OBJECTIVES: Agomelatine is a novel melatonin (MT) receptor agonist at MT1 and 2, serotonin receptor antagonist and an effective chronobiotic agent. The study was designed to evaluate the effects of agomelatine on body weight and food intake in restraint stress model in adult Swiss albino mice.

METHODS: After the approval of Institutional Animal Ethics Committee, 40 male Swiss albino mice were randomly divided into four groups of 10 animals each; two were treatment groups which received 25 mg/kg (low dose) agomelatine, 50 mg/kg (high dose) agomelatine, standard group given trazodone and the control group administered the vehicle (1% hydroxethyl cellulose [HEC]) intraperitoneally for the last 14 days in the 3 weeks study period. Chronic restraint stress was given for 4 hrs per day for all groups starting from day 0 to 21.

RESULTS: Using paired t-test, both 12 hrs (p=0.011) and 24 hrs (p<0.001) food intake in the high dose agomelatine group were significantly increased. Between groups using ANOVA test showed a statistically significant increase in food intake for this group when compared to the control group. Unlike the low dose agomelatine group (p=0.205), the mean body weight in the group treated with high dose agomelatine revealed a statistically significant rise compared to that of the control (p=0.001) in ANOVA test.

CONCLUSION: High dose agomelatine was effective in antagonizing the body weight lowering effect of restraint stress in addition to amelioration of reduced food intake. The study has potentially brought out the additional therapeutic benefit of agomelatine in improving the altered feeding and body weight changes when used in the treatment of the depression.

KEYWORDS: Agomelatine, Body weight, Food intake, Satiety, Circadian rhythm.
were individually housed and measuring the left-over food at the end of light phase (12 hrs) and dark phase (12 hrs). An accurate measurement was made by returning the spilled food at the bottom of the cage before measuring the weight of left-over food. Each animal was weighed and the body weight was recorded before the measurement of food intake on 0, 7, 14, and 21 days (Fig. 1).

RESULTS

All data were entered into excel and analyzed using SPSS software version 19. At baseline, a one way ANOVA test done showed that there was no significant difference in either the body weight (p=0.08) or the food intake, both the 12 hrs (p=0.53) and 24 hrs (p=0.05) in the four groups of animals indicating that there was no significant difference at baseline among the animals which were randomized to the four groups.

The food intake, both 12 hrs and 24 hrs in both the treatment groups (low dose and high dose) as well as the standard trazodone group showed an increase when compared between the 7th day intake and 21st day intake demonstrating the effects of drug treatment (Figs. 2 and 3). Using paired t-test, both 12 hrs (p=0.011) and 24 hrs (p<0.001) food intake in the high dose agomelatine group were found to be significantly increased. In addition, between groups analyses using ANOVA test showed a statistically significant increased food intake only in group 2 treated with high dose agomelatine when compared to control, but not the other two groups (Table 1).

A paired t-test done at the end of 7 days showed that there was a statistically significant reduction in weight in Groups 1-3 (Fig. 4) which were subsequently treated with low dose agomelatine, high dose agomelatine and trazodone respectively. The reduction in weight was induced as a result of the chronic restraint stress in this animal model.

DISCUSSION

Agomelatine is a MT receptor agonist, serotonin receptor 5HT2C antagonist and an effective chronobiotic agent. It has been found to be an effective antidepressant and an anxiolytic [6]. Agomelatine synchronizes the circadian rhythm and also ameliorates stress-related changes like depressive symptoms by modulating the cytoskeleton micro tubular dynamics and synaptic markers such as brain derived neurotrophic factor in amygdala and hippocampus [13,14]. Agomelatine antagonizes serotonin 2C receptor which is an important mediator of satiety [15]. It is well established from studies conducted earlier that restraint stress model in mice induces depression such as state in addition to the reduction in body weight and food intake by altered expression of food related genes like decreased ghrelin and increased Pro-opiomelanocortin [16,17].

A statistically significant increase in food intake was demonstrated only in the group treated with high dose agomelatine when compared to control. Using ANOVA test, the changes in mean body weight were not significant in the groups which were treated with low dose agomelatine or trazodone compared to the control group (Fig. 4 and Table 1). The rise in mean body weight in the group treated with high dose agomelatine (p=0.001) when compared to control, was statistically significant indicating that agomelatine at 50 mg/kg was effective in antagonizing the body weight lowering effect of restraint stress. This was also mirrored in the statistical analysis of food intake between the three groups done at the end of 21 days (Table 1).
to control, but not in groups which were treated with low dose agomelatine and trazodone (Table 1). This has confirmed that though there was an increased food intake evident in all the three groups, it was the high dose agomelatine which has significantly increased the food intake higher than that of the control group at the end of the treatment period, thereby effectively neutralizing the effect of restraint stress on the body weight. This also explains why the high dose agomelatine group had mean body weight significantly higher compared to that of control in contrary to the low dose agomelatine and trazodone groups.

The reasons for the effects of agomelatine on body weight and food intake are twofold. The first being the antidepressant activity of the drug, responsible for the therapeutic effect on the animals in depression-like state induced by chronic restraint stress which secondarily has led to the changes in body weight and improved food intake in the stressed animals. Second, this can be explained as due to the agomelatine’s action at the serotonin receptor 5HT2C, which is a serotonin receptor subtype that is involved in normal satiation following a meal. Agomelatine antagonizes the SHT2C receptor, and thereby it interferes with the satiety, increasing the food intake in the treated animals. The effect was well manifested in the group treated with high dose agomelatine. In contrast, the low dose agomelatine group did not show a similar response which probably could have been due to inadequate dosage to demonstrate such effects on weight and food intake. Thus, this study has delineated the effects of agomelatine on food intake and body weight when used as an antidepressant.

CONCLUSION
This study highlights the additional therapeutic benefit of agomelatine in the treatment of depression as it improves the altered feeding and body weight changes. The study clearly indicates the role of agomelatine in normalizing food intake and body weight in depressed patients with weight loss from poor feeding. These beneficial effects can be explained by its synchronizing action on circadian rhythm and antagonism of SHT2C receptor, an important mediator of satiety.

REFERENCES