 6-shogaol on depression. It was found that the isolated 6-shogaol could significantly avert the stress induced depression in mice and promote wakefulness and antidepressant effects. Thus the present investigation was able to confirm the possible role of 6-shogaol in antidepressant action of *Zingiber officinale* extracts.

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