Introduction
Depression is a major mood disorder which is characterized by altered mood with recurrent thoughts of suicide. It has been surveyed that depression may become the second-most disabling disease after cardiovascular disease by 2020 [1]. Various investigations have been reported for the explorations of pathophysiology of depression. Despite such growing evidences, there exist many limitations of current antidepressants treatment [2]. Considering such reports of limitations, it can be proposed that there is a need for more exploration of pathophysiology of depression. Further, the role of inflammation in the neurobiology of depression has received a considerable amount of research attention in the past few years [3-7]. It has been reported that there is an abnormal synthesis, suggesting a potential positive role in depression [17-18]. Several studies have reported that antidepressant drugs could inhibit PGE₃ synthesis including MAO inhibitors [19-22] and Tricyclic antidepressants [23].

Several studies indicated that there was an increase in levels of prostaglandin E₂ (PGE₂) in depressed individuals [8-10,13-14]. Further, a high prostaglandin E₂ (PGE₂) levels have repeatedly been described in major depression [15]. Further, an upregulation of cyclooxygenase-2 (COX-2) is associated with increased PGE₂ levels and neuronal apoptosis [16]. COX-2 inhibitors inhibited the PGE₂ synthesis, suggesting that there was an elevated level of prostaglandins (PGs) especially PGE₂ in depression [8-9,11]. Further, neuro-inflammation may be contributted by PGE₂, as concluded from various preclinical studies [12].

Results
The result of the present study indicated that mice treated with Venlafaxine and Loxoprofen showed a significant increase in the sucrose intake in stressed mice in chronic mild stress model. LPS-treated mice presented a decrease in sucrose intake when compared to controls. Similarly, Venlafaxine and Loxoprofen in the presence of LPS could increase the sucrose intake as compared to LPS treated stressed mice.

Conclusion
The results of the present study showed that Loxoprofen could influence LPS induced alterations in sucrose intake in mice in chronic mild stress model. It can also indicate the possible anti-depressant effect of Loxoprofen in mice subjected to chronic mild stress model of depression, having its possible implication in future treatment of depression.

Keywords: Chronic mild stress, Depression, Lipopolysaccharide, Loxoprofen, Mice.

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RESULTS

Effect of stress schedule on sucrose intake in stressed mice
There was a decrease in sucrose intake in mice of STR-I and STR-II group when compared with mice of VC-I and VC-II group, respectively. There was a significant decrease in sucrose intake in LPS treated stressed mice as compared to LPS treated normal mice (Table 1).

Effect of Venlafaxine and Loxoprofen on sucrose intake in stressed mice without treatment of LPS
The treatment of Venlafaxine showed significant increase in sucrose intake when compared to STR-I. The treatment of Loxoprofen showed significant increase in sucrose intake when compared to STR-II. The treatment of Loxoprofen showed a non-significant increase in sucrose intake when compared to Venlafaxine (Table 1).

Effect of Venlafaxine and Loxoprofen on sucrose intake in LPS treated stressed mice
The treatment of Venlafaxine showed significant increase in sucrose intake when compared to LPS treated stressed mice on day 21. Similarly, the treatment of Loxoprofen also significantly increases the sucrose intake when compared to LPS treated stressed mice on day 21 (Table 1).

DISCUSSION

The results of the present investigations indicated the potential antidepressant-like effect of Venlafaxine in chronic stress model of depression in mice. However, such results did not answer the question of whether behavioral sampling information of any of animal models of depression could reliably be compared with clinical outcome of depression since screening for the antidepressant agents through the animal models of depression always demand the accurate validation of models with its greater construct validity, predictive validity, and face validity. Chronic mild stress was reported as one of the chronic models of depression with higher construct validity which can establish empirical relationship between the feature being modeled and depression in humans [28]. However, despite higher constructive validity of CMS model which might enable us to correlate the clinical symptoms, more evidences are required to be furnished to confirm whether Loxoprofen may affect the behavior in animals.

The mechanism by which Loxoprofen indicated a significant antidepressant like action in chronic mild stress model remains to be elucidated. However, the previously reported inhibitory action of Loxoprofen on PGE₁ synthesis may show potential role of PGE₁ inhibition may be responsible for the antidepressant effect of Loxoprofen in animal models of depression. It can also be possible that antidepressant effect of Loxoprofen at specified dose as mentioned in the present study may be achieved by the inhibition of PGE₁ in brain. It is also possible that such Loxoprofen induced PGE₁ inhibition may be responsible for the inhibition of synthesis of inflammatory mediators.

Table 1: Effect of Venlafaxine and Loxoprofen on sucrose intake in stressed mice

| Group No | Treatment | Sucrose intake (g/kg) |
|----------|-----------|-----------------------|
|          | Day 00    | Day 03 | Day 06 | Day 09 | Day 12 | Day 15 | Day 18 | Day 21 |
| 1        | VC-I      | 154.6±19.80 | 159.61±19 | 105.09±9.07 | 72.96±69 | 92.75±9.9 | 89.6±11.7 | 98.9±5.7 | 146.7±19.2 |
| 2        | VC-II     | 140.50±8.84 | 166.69±22.87 | 72.79±10 | 81.92±7.74 | 93.28±8.48 | 52.89±6.65 | 51.30±7.25 | 56.58±11.58 |
| 3        | LPS       | 175.72±15.40 | 173.25±14.16 | 68.58±8.82 | 10.64±21.37 | 61.64±6.67 | 67.5±9.62 | 90.9±1.96 | 82.6±14.64 |
| 4        | STR-I     | 149.48±17.19 | 160.92±36.68 | 66.01±2.12* | 83.53±11.61 | 58.11±12.4* | 54.4±10.5* | 56.9±7.80* | 51.10±8.32* |
| 5        | STR-II    | 139.81±34.98 | 154.52±27.64 | 74.77±1.12 | 60.56±5.35* | 53.74±11.1 | 23.46±2.27 | 22.67±1.31 | 20.27±2.27* |
| 6        | STR+VEN   | 96.05±19.79 | 128.98±35.55 | 68.20±1.02 | 73.33±11.75 | 65.7±11 | 85.6±8.34* | 84.7±4.85* | 86.67±1.01* |
| 7        | STR+LOX   | 187.63±24.15 | 151.57±21.05 | 43.5±7.14 | 82.41±9.06* | 84.69±2.70** | 82.75±11.9 | 70.82±14.5** | 74.7±14.8** |
| 8        | STR+LPS   | 132.81±21.77 | 203.05±11.30 | 97.51±5.52 | 76.27±7.57 | 64.1±5.62 | 45.4±10.9 | 40.6±8.87 | 31.5±9.99* |
| 9        | STR+LPS+VEN | 125.26±7.12 | 114.52±22.73 | 60.98±1.57* | 63.16±13.77 | 44.7±7.57 | 60.3±5.82 | 36.4±8.74 | 61.25±8.4* |
| 10       | STR+LPS+LOX | 109.54±14.81 | 205.71±16.33 | 65.36±15.57 | 57.30±12.92 | 66.32±13.74 | 59.7±10.57 | 35.31±7.7 | 60.67±8.3c |

Each column expressed as mean±SEM of six animals after respective treatments. Data were analysed by One-way Analysis variance (ANOVA) followed by Tukey’s test.

*p<0.05 when compared with VC-I, *p<0.05 when compared with VC-II, **p<0.05 when compared with LPS, *p<0.05 when compared with STR-I, *p<0.05 when compared with STR-II, *p<0.05 when compared with STR+LPS
Although we were unable to measure brain PGE$_2$ levels in brain, further research work is suggested to examine if Loxoprofen induced alteration in brain PGE$_2$ levels may affect the molecular mechanism of depression such as alterations in expression of brain derived neurotrophic factor (BDNF) gene.

Although, the behavior sampling data of chronic mild stress model show the potential anti-depressant action of Loxoprofen in mice, further work is required for more exploration of the present investigations.

Regardless of the previous studies, these are the first results for the potential anti-depressant like effect of Loxoprofen in chronic mild stress model of depression in mice, having its potential implication in the pathophysiology and treatment of depression in future.

CONCLUSION

The results of the present study indicated that Loxoprofen could influence LPS induced alterations in sucrose intake in mice in chronic mild stress model. It also indicated the possible anti-depressant like effect of Loxoprofen in mice subjected to chronic mild stress model of depression, having its possible implication in future treatment of depression.

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AUTHOR’S CONTRIBUTIONS

Dr. Digvijay Rana designed the research study; Ms. Smita S. Kundu performed the study; Dr. Digvijay Rana prepared the manuscript; all authors approved the final submitted version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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