

Role of ibuprofen and lavender oil to alter the stress induced psychological disorders: A comparative study

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Abstract: Stress has become an integral feature of everyday living. Each individual that lives encounters some manifestation of stress in life. Stress causes certain alterations in the structure and functions of the body and is considered to be a major factor in many health problems. Many synthetic and natural compounds are used for the attenuation of stress induced changes in the body. Medicinal plants are used since ancient times to prevent from neurological disorders. Lavender (*Lavandula angustifolia*) is very efficacious and possesses the ability to improve several neurological disorders. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used against pain and inflammation. However, effectiveness of NSAIDs in the treatment of various psychiatric ailments is also reported. The present study investigated the effects of ibuprofen and lavender oil on stress induced behavioral and biochemical alterations in rats. The rats were subjected to restraint stress and behavioral parameters like open field test (OFT), light/dark transition box activity (LDT) and forced swim test (FST) were used to assess exploratory, anxiolytic and anti-depressant activity, respectively. Corticosterone, lipid peroxidation (LPO) and endogenous antioxidant enzymes activities were also estimated. Results of OFT, LDT and FST showed substantial effects of lavender oil and standard drug ibuprofen. A significant decrease in plasma corticosterone and LPO levels with increase in antioxidant enzyme activities was observed in the study. However, the effects of lavender oil were more as compared to standard drug ibuprofen in diminution of stress induced behavioral and biochemical changes in rats. This study demonstrates that lavender oil is more remedial than ibuprofen in stress related disorders.

Keywords: Anxiety, depression, ibuprofen, lavender oil, stress.

INTRODUCTION

It is a well known fact that stimulation of sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis in stressful situations have direct impact on the biological systems (Mc Ewen *et al.*, 1998). Stress is an influential risk factor for many physical and mental disorders and a major root of mortality in developing countries (Martins *et al.*, 2008). Psychological stress may alter many emotional, behavioral and biological responses and can be threatening to humans (Clark *et al.*, 2007). Studies in experimental animal showed that 2h restraint stress produce behavioral deficits (Haque *et al.*, 2013). Diminishing the stress levels not only protects from diseases but also improves the quality of life (Thoits, 2010). Various synthetic and natural compounds have been used extensively in attenuation of stress related neurological disorders. NSAIDs (nonsteroidal anti-inflammatory drugs) are amongst the most widely used drugs and have diverse pharmacological properties (Emad *et al.*, 2017). These drugs block the activity of cyclooxygenase (COX) via scavenging ROS and RNS and inhibit the activation of pro-inflammatory cytokines (Asanuma *et al.*, 2008). Cyclooxygenase is an enzyme that catalyzes the synthesis of prostaglandins (Schwab *et*

al., 2003). Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor, works by suppressing prostaglandin formation (Bancos *et al.*, 2009). It acts as an antioxidant and exhibit neuroprotection against several neurodegenerative diseases (Emad *et al.*, 2017). Role of ibuprofen in treatment of psychotic disorders has also been reported (Shang *et al.*, 2015). Essential oils and their volatile constituents are utilized broadly to prevent and treat human illness. Lavender is as an effective medicinal plant that is used in the prevention of various problem including inflammation, depression, stress, seizure and migraine by exerting protective effects through its antioxidant properties (Sasanejad *et al.*, 2012). There is also a developing confirmation that free radicals cause damages to cellular structures as observed in neurodegenerative ailments and leads to oxidative stress (Emerit *et al.*, 2004). Endogenous antioxidants are assumed to maintain ideal cellular functions. However, increased oxidative stress leads to decrease antioxidant enzyme activities and there is a need of dietary antioxidants to maintain ideal cellular functions in the body (Gospodaryov and Lushchak, 2012).

The current study is planned to investigate the neuroprotective effects of ibuprofen and lavender oil in attenuation of stress induced biochemical and behavioral changes in rats.

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MATERIALS AND METHOD

Experimental protocol

Locally breed albino Wistar rats (weight: 150-200 g) were taken from animal facility of International Center for Chemical and Biological Sciences, University of Karachi (voucher number: 6690). Animals were caged separately in their home cages so that the rats would adapt to the environment. Rats had free access to standard rodent diet and water for 24 h. Essential oil (lavender oil) was purchased from local market, whereas NSAIDs (ibuprofen) and all other reagents used in the study were purchased from Sigma Aldrich, USA. In this study, thirty-six rats were randomly categorized into unrestrained (n=18) and restrained (n=18) groups. Both groups were subdivided into control (n=6), ibuprofen (n=6) and lavender oil (n=6) groups. Control group rats received water during the study. Rats of ibuprofen group received an oral dose of 2 mg/kg of ibuprofen whereas the lavender oil group received an oral dose of 100 mg/kg of lavender oil (Alireza *et al.*, 2014). The selected dose of ibuprofen was calculated according to animal body weight from clinically prescribed dose which is 800 mg for an adult (Bushra and Aslam, 2010). The drug and oil administration was continued for 7 days to respective groups of rats. After 7th day following respective drug and oil treatments, rats were subjected to 2h restraint stress in restrainer tube. During this period, unrestrained rats remained in their home cages. After 2h of restraint stress, behavioral assessment was done and rats were decapitated. The brain and plasma samples were collected and stored at -70°C for biochemical estimations. The experiment was performed after the formal approval from Institutional Review Board (IRB) with reference No. 02810/SC-2014. The rules of Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1995) were strictly followed.

Restraining procedure

Restraint stress is a most authentic procedure of stress in rats due to minimal movement including tail and causes no harm to rats. The animals were restricted in plastic tubes with holes in it for passage of air (Delaney *et al.*, 2012).

Behavioral analysis

Open field test (OFT)

OFT monitors exploratory activity. The method was same as previously described (Naqvi *et al.*, 2012).

Light/dark transition activity box (LDT)

Anxiolytic/anxiogenic response in rats was observed by LDT. The method followed was same as reported previously (Khaliq *et al.*, 2012).

Forced swim test (FST)

FST is used to assess depressive behaviors in rats (Cryan *et al.*, 2004). The method of FST was same as described

and performed earlier in our laboratory (Perveen *et al.*, 2018).

Determination of plasma corticosterone levels

The procedure for the estimation of plasma corticosterone was same as mentioned earlier (Perveen *et al.*, 2018).

Determination of lipid peroxidation (LPO) and antioxidant enzyme activities

LPO and other antioxidant enzyme activities were determined according to the method described by (Haider *et al.*, 2015). LPO is presented as μ moles of MDA/g of brain tissue. Superoxide dismutase (SOD) activity was evaluated when nitro blue tetrazolium chloride (NBT) is reduced to blue formazan, a water-insoluble complex (Singh *et al.*, 2002). It is represented as U/g of brain and its single unit is equivalent to the amount of the enzyme that restricts 50% reduction of NBT. Catalase activity (CAT) is represented as utilization of H_2O_2 μ mol/min/g of brain. Glutathione peroxidase (GPx) activity was represented as μ mol/min/g of brain.

STATISTICAL ANALYSIS

Data is represented as mean \pm SD. Data of behaviors and biochemical estimations were analyzed by two-way ANOVA and Tukey's test using SPSS version 20.0 software. $p > 0.05$ was considered as non-significant.

RESULTS

Effect of ibuprofen and lavender oil on behaviors in unrestrained and 2h restrained rats

Open field test

Fig. 1 shows the effects of ibuprofen and lavender oil on the locomotor activity of rats. Results indicate significant effect of stress ($df = 1, 30$; $F = 9.675$; $p < 0.01$), drugs ($df = 2, 30$; $F = 29.136$; $p < 0.01$) and interaction among two factors ($df = 2, 30$; $F = 6.834$; $p < 0.01$). Tukey's test revealed that 2h restraint stress significantly ($p < 0.01$) decreased number of squares crossing in stressed rat. Ibuprofen and lavender oil significantly ($p < 0.01$) increased squares crossing in stressed rats.

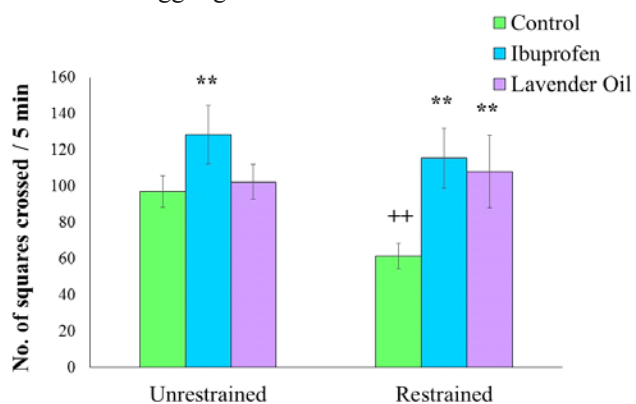
Light/dark transition box activity

Fig. 2 shows the effect of ibuprofen and lavender oil on level of anxiety in rats. Results indicate significant effect of stress ($df = 1, 30$; $F = 20.586$; $p < 0.01$), drugs ($df = 2, 30$; $F = 48.979$; $p < 0.01$) and interaction among two factors ($df = 2, 30$; $F = 11.327$; $p < 0.01$). Tukey's test revealed that 2h restraint stress significantly ($p < 0.01$) decreased time spent in light box in stressed rats. Ibuprofen and lavender oil significantly ($p < 0.01$) increased time spent in light box in stressed rats.

Forced swim test

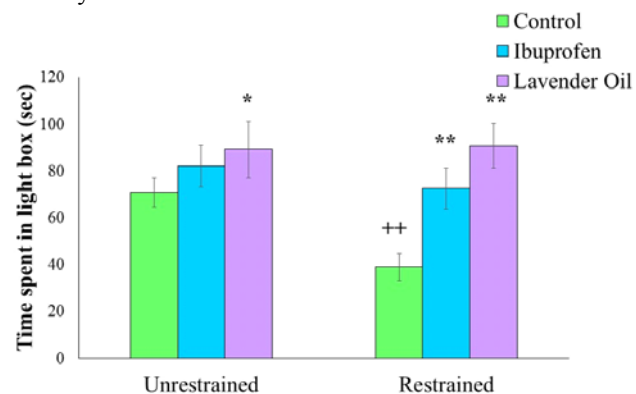
Fig. 3 shows the effects of ibuprofen and lavender oil on forced swim test in rats. Results indicate significant effect of stress ($df = 1, 30$; $F = 4.003$; $p > 0.05$), drugs ($df = 2, 30$;

F = 81.468; $p < 0.01$) and interaction among two factors ($df = 2,30$; $F = 35.307$; $p < 0.01$). Tukey's test demonstrates that 2h restraint stress significantly ($p < 0.05$) decreased the struggling time in stressed rats. Ibuprofen and lavender oil significantly ($p < 0.05$) increased struggling time in stressed rats. Lavender oil also significantly ($p < 0.01$) increased struggling time in unstressed rats.



Values are mean \pm SD ($n=6$). Significant differences by Tukey's test: ** $p < 0.01$ from their respective saline treated controls, ++ $p < 0.01$ from their respective unrestrained controls.

Fig. 1: Effect of ibuprofen and lavender oil on open field activity in rats.



Values are mean \pm SD ($n=6$). Significant differences by Tukey's test: * $p < 0.05$, ** $p < 0.01$ from their respective saline treated controls, ++ $p < 0.01$ from their respective unrestrained controls.

Fig. 2: Effect of ibuprofen and lavender oil on light/dark transition box activity in rats.

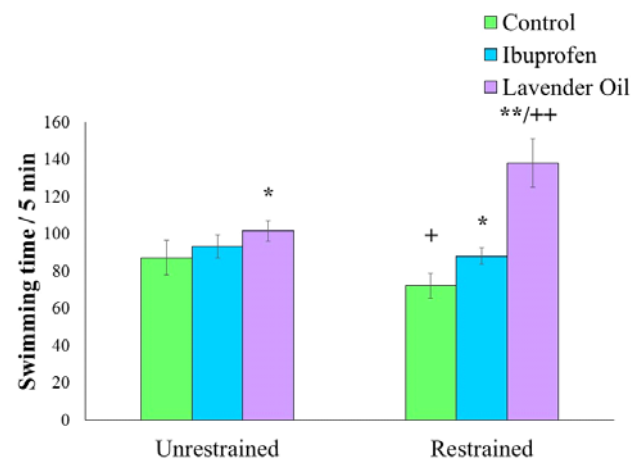
Effect of ibuprofen and lavender oil on biochemical parameters in unrestrained and 2h restrained rats

Effect on plasma corticosterone levels

Results in table 1 indicate significant effect of stress ($df = 1,30$; $F = 4.154$; $p < 0.05$), drugs ($df = 2,30$; $F = 109.48$; $p < 0.01$) and interaction between two factors ($df = 2,30$; $F = 6.663$; $p < 0.01$). Tukey's test revealed that plasma corticosterone levels were significantly ($p < 0.01$) high in stressed rats. Ibuprofen and lavender oil significantly ($p < 0.01$) lowered corticosterone levels in both stressed and unstressed groups.

Effect on lipid peroxidation (LPO)

Results in Table 1 indicate significant effect of stress ($df = 1, 30$; $F = 6.137$; $p < 0.05$), significant effect of drugs ($df = 2,30$; $F = 71.804$; $p < 0.01$) and interaction among two factors ($df = 2,30$; $F = 5.210$; $p < 0.05$). Tukey's test demonstrates significantly ($p < 0.05$) increased LPO in stressed rats. Ibuprofen ($p < 0.05$) and lavender oil ($p < 0.01$) significantly decreased LPO in unstressed and stressed rats.



Values are mean \pm SD ($n=6$). Significant differences by Tukey's test: * $p < 0.05$, ** $p < 0.01$ from their respective saline treated controls, + $p < 0.05$, ++ $p < 0.01$ from their respective unrestrained controls.

Fig. 3: Effect of ibuprofen and lavender oil on forced swim test in rats.

Effect on superoxide dismutase (SOD)

Results in Table 1 indicate non-significant effect of stress ($df = 1,30$; $F = 3.865$; $p > 0.05$), significant effect of drugs ($df = 2,30$; $F = 58.160$; $p < 0.01$) and interaction between two factors ($df = 2,30$; $F = 10.404$; $p < 0.01$). Tukey's test revealed significantly ($p < 0.01$) decreased SOD activity in stressed rats. Ibuprofen and lavender oil significantly ($p < 0.01$) increased SOD activity in stressed rats.

Effect on catalase (CAT)

Results in table 1 indicate significant effect of stress ($df = 1,30$; $F = 5.610$; $p < 0.05$), drugs ($df = 2,30$; $F = 9.975$; $p < 0.01$) and non-significant interaction between two factors ($df = 2,30$; $F = 0.807$; $p > 0.05$). Tukey's test revealed that lavender oil significantly ($p < 0.05$) increased CAT activity in stressed rats.

Glutathione peroxidase (GPx)

Results in table 1 indicate non-significant effect of stress ($df = 1,30$; $F = 2.212$; $p > 0.05$), significant effect of drugs ($df = 2,30$; $F = 28.605$; $p < 0.01$) and interaction between two factors ($df = 2,30$; $F = 3.846$; $p < 0.05$). Tukey's test revealed significantly ($p < 0.01$) decreased GPx activity in stressed rats. Ibuprofen significantly ($p < 0.01$) and lavender oil ($p < 0.05$) increased GPx activity in stressed rats.

DISCUSSION

Stress is an obligatory part of an individual’s life and an important etiological factor in depression (Hammen, 2005). The results from the present study show several behavioral alterations in 2h restrained rats. The 2h restraint stress related behavioral and biochemical alterations have also been reported previously (Sadaf *et al.*, 2017). In present study 2h restraint stress significantly decreased locomotor activity as observed by less number of squares crossed in OFT. Decrease in locomotor activity under stressful conditions has also been reported previously (Perveen *et al.*, 2016). Ibuprofen and lavender oil administration significantly increased number of squares crossing in restrained animals. Anxiogenic effects were also observed in present study as the time spent in light box in LDT was decreased in 2h restrained rats. Stress induced anxiogenic and depressive effects were also reported previously (Sevgi *et al.*, 2006). We also observed significantly high levels of corticosterone in unrestrained and restrained rats. Anxiogenic effects in rats might be due to high levels of serotonin (5-HT) in neurons (Perveen *et al.*, 2016). Stress increases 5-HT levels in the brain and its excitation to HPA axis causes secretion of stress hormones that is involved in fear and anxiety (Shin *et al.*, 2010). Pretreatment with ibuprofen and lavender oil produce anxiolytic effects in restrained rats. In the current study, treatment with ibuprofen and lavender oil also significantly lowers the level of corticosterone in unrestrained and restrained rats. As 5-HT receptors more specifically 5-HT-1A regulates emotions and behaviors, therefore it is suggested that lavender oil exerts anxiolytic effect by affecting autonomic neurotransmission through 5-HT-1A receptors in the brain (Chioca *et al.*, 2013). It is also observed in the study that lavender oil lowers the levels of corticosterone thus by normalizing brain 5-HT levels and produces anxiolytic effect. In present study 2h restraint stress also produced depressogenic effects as observed by decrease in struggling time in FST. The excessive activation of HPA axis in stress condition can lead to depression and increases the level of glucocorticoids that damage the hippocampal neuron and cause the release of inflammatory cytokines (Capuron and Dantzer, 2003). NMDA receptors activation has a crucial role in depression (Marrannes *et al.*, 1988). Corticosterone stimulates the presynaptic neurotransmission of glutamate via calcium mediated postsynaptic NMDA receptors activation (Mikasova *et al.*, 2017). The binding of glutamate to NMDA receptors allows entry of calcium (Ca⁺) inside the neuron and activation of enzymes that depend on calcium like protein kinase C, phospholipase C and phospholipase A2 that accelerate the release of arachidonic acid by cell membrane along with the factors associated with inflammation (Colbran, 2004). Lavender oil possesses strong lipoxygenase inhibitory activity by modulating voltage dependent calcium channels in

Table 1: Effect of ibuprofen and lavender oil on biochemical parameters in rats.

Biochemical Parameters	Units	Unrestrained			Restrained		
		Control	Ibuprofen	Lavender Oil	Control	Ibuprofen	Lavender oil
Lipid peroxidation (LPO)	MDA levels (µmol/g)	64.21±4.05	53.24±5.11*	45.01±3.00**	75.51±7.18 ⁺	58.11±6.20**	42.16±5.62**
Superoxide dismutase (SOD)	U/g	1.208±0.15	1.215±0.15	1.616±0.13**	0.828±0.11 ⁺⁺	1.318±0.11**	1.623±0.15**
Catalase (CAT)	µmol/min/g	129.37±3.68	125.68±6.78	135.82±6.87	130.53±4.43	132.44±7.93	142.25±5.54*
Glutathione peroxidase (GPx)	µmol/min/g	274.57±26.92	343.04±33.24	363.29±40.29*	189.56±16 ⁺	350.31±65.12**	370.91±73.37**
Corticosterone (CORT)	µg/dl	395.25±45.78	304.51±34.05**	233.34±37.05**	477.60±38.43 ⁺⁺	316.18±13.19**	211.85±36.29**

Values are mean ± SD (n=6). Significant differences by Tukey’s test: * p < 0.05, ** p < 0.01 from their respective saline treated controls, ⁺p<0.05, ⁺⁺p<0.01 from their respective unrestrained controls.

synaptosomes (Schuwald *et al.*, 2013). Pretreatment with ibuprofen and lavender oil produced anti-depressant effects in restrained rats. It can be suggested that antidepressant effects produced by ibuprofen and lavender oil could be due to desensitization of NMDA receptors and inhibiting the enzymes that convert arachidonic acid into prostaglandin (Bancos *et al.*, 2009, Schuwald *et al.*, 2013).

Antioxidants are health promoting agents that provide protection against several diseases (Kamat *et al.*, 2008). The present study demonstrates that 2h restraint stress increase lipid peroxidation as observed by high malondialdehyde (MDA) levels. The present study also demonstrates lower levels of antioxidant enzymes which reflect the brain vulnerability to stress. MDA is a marker of lipid peroxidation produced during oxidizing stress (Omodeo-sale F *et al.*, 1998). Oxidizing stress gives rise to reactive free radicals that alters the lipid bilayer membrane and cause peroxidation of polyunsaturated fatty acids (Barrera, 2012). Pre-treatment with ibuprofen and lavender oil significantly reduced lipid peroxidation in unrestrained and restrained rats. Suppression of intracellular production of ROS by ibuprofen also causes a significant inhibition of lipid peroxidation at the remedial concentration (Orhan *et al.*, 2001). Lavender oil also exerts the intense antioxidant activity against lipid peroxidation (Lu Hui *et al.*, 2010). Present study also demonstrates that ibuprofen and lavender oil significantly increase SOD and GPx activity in restrained rats and unrestrained rats and increased catalase activity in restrained rats. Hydrogen peroxide generated by SOD is further destroyed by high levels of GPx by ibuprofen and lavender oil in restrained rats. Catalase also destroys the high levels of H₂O₂ in restrained rats treated with lavender oil. Thus, it can be suggested that antioxidants also have a major role in attenuating stress mediated behavioral and biochemical deficits in rats.

CONCLUSION

Present study reveals that ibuprofen and lavender oil attenuate stress induced behavioral and biochemical alterations in rats. We observe the positive outcomes on administration of ibuprofen and lavender oil due to its antioxidant activity. However, the effectiveness of lavender oil is comparatively more than ibuprofen. Therefore, it is suggested to rely on natural compounds for the treatment of neuropsychiatric disorders.

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