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Research Report

Analysis of anti-depressant potential of curcumin against depression induced male albino wistar rats

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ABSTRACT

The present study investigated the antidepressant potential of curcumin in olfactory bulbectomy and forced swimming test models of depression in male albino rats under chronic treatment. The experimental animals were divided into four groups, and curcumin was administered for 45 days. Our results showed that the curcumin significantly reduced olfactory bulbectomy-induced behavioral abnormalities including deficits in step-down passive avoidance, increased activity in the open area and immobility time. Chronic administration of curcumin significantly reversed levels of 3, 4-dihydroxyphenylacetic acid, noradrenaline, serotonin and 5-hydroxyindoleacetic acid in the hippocampus region of male albino rats. Also, curcumin normalizes the levels of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid in the frontal cortex of rats. Taking all these results together, it may suggest that curcumin is potent compound acting against the depression in the male albino rats.

1. Introduction

Curcumin is an essential curcuminoid of turmeric, which comes under the family of ginger. Turmeric presents as desmethoxycurcumin and bis-desmethoxycurcumin forms. Natural phenols provide the yellow color of turmeric and exist as 1, 3-diketo and enol forms. The keto form is weaker than enol form (Manolova et al., 2014). Curcumin has been reported to have antioxidant and anti-inflammatory effects (Dutta et al., 2005; Weber et al., 2005; Lim et al., 2005; Biswas et al., 2005). Thiyagarajan and Sharma (2004) have reported the immunomodulatory, anti-inflammatory, antioxidant and neuroprotective effects. In Chinese traditional medicine, the curcumin has been used mental stress and hypochondriac distensive mania and pain. Yu et al. (2002) have reported the anti-depressant effect of curcumin in mice.

Schloss and Henm (2004) have reported the depressive disorders are commonly occurs in the Western countries.

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Even though, there are several drugs available for depression-related disorders that are producing adverse effects. Therefore, the discovery of natural medicinal products for this kind of disorders could minimize the negative impact. Chen and Tang (2004) have reported the potential of using Chinese traditional medicines for this type of disorders. Mazzio et al. (1998) have reported the inhibition of monoamine oxidase enzyme activity under curcumin treatment in C6 glial cells and this enzyme is known to play a fundamental role in depression-related disorders. Dar and Khatoon (2000) have reported the monoamine oxidase inhibitor-induced increase of monoaminergic neuro transamination and its role in depression-related disorders.

However, information and mechanism of curcumin action on depression-related disorders yet to be investigated. Therefore, the present study was aimed to investigate the chronic administration of curcumin against bilateral olfactory bulbectomy model and forced swim test in the male albino rats.

2. Results

2.1. *Curcumin effect on passive avoidance in olfactory bulbectomy rats*

Male albino rats with bilateral olfactory bulb ablation required 12 number of trial counts to attain the criteria. Trial counts were determined, and it was found to be 9 and 21 in the sham control and olfactory bulbectomy rats respectively. Curcumin administration significantly reduced the learning deficit in the olfactory bulbectomy rats. Curcumin treatment reduced the number trial counts 18, 15 and 12 at 10, 20 and 40 mg/kg bwt respectively (Fig. 1).

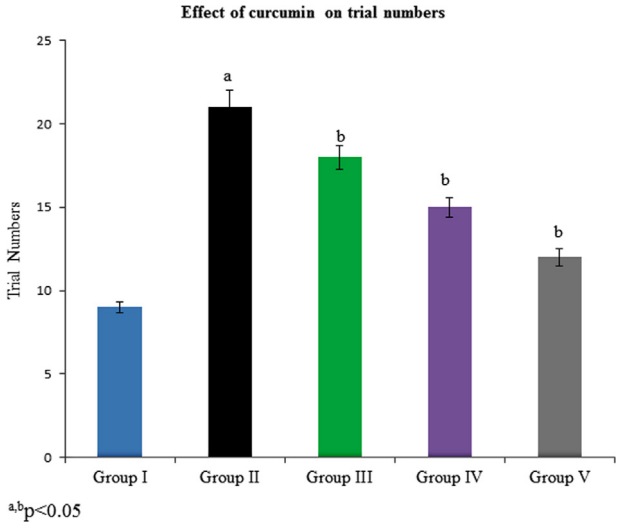

Fig. 1 – Chronic effect of curcumin administration on passive avoidance in the olfactory bulbectomy model of male albino rats. Curcumin was diluted in normal saline and administered orally for 45 consecutive days. Values were expressed mean ± SD. $^{ab}p < 0.05$. The olfactory bulbectomy (lesion) group was compared with sham control group ($^{a}p < 0.05$). Curcumin treated groups were compared with an olfactory bulbectomy (lesion) group ($^{b}p < 0.05$).

2.2. *Curcumin effect on the open field test in olfactory bulbectomy rats*

The number of peepings and rearings and ambulation counts was determined in the sham control and olfactory bulbectomy rats. The number of peepings and rearings was found to be 15.1 and 30.3 in the sham control and olfactory bulbectomy rats respectively. The number of peepings and rearings and ambulation counts was found to increase in the olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly reduced the hyperactivity in the olfactory bulbectomy rats. Curcumin treatment reduced the number peepings and rearings 27.1, 24.1 and 18.6 at 10, 20 and 40 mg/kg bwt respectively (Fig. 2A). The number of ambulation counts was found to be 51.4 and 119 in the sham control and olfactory bulbectomy rats respectively. Curcumin treatment reduced the ambulation counts 101, 80 and 62.3 at 10, 20 and 40 mg/kg bwt respectively (Fig. 2B).

2.3. *Curcumin effect on the serotonin*

Serotonin level was determined in the hippocampus and cortex region of the brain. The quantity of serotonin was found to 279.2 and 141.4 ng/g in the hippocampus region of sham control and olfactory bulbectomy rats respectively. The quantity of serotonin was found to decrease in the hippocampus and frontal cortex of olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly increased the serotonin level in the hippocampus and frontal cortex of olfactory bulbectomy rats. Curcumin treatment significantly increased the serotonin level 162.3, 210.3 and 257.7 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the hippocampus of olfactory bulbectomy rats (Fig. 3). The quantity of serotonin was found to 635 and 378.4 ng/g in the cortex region of sham control and olfactory bulbectomy rats respectively. Curcumin treatment significantly increased the serotonin level 507.4, 570.8 and 605 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the frontal cortex of olfactory bulbectomy rats (Fig. 4).

2.4. *Curcumin effect on the dopamine*

Dopamine level was determined in the hippocampus and cortex region of the brain. The quantity of dopamine was found to 315 and 215.5 ng/g in the hippocampus region of sham control and olfactory bulbectomy rats respectively. The quantity of dopamine was found to decrease in the hippocampus and frontal cortex of olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly increased the dopamine level in the hippocampus and frontal cortex of olfactory bulbectomy rats. Curcumin treatment significantly increased the dopamine level 247.4, 265.8 and 290.6 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the hippocampus of olfactory bulbectomy rats (Fig. 3). The quantity of dopamine was found to 287 and 166.6 ng/g in the cortex region of sham control and olfactory bulbectomy rats respectively. Curcumin treatment significantly increased the dopamine level 191.4, 222 and 261.4 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the frontal cortex of olfactory bulbectomy rats (Fig. 4).

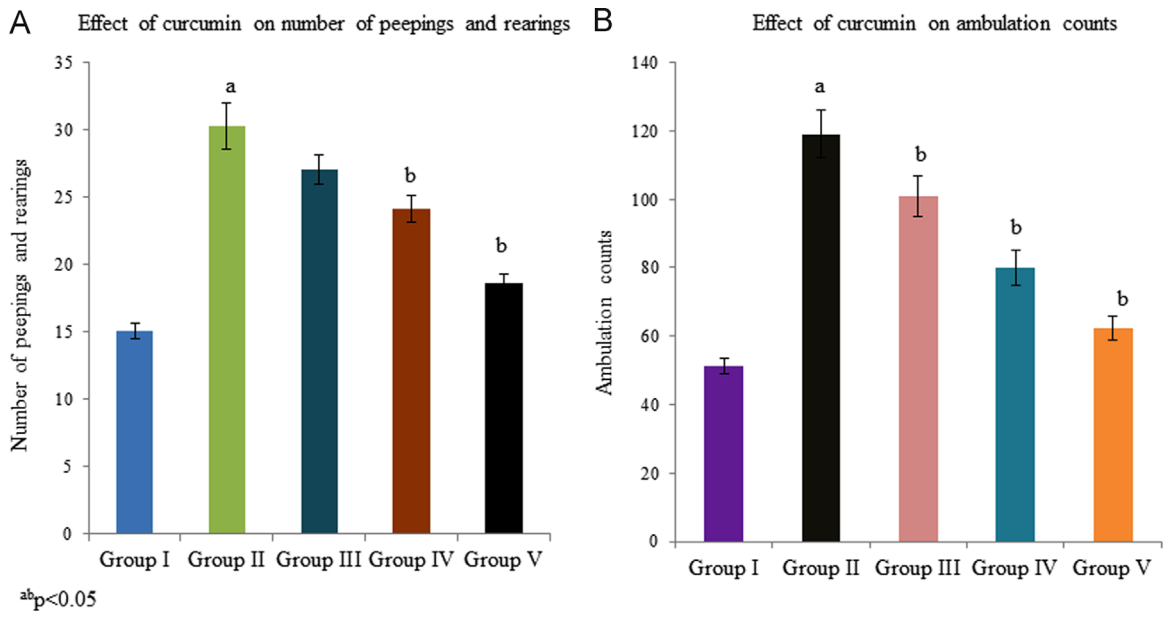

Fig. 2 – Chronic effect of curcumin administration on peepings and rearings and ambulation counts in the olfactory bulbectomy model of male albino rats. Curcumin was diluted in normal saline and administered orally for 45 consecutive days. A number of peepings and rearings (A) and ambulation counts (A) were given. Values were expressed mean ± SD. $^{ab}p<0.05$. The olfactory bulbectomy (lesion) group was compared with sham control group ($^{a}p<0.05$). Curcumin treated groups were compared with an olfactory bulbectomy (lesion) group ($^{b}p<0.05$).

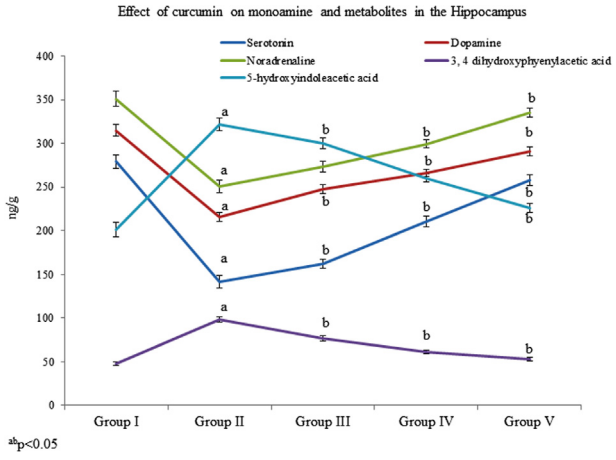

Fig. 3 – Chronic effect of curcumin administration on serotonin, dopamine, noradrenaline, 3, 4-dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid levels in the Hippocampus region of olfactory bulbectomy model of male albino rats. Curcumin was diluted in normal saline and administered orally for 45 consecutive days. Values were expressed mean ± SD. $^{ab}p<0.05$. The olfactory bulbectomy (lesion) group was compared with sham control group ($^{a}p<0.05$). Curcumin treated groups were compared with an olfactory bulbectomy (lesion) group ($^{b}p<0.05$).

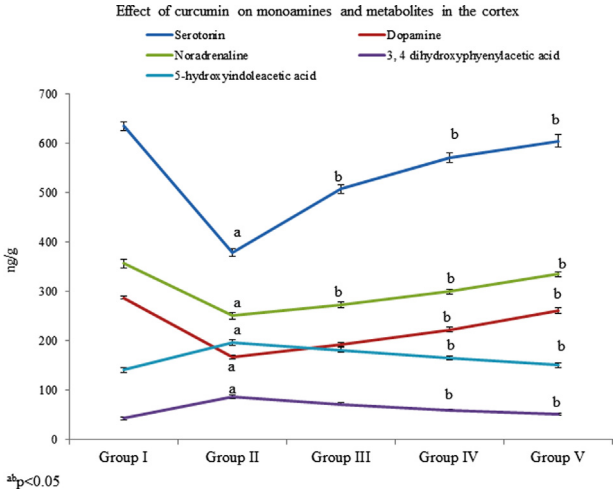

Fig. 4 – Chronic effect of curcumin administration on serotonin, dopamine, noradrenaline, 3, 4-dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid levels in the Cortex region of olfactory bulbectomy model of male albino rats. Curcumin was diluted in normal saline and administered orally for 45 consecutive days. Values were expressed mean ± SD. $^{ab}p<0.05$. The olfactory bulbectomy (lesion) group was compared with sham control group ($^{a}p<0.05$). Curcumin treated groups were compared with an olfactory bulbectomy (lesion) group ($^{b}p<0.05$).

2.5. *Curcumin effect on the noradrenaline*

Noradrenaline level was determined in the hippocampus and cortex region of the brain. The quantity of noradrenaline was found to 351 and 250.5 ng/g in the hippocampus region of sham control and olfactory bulbectomy rats respectively. The quantity of noradrenaline was found to decrease in the hippocampus and frontal cortex of olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly increased the noradrenaline level in the hippocampus and frontal cortex of olfactory bulbectomy rats. Curcumin

treatment significantly increased the noradrenaline level 273, 299.5 and 335 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the hippocampus of olfactory bulbectomy rats (Fig. 3). The quantity of noradrenaline was found to 356 and 250.5 ng/g in the cortex region of sham control and olfactory bulbectomy rats respectively. Curcumin treatment significantly increased the noradrenaline level 375.7, 390.8 and 411.5 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the frontal cortex of olfactory bulbectomy rats (Fig. 4).

2.6. *Curcumin effects on the 3, 4-dihydroxyphenylacetic acid*

The quantity of 3, 4-dihydroxyphenylacetic acid was determined in the hippocampus and cortex region of the brain. The quantity of 3, 4-dihydroxyphenylacetic acid was found to 47 and 98.3 ng/g in the hippocampus region of sham control and olfactory bulbectomy rats respectively. The quantity of 3, 4-dihydroxyphenylacetic acid was found to increase in the hippocampus and frontal cortex of olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly reduced the 3, 4-dihydroxyphenylacetic acid level in the hippocampus and frontal cortex of olfactory bulbectomy rats. Curcumin treatment is significantly reduced the 3, 4-dihydroxyphenylacetic acid level 76.5, 61.5 and 53.4 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the hippocampus of olfactory bulbectomy rats (Fig. 3). The quantity of 3, 4-dihydroxyphenylacetic acid was found to 43 and 86.4 ng/g in the cortex region of sham control and olfactory bulbectomy rats respectively. Curcumin treatment is significantly reduced the 3, 4-dihydroxyphenylacetic acid level 71.4, 58.6 and 50.3 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the frontal cortex of olfactory bulbectomy rats (Fig. 4).

2.7. *Curcumin effects on the 5-hydroxyindoleacetic acid*

The quantity of 5-hydroxyindoleacetic acid was determined in the hippocampus and cortex region of the brain. The quantity of 5-hydroxyindoleacetic acid was found to 201 and 321.7 ng/g in the hippocampus region of sham control and olfactory bulbectomy rats respectively. The quantity of 5-hydroxyindoleacetic acid was found to increase in the hippocampus and frontal cortex of olfactory bulbectomy rats compared to sham control rats. Chronic administration of curcumin significantly reduced the 5-hydroxyindoleacetic acid level in the hippocampus and frontal cortex of olfactory bulbectomy rats. Curcumin treatment is significantly reduced the 5-hydroxyindoleacetic acid level 300, 260.4 and 225.6 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the hippocampus of olfactory bulbectomy rats (Fig. 3). The quantity of 5-hydroxyindoleacetic acid was found to 141 and 195.6 ng/g in the cortex region of sham control and olfactory bulbectomy rats respectively. Curcumin treatment is significantly reduced the 5-hydroxyindoleacetic acid level 181, 165.5 and 150.2 ng/g at 10, 20 and 40 mg/kg bwt respectively, in the frontal cortex of olfactory bulbectomy rats (Fig. 4).

2.8. *Curcumin effect on the forced swims test*

The immobility time was determined in the sham control, and olfactory bulbectomy rats were determined, and it was found to be 59 and 143 s respectively. The immobility time was significantly reduced following chronic administration of curcumin in the male albino rats. Curcumin treatment reduced the immobility time 9.8%, 36.4% and 53.1% at 10, 20 and 40 mg/kg bwt respectively (Fig. 5).

3. Discussion

We have investigated the antidepressant activity of curcumin in the olfactory bulbectomy and forced swim test rat model of depression. The immobile time was significantly reduced following chronic administration of curcumin. The increased activity in the open field test has been reversed following curcumin treatment, and reversal of deficit in step-down passive avoidance learning has been observed in the olfactory bulbectomy male albino rats. These results agreed with the report of Janscar and Leonard (1983), indicated the chronic effect of typical and atypical antidepressants administration. No tolerance development was observed to curcumin in the male albino rats were administered for 45 consecutive days.

The clear mechanism regarding the depression development in the olfactory bulbectomy male albino rats yet to be investigated. Alberts and Friedman (1972) have reported the selective ablation of olfactory sensory receptors not involving in the production of olfactory bulbectomy symptoms. The huge influence on the emotional behavior is due to the projection of neuron to the limbic system. Masini et al. (2004) have reported the symptoms produced by bilateral

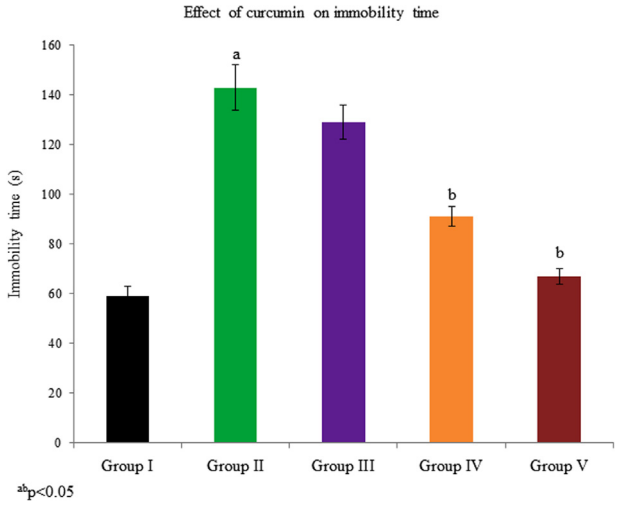

Fig. 5 – Chronic effect of curcumin administration on immobility time in the forced swim test model of male albino rats. Curcumin was diluted in normal saline and administered orally for 45 consecutive days. Values were expressed mean ± SD. Values were expressed mean ± SD. $^{ab}p < 0.05$. The olfactory bulbectomy (lesion) group was compared with sham control group ($^{a}p < 0.05$). Curcumin treated groups were compared with an olfactory bulbectomy (lesion) group ($^{b}p < 0.05$).

olfactory bulbectomy are similar to the symptoms of clinical depression. Harkin et al. (2003) have reported the emerge of passive avoidance and open field hyperactivity in response to curcumin administration in the olfactory bulbectomy rats.

In other hand, monoamines of brain system have been significantly altered in the olfactory bulbectomy male albino rats (Grecksch et al., 1997). Thus, olfactory bulbectomy model of rats was appeared to be an appropriate model for studying the mechanism of antidepressant drugs and pathology of neuro-disorders. Mudunkotuwa and Horton (1996) have reported the chronic administration of antidepressant drugs renormalizes the immobility and behavioral deficits. Our results agreed with a report of Iwasaki et al. (1986) have used desipramine as an antidepressant in the olfactory bulbectomy rats. McLoughlin and Hodge (1990) have reported the diverse mechanism of antidepressant drugs.

Elhwuegi (2004) have reported the serotonin, dopamine and noradrenaline are actively participating in the depression development. The monoamines level usually elevated under the antidepressant administration (Schloss and Henm 2004). Van Rijzingen et al. (1995) have reported serotonin, noradrenaline, and 5-hydroxyindoleacetic acid levels are decreased in the olfactory bulbectomy models. In our present study, we have selected two brain regions such as the hippocampus and frontal cortex. Butterweck et al. (2002) have reported the depression has been associated with the emotional and motivation behavior of these two brain regions.

The impaired hippocampal function has been observed in the olfactory bulbectomy model of animals (Nowak et al., 2003). Wrynn et al. (2000) have reported the changes in the signal intensity of frontal cortex may be associated with behavioral changes. Therefore, we have selected these two regions for the determination of monoamines and their implication on depression in the olfactory bulbectomy rat model. In our experiments, serotonin and noradrenaline were decreased in the hippocampus and frontal cortex, while 4-dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid were reduced. Lumia et al. (1992) have reported the olfactory bulbectomy is an excellent model of hypo-noradrenergic and hypo-serotonergic depression. Maier et al. (2010) have reported the colorant curcumin significantly suppressed Th1-type immune response in human peripheral blood mononuclear cells *in vitro* in a dose-dependent manner. Our results indicate the chronic administration of curcumin renormalizes the noradrenaline and serotonin levels in the frontal cortex and hippocampus. Curcumin chronic administration also reduced 5-hydroxyindoleacetic acid in the frontal cortex and hippocampus of olfactory bulbectomy male albino rats.

4. Conclusion

In summary, the chronic administration of curcumin could exert antidepressant activity in the olfactory bulbectomy and forced swim test model of depression. The results suggest that this effect could be mediated through monoaminergic neurotransmitter pathway. Therefore, it may suggest that the curcumin can be used as a potent agent for the antidepressant therapy.

5. Experimental procedure

5.1. *Materials*

Healthy male albino Wistar rats (180–200 g) were purchased from the animal house, Beijing, China. They kept in polypropylene cages, at temperature 25 ± 0.5 C, relative humidity 60 ± 5% and a photoperiod of 12 h/day. There were 30 male albino Wistar strain rats used in this study and were grouped into five groups of six rats each. Dopamine, curcumin, noradrenaline, 5-hydroxyindoleacetic acid, 5-hydroxytrytamine and 3, 4-dihydroxyphenylacetic acid were purchased from Sigma-Aldrich (USA). All the animals were treated according to internally accepted ethical committee procedure (2013KY-006-01).

5.2. *Experimental groups*

Group I: Sham control.
Group II: Olfactory bulbectomy (lesion).
Group II: 10 mg/kg bwt of curcumin.
Group III: 20 mg/kg bwt of curcumin.
Group IV: 40 mg/kg bwt of curcumin.

5.3. *Treatment*

Curcumin was dissolved in normal saline and administered orally for 45 consecutive days, and normal saline served as control. At the end of 45 days, animals were used for our further investigations.

5.4. *Olfactory bulbectomy*

Olfactory bulbectomy was carried out by administration of tribromoethanol in the male albino rats (Kelly et al., 1997). In the skull, 6 mm holes were drilled anterior to bregma. Also, 2 mm holes were drilled on both sides of midline point corresponds to the posterior side of eye orbit. The holes were filled with a hemostatic sponge after removal of the olfactory bulb to prevent bleeding. Male albino rats were administered procaine penicillin (30000 IU/kg) following surgery to prevent infection. Rats were allowed for 15 days to recover from the surgery. After complete recovery from the surgery, rats were given curcumin for 45 consecutive days.

5.5. *Passive avoidance test*

Olfactory bulbectomy animals were subjected passive avoidance test under chronic (45 days) administration of curcumin. The examination was carried out according to Nowak et al. (2003). The apparatus was made with open box ($55 \times 55 \times 55$ cm^3) with stainless steel grid floor with a black wall. The electrified rod (1.5 cm) was connected to the end of shock generator. The shock has been given to the rats with 0.70 mA constant intensity for 1 s. The wooden surface was present in the center of the box, and all the rats were placed on this wooden surface. Male albino rats were removed from the apparatus and kept in the cage. The next trail was started

after 60 s and a total number of trials required for animals to reach 60 s as criteria for learning index.

5.6. *Open field test*

Olfactory bulbectomy animals were subjected to open field test on the 45th day of curcumin administration. All the animals were kept in the center of open field apparatus, and examination was carried out according to Redmond et al. (1999). The open field apparatus was made up with a diameter of $85 \times 70\ cm^2$ (diameter and height) with the aluminum wall. A light bulb (60 W) was placed 80 cm above the base of the area to provide light illumination to a testing area. All the rats were placed in the center of testing apparatus. The number of peepings and rearings and ambulation counts was determined during 5 min.

5.7. *Measurement of monoamines*

At the end of 45 days of chronic treatment, rats were killed by decapitation and brain tissue was removed and used for the investigation. The frontal cortex and hippocampus region of brain tissues were dissected and kept on ice. The tissues were homogenized and centrifuged at 20,000*g* for 15 min at 4 °C. HPLC assay was carried out for the homogenates. The supernatant was collected and filtered through a membrane by centrifugation at 6000*g*. From that, 50-µl aliquots were analyzed for serotonin with the use of fluorometric detection. The amounts of dopamine and their metabolites were determined by electrochemical detection (Visser et al., 2011).

5.8. *Forced swim test*

The forced swim test was carried out at the end of 45 days of curcumin administration. Animals were placed separately in glass chambers filled with water 25 cm at room temperature.

After 10 min of the testing period, animals were removed and returned to cages. After 24 h, the experiment was repeated. Also, the immobile time recorded (Mezadri et al., 2011).

5.9. *Statistical analysis*

All the experimental values were expressed mean ± SD. The difference between control and treated were compared by Student "*t*" test and followed by ANOVA analysis. A $p < 0.05$ is considered as statistically significant. $^{ab}p < 0.05$. Sham control was compared with olfactory bulbectomy (lesion) rats ($^{a}p < 0.05$) and curcumin treated rats were compared with olfactory bulbectomy (lesion) rats ($^{b}p < 0.05$).

REFERENCES

Alberts, J.R., Friedman, M.I., 1972. Olfactory bulb removal but not anosmia increases emotionality and mouse killing. Nature 238, 454–455.

Biswas, S.K., McClure, D., Jimenez, L.A., Megson, I.L., Rahman, I., 2005. Curcumin induces glutathione biosynthesis and inhibits NF-kappaB activation and interleukin-8 release in alveolar epithelial cells: mechanism of free radical scavenging activity. Antioxid. Redox Signal. 7, 32–41.

Butterweck, V., Bockers, T., Korte, B., Wittkowski, W., Winterhoff, H., 2002. Long-term effects of St John's wort and hypericin on monoamine levels in rat hypothalamus and hippocampus. Brain Res. 930, 21–29.

Chen, J.X., Tang, Y.T., 2004. Effect on xiaoyao powder on changes of relative brain zone CRF gene expression in chronic restrained stress rats. Chin. J. Appl. Physiol. 20, 7174.

Dar, A., Khatoon, S., 2000. Behavioral and biochemical studies of dichloromethane fraction from the Areca catechu nut. Pharmacol. Biochem. Behav. 65, 1–6.

Dutta, S., Padhye, S., Priyadarsini, K.I., Newton, C., 2005. Antioxidant and antiproliferative activity of curcumin semicarbazone. Bioorg. Med. Chem. Lett. 15, 2738–2744.

Elhwuegi, A.S., 2004. Central monoamines and their role in major depression. Prog. Neuro-Psychopharmacol. 28, 435–451.

Grecksch, G., Zhou, D., Franke, C., Schroder, U., Sabel, B., Becker, A., 1997. Influence of olfactory bulbectomy and subsequent imipramine treatment on 5-hydroxytryptaminergic presynapses in the rat frontal cortex: behavioral correlates. Br. J. Pharmacol. 122, 1725–1731.

Harkin, A., Kelly, J.P., Leonard, B.E., 2003. A review of the relevance and validity of olfactory bulbectomy as a model of depression. Clin. Neurosci. Res. 3, 253–262.

Iwasaki, K., Fujiwara, M., Shibata, S., Ueki, S., 1986. Changes in brain catecholamine levels following olfactory bulbectomy and the effect of acute and chronic administration of desipramine in rats. Pharmacol. Biochem. Behav. 24, 1715–1719.

Janscar, S., Leonard, B.E., 1983. The olfactory bulbectomized rat as a model of depression. In: Usdin, E., Goldstein, M., Friedhoff, A.J., Georgotas, A. (Eds.), Frontiers in neuropsychiatric research. New York. Macmillan Press, pp. 357–372.

Kelly, J.P., Wrynn, A.S., Leonard, B.E., 1997. The olfactory bulbectomized rat as a model of depression: an update. Pharmacol. Ther. 74, 299–316.

Lim, C.S., Jin, D.Q., Mok, H., Oh, S.J., Lee, J.U., Hwang, J.K., Ha, I., Han, J.S., 2005. Antioxidant and anti-inflammatory activities of xanthorrhizol in hippocampal neurons and primary cultured microglia. J. Neurosci. Res. 82, 831–838.

Lumia, A.R., Teicher, M.H., Slachli, F., Ayers, E., Possidente, B., 1992. Olfactory bulbectomy as a model of agitated hypo serotonergic depression. Brain Res. 587, 181–185.

Maier, E., Kurz, K., Jenny, M., Schennach, H., Ueberall, F., Fuchs, D., 2010. Food preservatives sodium benzoate and propionic acid and colorant curcumin suppress Th1-type immune response *in vitro*. Food Chem. Toxicol. 48, 1950–1956.

Manolova, Y., Deneva, V., Antonov, L., Momekova, D., Lambov, N., 2014. The effect of the water on the curcumin tautomerism: a quantitative approach. Spectrochim. Acta 132A, 815–820.

Masini, C.V., Holmes, P.V., Freeman, K.G., Maki, A.C., Edwards, G. L., 2004. Dopamine overflow is increased in olfactory bulbectomized rats: an *in vivo* microdialysis study. Physiol. Behav. 81, 111–119.

Mazzio, E.A., Harris, N., Soliman, K.F., 1998. Food constituents attenuate monoamine oxidase activity and peroxide levels in C6 astrocyte cells. Planta Med. 64, 603–606.

McLoughlin, I.J., Hodge, J.S., 1990. Zinc in depressive disorder. Acta Psychiatr. Scand. 82, 451–453.

Mezadri, T.J., Batista, G.M., Portes, A.C., Marino-Neto, J., Lino-de-Oliveira, C., 2011. Repeated rat forced swim test: reducing the number of animals to evaluate gradual effects of antidepressants. J. Neurosci. Methods. 195, 200–205.

Mudunkotuwa, N.T., Horton, R.W., 1996. Desipramine administration in the olfactory bulbectomized rat: changes in brain h-adrenoceptor and 5-HT2A binding sites and their relationship to behavior. Br. J. Pharmacol. 117, 1481–1486.

Nowak, G., Szewczyk, B., Wieronska, J.M., Branski, P., Palucha, A., Pilc, A., Sadlik, K., Piekoszewski, W., 2003. Antidepressant-like effects of acute and chronic treatment with zinc in forced swim test and olfactory bulbectomy model in rats. Brain Res. Bull. 61, 159–164.

Redmond, A.M., Kelly, J.P., Leonard, B.E., 1999. The determination of the optimal dose of milnacipran in the olfactory bulbectomized rat model of depression. Pharmacol. Biochem. Behav. 62, 619–623.

Schloss, P., Henm, F.A., 2004. New insights into the mechanisms of antidepressant therapy. Pharmacol. Ther. 102, 47–60.

Thiyagarajan, M., Sharma, S.S., 2004. Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. Life Sci. 74, 969–985.

Visser, A.K.D., van Waarde, A., Willemsen, A.T.M., 2011. Measuring serotonin synthesis: from conventional methods to PET tracers and their (pre)clinical implications. Eur. J. Nuclear Med. Mol. Imaging 38, 576–591.

Van Rijzingen, I.M., Gispen, W.H., Spruijt, B.M., 1995. Olfactory bulbectomy temporarily impairs morris maze performance: an ACTH (4-9) analogue accelerates the return of function. Physiol. Behav. 58, 147–152.

Weber, W.M., Hunsaker, L.A., Abcouwer, S.F., Deck, L.M., Vander Jagt, D.L., 2005. Anti-oxidant activities of curcumin and related enones. Bioorg. Med. Chem. 13, 3811–3820.

Wrynn, A.S., Sweeney, C.P.M., Franconi, F., Lemaire, L., Pouliquen, D., Herlidou, S., 2000. An *in-vivo* magnetic resonance imaging study of the olfactory bulbectomized rat model of depression. Brain Res. 879, 193–199.

Yu, Z.F., Kong, L.D., Chen, Y., 2002. Antidepressant activity of aqueous extracts of Curcuma longa in mice. J. Ethnopharmacol. 83, 161–165.