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Dose-dependent alteration of neurobehavioral activities by geraniol a component of essential oil: A study in rats

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Abstract: Geraniol, a component of essential oil, is reported to have various pharmacological properties. The current study was conducted to demonstrate the dose-dependent neurobehavioral effects of geraniol. Rats were divided into 5 groups (n=7), comprising of control and four test groups for different doses of geraniol including 10, 30, 50 and 100 mg/kg. Geraniol was given for 15 days through intraperitoneal route. Following the administration, anxiety-, depression-like behaviors and memory function were evaluated. Extent of oxidative stress in rat's brain was also assessed by determining the levels of malondialdehyde and antioxidant enzymes activity. The present study revealed that low doses of geraniol produced more potent anxiolytic, antidepressant, nootropic, and antioxidant effects as compared to the higher doses. The findings highlight the dual characteristic of geraniol, acting as antioxidant at lower doses while at higher doses it produces pro-oxidant effects. The results are discussed in the context of dual characteristic of antioxidant compounds.

Keywords: Antioxidant activity, anxiety, depression, geraniol, memory.

INTRODUCTION

Monoterpenoids are a major constituent of essential oils found in plants. The monoterpenoids consist of two 5-carbon molecules, dimethylallyl diphosphate and isopentenyl diphosphate. These molecules form the basic skeleton of all the compounds found in terpenoid super family and thus by default also form the basic structure of monoterpenoids (Lei *et al*., 2021). Furthermore, C10 unit in monoterpenoids is bonded with various functional groups (Rajput *et al*., 2018). These molecules have been of interest to researchers largely because of their extensive biological activities such as (+)-α-pinene, γ-terpinene (Zamyad *et al*., 2016) and α-phellandrene (Lima *et al*., 2012) showed antinociceptive activity while myrcene is reported to have inflammation reducing property (Yang and Liao, 2021). Similarly, para-cymene has shown analgesic potential whereas the mixture of β-cyclodextrin and para-cymene showed a prolonged analgesic effect (Quintans *et al*., 2013). A widely known monoterpenoid, menthol is also known to possess analgesic effects (Salakhutdinov *et al*., 2017), while another important monoterpenoid is geraniol that encompasses a wide variety of pharmacological activities and is also frequently being utilized in fragrance industry. Geraniol is an open chain monoterpene alcohol which is extracted from plants such as lemongrass, lavender and rose. It is a component of more than 250 essential oils such as rose oil, palmarosa oil, ninde oil, and oil extracted from *Monarda fistulosa* (Maczka *et al*., 2020).

Structurally geraniol possesses a 10-carbon chain (fig. 1) with alcoholic functional group and has a characteristic sweet smell making it a prime ingredient in fragrance industry (Chen and Viljoen, 2010). Along with its commercial use in fragrance industry, it has also become a point of interest for researchers due to a wide range of biological activities. These activities include potent anti-neoplastic, antimicrobial, insecticidal, and inflammation lowering activity. Additionally, the most important characteristic of geraniol is that it can rapidly cross the blood-brain barrier (Mączka *et al*., 2020). The pharmacological properties of geraniol have been reviewed by Lei *et al*., (Lei *et al*., 2019) in which it has been suggested as a potential drug candidate for the treatment of variety of ailments. The studies on neurobehavioral effects of geraniol are limited which have reported different doses of this compound. In a mouse model of chronic unpredictable mild stress, Deng *et al*. (Deng *et al*., 2015) investigated the antidepressant effects of geraniol at dosages of 20 and 40 mg/kg. Moreover, Majdi and co-workers (Majdi *et al*., 2019) reported antidepressant effects of geraniol in chronic

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restraint stress mice model at a single dose of 50 mg/kg whereas anti-Parkinson's effect has been shown at 100 mg/kg dose (Rekha *et al*., 2013). The dose-dependent studies of geraniol to demonstrate its neurobehavioral effects are lacking in the literature. The current study was, therefore, conducted to identify the dose-dependent effects of geraniol on neurobehavioral activity in rats within the ranges of 10-100 mg/kg. The associated antioxidant effects were also examined to determine its potential use in neurological ailments.

MATERIALS AND METHODS

Animals

Thirty-five male, albino Wistar rats were taken from the animal house of the ICCBS, University of Karachi. Rats were kept in standard cages under a measured room temperature (24±2°C) and 12:12 light-dark cycle with food and water *ad libitum*. The animals were habituated for a period of one week before starting the dosing period. The procedures conducted in this study conformed to the guidelines provided by the Institutional Animal Care and Use Committee (IACUC) under the protocol number 2021-001 and were in complete conformation with the National Institute of Health Guide for Care and Use of Laboratory Animals (NIH Publication no. 85-23, revised 2011).

Chemicals

Geraniol 97% was purchased from Alfa Aesar (Germany), thiobarbituric acid, trichloroacetic acid, nitro blue tetrazolium and dithiobisnitrobenzoic acid was purchased from British Drug House (BDH, Dorset, UK). Hydroxylamine hydrochloride was purchased from Sigma Chemicals (St. Louis, USA). Glutathione standard was purchased from Calbiochem and hydrogen peroxide was purchased from Merck.

Study design

The study was performed at the ICCBS, University of Karachi. Animals were arbitrarily placed into 5 groups (where n=7). The second, third, fourth, and fifth group received geraniol via intraperitoneal (i.p.) route at doses 10mg/kg, 30mg/kg, 50mg/kg and 100mg/kg, respectively. The geraniol was dissolved in 0.4% Tween 80 prepared in saline. The first group was control which received vehicle only. Habituation was conducted for five days which was followed by dosing period of 15 days. As the dosing period concluded, behavioral analyses were carried out comprising of forced swim test (FST), water maze test (WMT) and light/dark transition (LDT) test. Upon completion of behavioral experiments, decapitation was carried out to isolate the brain samples. Brain samples were kept in liquid nitrogen after collection and later kept at -20°C till biochemical analysis were done (fig. 2).

Light/dark test (LDT)

LDT test was carried according to the protocol as published earlier (Haider *et al*., 2015) to evaluate anxious behavior. The LDT apparatus comprised of light and dark compartments having same dimensions (27.5×27.5 cm). Briefly, the rat was positioned in the illuminated compartment of LDT apparatus and permitted to wander for 5 min. Diminished latency to move into the dark box, and increased time spent and number of entrances into the illuminated box were taken as an index of anxiolytic behavior.

Forced swim test (FST)

FST was utilized to asses effects of depression in rats treated with geraniol and vehicle. The protocol described by Slattery and Cryan (2012) was followed in this study. In summary, rats were coerced to swim in a rectangular container (51×20×20 cm, transparent glass tank) filled with water in a pre-test for 15 min. After 24h of pre-test, the testing was performed for 5 min during which immobility time was observed. Decreased immobility time during test session was considered as depression-like effects.

Water maze test (WMT)

The protocol reported earlier (Haider *et al*., 2020) was used to assess recall activity. The equipment comprised of a black-painted round water reservoir (65 cm in height and 90 cm in diameter) which was divided into four quadrants (NW, SE, SW and NE). A black-painted circular hidden platform (8 cm diameter, 12 cm height) was placed in NW quadrant. Water was filled 2 cm above the platform. The test consisted of training and test periods. In training period rat was introduced into each quadrant to locate the hidden platform. There was a 30 min interval between each trial. 60 min after training, test was conducted in which platform was taken out of the tank and activity of rat was monitored for its memory function. Decreased escape latency, and increased time spent and number of crossings through the quadrant of interest were defined as the improved memory function.

Biochemical analysis

Measurement of formation of lipid peroxidated (LPO) products was done by assessing the amount of malondialdehyde (MDA) in rat brain and expressed in μmol/g of brain. Activity of super oxide dismutase (SOD) is expressed as U/g. Reduced glutathione (GSH) levels were expressed in nmol/g of brain whereas the activity of glutathione peroxidase (GPx) was indicated in terms of μmol/min/g of brain. These analyses were performed according to the protocols provided in the study of Haider *et al*. (2015).

STATISTICAL ANALYSIS

IBM SPSS for Windows version 19 was used to conduct statistical analysis. Assessment of dissimilar groups was

Table 1: Oxidative stress biomarkers in rat whole brain. Values are mean±SD (n=7). Statistically significant difference was observed as compared to controls by one-way ANOVA using Tukey's *post-hoc* analysis: **P<0.01.

	mg/kg	MDA (µmol/g)	SOD (U/g)	GSH (nmol/g)	GPx (µmol/g/min)
Control	0	33.0±5.6	35.0±2.1	138.1±10.5	55.9±1.1
Geraniol	10	23.0±4.5**	41.5±2.5**	139.7±9.3	55.9±1.9
	30	21.1±3.6**	40.8±2.5**	180.7±10.7**	58.2±1.0*
	50	29.9±5.0	35.4±3.1	129.6±9.9	55.3±2.5
	100	40.2±6.8	32.9±3.6	106.3±8.1**	54.4±1.9

done by the use of one-way ANOVA after which *post-hoc* analysis consisting of Tukey's analysis was conducted. The P values <0.05 were considered as significant.

RESULTS

Anxiolytic behavior

The latency to enter into the dark box was significantly affected by geraniol treatment ($F_{4,30}$=62.246, P<0.01). The latency time exhibited by dosage groups of 30 and 50 mg/kg was significantly increased (P<0.01) as compared to the controls while the group treated with the dose of 100 mg/kg did not show significant difference as compared to controls. Time spent in light box was also significantly impacted by geraniol treatment ($F_{4,30}$=8.774, P<0.01). The dose of 10 mg/kg (P<0.05) and 30 mg/kg (P<0.01) showed a significant increase in the time spent in light box as compared to controls. While the third parameter observed through the LDT was the number of entries into light box which was also significantly affected by treatment of geraniol ($F_{4,30}$=4.952, P<0.01). *Post-hoc* analysis showed that the group treated with 10 mg/kg (P<0.05) and 30 mg/kg (P<0.01) of geraniol dosage showed a significant increase in number of entries in light box as compared to the control group (fig. 3).

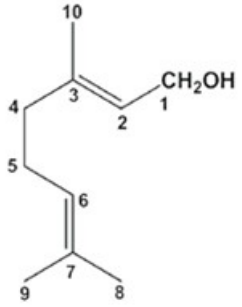

Fig. 1: Chemical structure of geraniol [taken from (Chen and Viljoen, 2010)].

Fig. 2: Schematic representation of study protocol.

Antidepressant behavior

Effects of geraniol on depression were evaluated using FST following 15 days of geraniol administration. Geraniol dosing significantly ($F_{4,30}$=90.168, P<0.01) affected FST activity. Tukey's *post-hoc* test showed dose-dependent effects on immobility time. The immobility time was found to be significantly (P<0.01) reduced in the groups received 10 and 30 mg/kg of geraniol as compared to the control group. While the groups treated with 50 and 100 mg/kg of geraniol showed a significant (P<0.01) increase in immobility time as compared to the control group (fig. 4).

Memory function

Memory was tested using WMT paradigm in rats. The parameters of latency to move into target quadrant ($F_{4,30}$=52.36, P<0.01), time spent in target quadrant ($F_{4,30}$=26.950, P<0.01), and the number of crossings through the target quadrant ($F_{4,30}$=11.225, P<0.01) were significantly affected by geraniol treatment. *Post-hoc* analysis showed that the all the dosage groups (10, 30, 50, 100 mg/kg) exhibited significantly (P<0.01) decreased latency to reach the target quadrant as compared to the control group. Time spent in target quadrant for 30 mg/kg group was significantly (P<0.01) increased as compared to the control group. The group treated with 10 mg/kg also showed an increase in time spent in target quadrant as compared to the controls, however, the difference was not significant. Number of crossings exhibited by the groups of 10 and 30 mg/kg were significantly (P<0.01) increased as compared to the control group (fig. 5).

Malondialdehyde (MDA) levels

Oxidative stress in the rat brain was measured by the estimation of lipid peroxidation through analysis of MDA levels (table 1). The levels of MDA were significantly affected by the treatment of geraniol ($F_{4,30}$=15.256, P<0.01). Tukey's *post-hoc* analysis showed that the MDA levels were significantly decreased in the groups treated with 10 and 30 mg/kg of geraniol as compared to the control group (P<0.01).

Superoxide dismutase (SOD)

Antioxidant enzyme SOD was found to be significantly ($F_{4,30}$=10.657, P<0.01) affected by treatment of geraniol. The doses of 10 and 30 mg/kg showed significantly (P<0.01) elevated activity of SOD as compared to the control group. While the dosage groups of 50 and 100 mg/kg showed no significant results (table 1).

Reduced glutathione (GSH)

GSH estimation showed that its levels in rat brain were significantly ($F_{4,30}$=48.824, P<0.01) affected by geraniol treatment. Further analysis showed that the group treated with the dose of 30 mg/kg exhibited significantly (P<0.01) elevated levels of GSH as compared to the controls. However, 100 mg/kg significantly (P<0.01) reduced the levels of GSH as compared to the control group (table 1).

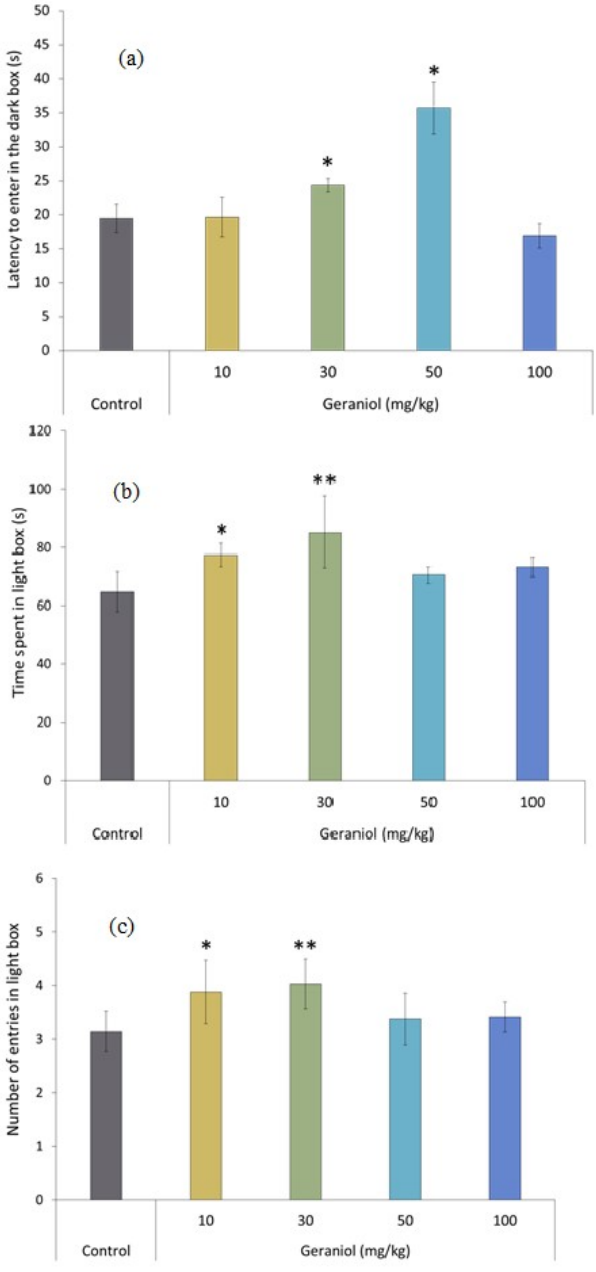

Fig. 3: Activity of rats receiving different doses of geraniol in the light/dark transition test assessed through the parameters including (a) latency to enter dark box, (b) time spent in light box, (c) number of entries in light box. Values are mean ± SD (n=7). Statistically significant difference was found as compared to the control group by one-way ANOVA using Tukey's *post-hoc* analysis: *P<0.05, **P<0.01.

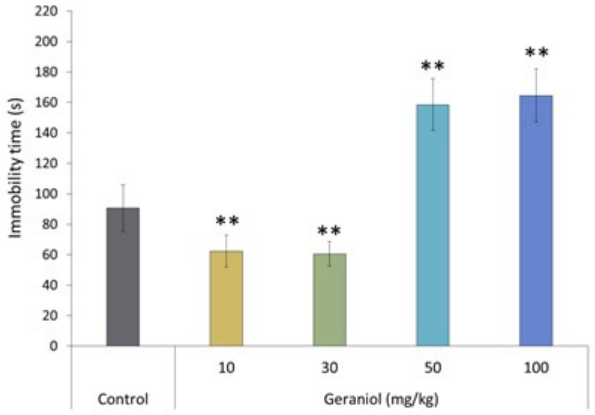

Fig. 4: Assessment of depression-like behavior of rats receiving different doses of geraniol through forced swim test. Immobility time is observed as a measure of behavioral despair where values are mean ± SD (n=7). Statistically significant difference was found as compared to the control group by one-way ANOVA using Tukey's *post-hoc* analysis: *P<0.05, **P<0.01.

Glutathione peroxidase (GPx)

GPx estimation showed that geraniol treatment had a significant ($F_{4,30}$=5.186, P<0.01) effect on its activity in rat brain. *Post-hoc* analysis showed that the levels of GPx were significantly (P<0.05) elevated in the dosage group of 30 mg/kg as compared to the control group. None of the other groups differed significantly from the control group (table 1).

DISCUSSION

The current study demonstrated the dose-dependent effects of geraniol on neurobehavioral activities and associated anti-oxidative potential. To the best of our knowledge, this is the first study determining the optimum dose of geraniol that may be effective against neurological disorders. The treatment of geraniol doses from 10-100 mg/kg produced different behavioral effects in rats. The anxiety-like effects were significantly reduced at the lower doses of 10 and 30 mg/kg whereas higher doses, 50 and 100 mg/kg, were found to be ineffective. The lower doses were also found to reduce depression-like symptoms which were increased by the higher doses of geraniol. Moreover, the memory function was also affected by the geraniol treatment. The doses from 10-100 mg/kg showed increased memory function as evidenced by lower escape latency in all groups when compared to controls. However, more memory enhancing effects were observed by 10 and 30 mg/kg doses as observed by improved time spent and number of entries in the target quadrant.

The oxidative load was also differentially affected by the geraniol doses. The doses of 10 and 30 mg/kg showed more prominent anti-oxidative potential than the higher doses of geraniol. Previous studies have demonstrated the antioxidant property of geraniol. Gateva *et al*. (2019) reported antioxidant activity of geraniol *in vitro* study.

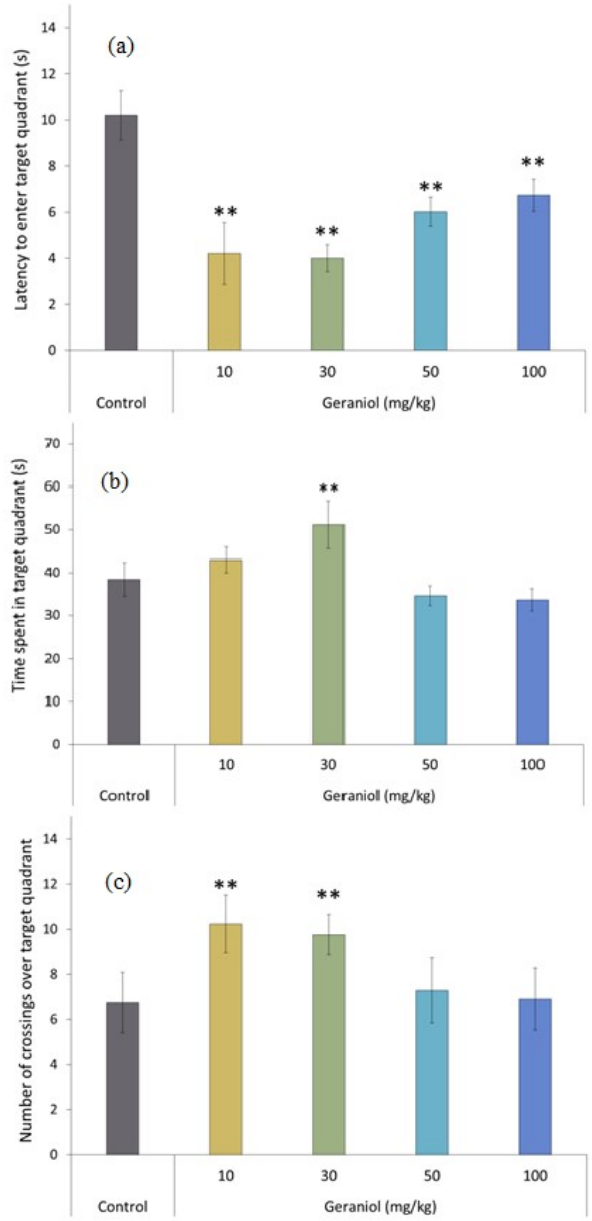

Fig. 5: Assessment of spatial memory in rats through water maze test (a) latency to enter target quadrant, (b) time spent in target quadrant, (c) number of crossings over target quadrant. Values are given as mean ±S.D (n=7). Statistically significant difference was found as compared to the control group through one-way ANOVA using Tukey's *post-hoc* analysis: *P<0.05, **P<0.01.

They found radical scavenging and enzymatic antioxidant enhancing activity following the treatment of geraniol which was similar to ascorbic acid and α-tocopherol (Gateva *et al*., 2019). Previously, Madankumar and co-workers (Madankumar *et al*., 2013) also showed enhanced enzymatic and non-enzymatic antioxidant activity by geraniol treatment and demonstrated its chemopreventive characteristic. Researchers have described that the antioxidant potential of geraniol lies in its chemical structure. Analysis of the structure of geraniol suggests direct radical scavenging ability due to the presence of allylic carbons at positions 1, 4 and 5. The suggested anti-oxidative mechanism of geraniol involves the transfer of hydrogen atom from C-H bonds. This hydrogen atom then reduces the oxidative radicals making them harmless to an extent. The deprotonation may preferentially happen from the C-1 position adjacent to the double bond (Stobiecka, 2015). In this study, lower doses of geraniol significantly reduced MDA levels demonstrating decreased lipid peroxidation. These doses also showed a direct effect on antioxidant enzymes as evident by increased activity of SOD. Moreover, GSH level and GPx activity were significantly increased by 30 mg/kg geraniol. These findings revealed that geraniol has the ability to reduce oxidative load in the rat brain possibly by scavenging the oxidative radicals and potentiating the endogenous antioxidant system. Consistent with these results, Majdi and colleagues also showed the antioxidant potential of geraniol. They observed increased levels of GPx, GSH, and catalase in mice undergoing chronic unpredictable mild stress following the administration of geraniol (Majdi *et al*., 2019), which can be considered as a healing effect as these antioxidant enzymes are found to be decreased in depression and anxiety-like states which is a contributing factor in the etiology of anxiety and depressive disorders (Fedoce *et al*., 2018).

The higher doses of geraniol (50 and 100mg/kg) produced a different effect on oxidative load. These doses showed a tendency to increase MDA levels whereas GSH levels were decreased as compared to the control animals. The effects observed at lower doses of geraniol on SOD and GPx were also found to be diminished by the higher doses. These results demonstrate a potential pro-oxidant effect of geraniol. The pro-oxidant nature of most of the antioxidants is well known. Previously, many compounds including polyphenols, terpenes, ascorbic acid, and α-tocopherol have been reported to act as pro-oxidant and induce oxidative stress (Zhang and Omaye, 2001; Putchala *et al*., 2013; Llana-Ruiz-Cabello *et al*., 2015). The well-known monoterpenes carvacol and thymol have shown pro-oxidant effects on intestinal Caco-2 cell line (Llana-Ruiz-Cabello *et al*., 2015). Consistently, our study also demonstrated pro-oxidant effect of geraniol at higher doses. Geraniol has been reported to be a potent cytotoxic agent and has shown efficacy against tumor in various studies (Queiroz *et al*., 2017; Polo *et al*., 2011; Qi *et al*., 2018). It is observed that anti-neoplastic agents up to some extent use their ability to generate reactive oxygen

species (ROS) to kill neoplastic cell. In case of geraniol, it is hypothesized that its ability to produce ROS is because of the auto-oxidation of molecule. Crespo and colleagues (2020) found that geraniol when tested for its cytotoxicity showed increased lipid peroxidation which can be related to its ability of ROS formation. Knowing this dual nature of antioxidants, it is important to maintain them at an optimum concentration.

The corresponding dose-dependent effects of geraniol were also determined through behavioral analysis that also yielded similar results showing anxiolytic and antidepressant potential at lower doses of 10 and 30 mg/kg compared to controls. The neuropsychiatric behavior and oxidative stress are extensively interlinked with each other (Salim, 2014). The oxidative stress induced by the over production of oxygen-derived molecules is suggested to cause oxidative damage to membrane which is rich in poly-unsaturated fatty acids leading to oxidation of lipid bilayer. This produces diminutive membrane fluidity, impaired membrane protein, and deactivation of ion channels, enzymes, and receptors (Ayala *et al*., 2014). Consequently, alteration in neuronal function, neurotransmission, and brain activity occur under oxidative load (Salim, 2014). Compounds with antioxidant potential have also shown to reduce anxiety- and depression-like symptoms in pre-clinical and clinical studies (Ribeiro, 2015; Aburawi *et al*., 2014; Scapagnini *et al*., 2004). Consistently, the antioxidant effects of our test compound at lower doses are concomitant with anxiolytic and antidepressant effects, indicating improved neuronal integrity following the administration of geraniol. On the hand, the association of oxidative stress and neuropsychiatric behavior was observed at higher doses of geraniol. The pro-oxidant effects of geraniol may be responsible for reduced anxiolytic and antidepression-like effects at higher doses. Results of memory assessment also reflected the same pattern, lower doses of geraniol were more effective to improve memory function as compared to higher doses of geraniol. Therefore, the balance between antioxidant and pro-oxidant effects of a compound is crucial for a healthy brain function.

CONCLUSION

In conclusion, the low doses of geraniol showed optimum neurobehavioral effects may be in-part due to its ability to potentiate endogenous antioxidant system. This suggests the use of geraniol against neurological ailments at the doses of 10 and 30mg/kg. Moreover, this study also highlights the dual characteristic of geraniol. At higher doses geraniol may behave like a pro-oxidant as shown by the findings of behavioral and antioxidant analyses. These results are important to be considered because geraniol is being used as a prime constituent in fragrance industry.

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