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# Targeting the Gut – Brain Axis with Agomelatine and Rifaximin in Corticosterone induced depression in Rats

***N.Rohini[1], Dr. S.Swarnalatha[2], Dr. J.Karthi[3], M.Vignesh[4]***

[1]- Department of Pharmacology – Pallavan Pharmacy College, Kanchipuram
[2]- Head of the Department of Pharmacology – Vice Principal Pallavan Pharmacy College, Kanchipuram
[3]- Head of the Department of Pharmacognosy – Principal of Pallavan Pharmacy College, Kanchipuram.
[4]- Department of Pharmacology – Assistant Professor – Pallavan Pharmacy College, Kanchipuram.

**Corresponding Author: N.Rohini**

**E.Mail:** rohininatarajan1101@gmail.com

**ABSTRACT:**

Depression is a complex neuropsychiatric disorder associated with behavioural, neurochemical, inflammatory, oxidative and neuroendocrine alterations. Increasing evidence suggests that the microbiota–gut–brain axis plays an important role in the pathophysiology of depression and may provide a potential target for therapeutic intervention. The present study was undertaken to evaluate the antidepressant effect of the combination of Agomelatine and Rifaximin in a corticosterone-induced depression model in rats and to investigate the possible involvement of the microbiota–gut–brain axis. Depression-like behaviour was induced by repeated corticosterone administration. Experimental animals were divided into appropriate control, corticosterone-induced, Agomelatine-treated, Rifaximin-treated and combination-treated groups. Antidepressant activity was evaluated using Behavioralparameters, including the sucrose preference test, along with biochemical, gastrointestinal, gut microbiota, gut–brain-axis-related and histopathological evaluations. Chronic corticosterone administration produced marked depression-like Behavioralchanges accompanied by oxidative stress, altered neurotransmitter levels, gastrointestinal disturbances and increased TNF-α levels. Treatment with Agomelatine and Rifaximin individually attenuated several of these alterations, whereas the combination treatment produced comparatively greater improvement across most evaluated parameters. The findings suggest that simultaneous modulation of central antidepressant mechanisms by Agomelatine and gut-related microbial mechanisms by Rifaximin may provide enhanced protection against corticosterone-induced depression-like changes. Overall, the study supports the possible involvement of microbiota–gut–brain-axis modulation in the antidepressant-like effects of the Agomelatine–Rifaximin combination and highlights its potential as a complementary therapeutic approach for stress-associated depression.

**Keywords:**

- Depression
- Agomelatine
- Rifaximin
- Corticosterone
- Gut microbiota
- Microbiota–gut–brain axis
- Antidepressant activity
- Oxidative stress
- Neurotransmitters

## 1. Introduction:

Depression is a common and clinically important neuropsychiatric disorder characterized by persistent low mood, loss of interest or pleasure, and disturbances in emotional, cognitive, Behavioraland physical functioning. The pathophysiology of depression is complex and involves the interaction of multiple biological mechanisms, including alterations in neurotransmission, neuroinflammation, oxidative stress, neuroendocrine regulation and neuroplasticity. Chronic or repeated exposure to stress is particularly relevant because prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis and altered glucocorticoid signalling have been associated with depression-related Behavioraland neurobiological changes.

Classical neurotransmitter systems, particularly serotonin, dopamine and noradrenaline, have an important role in the regulation of mood, motivation, reward, cognition and emotional responses. Alterations in these systems may contribute to depressive symptoms. In addition,

neuroinflammatory processes and oxidative stress have increasingly been recognized as important components of depression. Chronic stress may promote inflammatory signalling and oxidative imbalance, which can adversely affect neuronal function, synaptic plasticity and neurogenesis.

The microbiota–gut–brain axis is a bidirectional communication network connecting the gastrointestinal tract, intestinal microbiota and central nervous system through neural, endocrine, immune, metabolic and microbial pathways. Alterations in intestinal microbial composition or function may influence intestinal barrier integrity, immune responses, microbial metabolites and neurotransmitter-related pathways, thereby affecting brain function and behaviour. Conversely, psychological stress and altered central nervous system activity may influence gastrointestinal physiology and the intestinal microbial environment.

Experimental studies have demonstrated a relationship between chronic stress, gut microbial alterations and depression-like behaviour. Rifaximin, a minimally absorbed gut-directed antimicrobial agent, has attracted interest because of its ability to modify the intestinal microbial environment. Previous studies have reported that rifaximin can improve depression-like behaviour in chronic stress models and may influence intestinal microbiota, tryptophan metabolism, microbial metabolites and microglial function.

Agomelatine is an antidepressant with melatonergic receptor agonist and 5-$HT_2C$ receptor antagonist properties. Previous experimental studies have demonstrated antidepressant-like effects of agomelatine in chronic stress models. Thus, agomelatine may provide a centrally acting antidepressant mechanism, whereas rifaximin may influence gut-associated mechanisms relevant to the microbiota–gut–brain axis.

Although the individual effects of agomelatine and rifaximin have been investigated in experimental models of depression, the combined effects of these agents in a corticosterone-induced depression model, particularly in relation to gut–brain-axis-associated mechanisms, remain insufficiently explored. Therefore, the present study was designed to evaluate the antidepressant effect of the Agomelatine–Rifaximin combination in corticosterone-induced depression in rats and to investigate its possible involvement in behavioural, neurochemical, oxidative, inflammatory, gastrointestinal and gut–brain-axis-related alterations.

## 2. Materials and Methods

### *2.1 Experimental Drugs:*

Agomelatine and Rifaximin were procured from a reputed and authorized pharmaceutical supplier in commercially available pharmaceutical-grade formulations. The drugs were stored according to the manufacturer's recommended storage conditions until further use. Before administration, the identity and physical appearance of the formulations were verified.

### *2.2 Experimental Animals:*

Healthy Wistar albino rats were selected for the experimental study. The animals were maintained under standard laboratory conditions and provided with standard laboratory pellet diet and purified drinking water ad libitum. Animals were allowed to acclimatize to the laboratory environment for 7 days before commencement of the experimental procedures. During acclimatization, the animals were monitored for general health, behaviour, food and water intake and visible abnormalities.

Animal housing, handling and experimental procedures were carried out in accordance with CPCSEA guidelines and the protocol approved by the Institutional Animal Ethics Committee (IAEC).

### *2.3 Experimental Design and Grouping:*

After acclimatization, the animals were randomly allocated into five experimental groups with six animals in each group (n = 6).

**Group I – Normal control:** Animals received vehicle only.

**Group II – Corticosterone-induced disease control:** Animals received corticosterone at 40 mg/kg/day by intraperitoneal administration once daily for 21 consecutive days.

**Group III – Corticosterone + Agomelatine:** Animals received corticosterone at 40 mg/kg/day intraperitoneally for 21 days and Agomelatine at 10 mg/kg/day orally.

**Group IV – Corticosterone + Rifaximin:** Animals received corticosterone at 40 mg/kg/day intraperitoneally for 21 days and Rifaximin at 150 mg/kg/day orally.

**Group V – Corticosterone + Agomelatine + Rifaximin:** Animals received corticosterone at 40 mg/kg/day intraperitoneally together with Agomelatine 10 mg/kg/day and Rifaximin 150 mg/kg/day orally.

### *2.4 Induction of Corticosterone-Induced Depression*

Depression-like Behavioralalterations were induced by repeated administration of corticosterone at 40 mg/kg/day by the intraperitoneal route for 21 consecutive days. The corticosterone-induced group served as the disease control for evaluating treatment-associated changes.

### *2.5 Behavioral Assessment*

Behavioral assessment was performed using selected Behavioral paradigms to evaluate anxiety-like behavior, locomotor activity, anhedonia, Behavioral alterations and motor coordination.

**2.5.1 Elevated Plus Maze Test**

The elevated plus maze test was used to assess anxiety-related behavior. The apparatus consisted of two open arms and two closed arms arranged in a plus configuration and elevated above the floor. Behavioral parameters were recorded according to the experimental protocol.

**2.5.2 Open Field Test**

The open field test was used to evaluate locomotor and exploratory activity. The distance travelled by the animals during the test period was recorded and compared between experimental groups.

**2.5.3 Sucrose Preference Test**

The sucrose preference test was used to assess anhedonia-like behaviour. Animals were provided access to sucrose solution and water, and the volume consumed was recorded. Sucrose preference was calculated as:

**Sucrose preference (%) = [Sucrose solution consumed / (Sucrose solution consumed + water consumed)] × 100**

**2.5.4 Marble Burying Test**

The marble burying test was used to assess Behavioral alterations. Twenty glass marbles were arranged evenly over a uniform layer of bedding material. Animals were allowed to explore the cage for 30 min, after which the number of marbles buried by at least two-thirds of their depth was counted.

**2.5.5 Rotarod Test**

The rotarod test was used to assess motor coordination and performance. Animals were placed individually on a rotating rod and the latency to fall was recorded. Multiple trials were conducted according to the experimental protocol.

### *2.6 Biochemical Evaluation*

At the end of the experimental period, the required biological samples were collected according to the approved experimental protocol. Biochemical parameters associated with oxidative stress, antioxidant defence, neurotransmission and inflammation were evaluated.

**2.6.1 Lipid Peroxidation**

Lipid peroxidation was assessed by measuring malondialdehyde-related thiobarbituric acid reactive substances. Tissue homogenate was reacted with thiobarbituric acid under acidic and high-temperature conditions and absorbance was measured spectrophotometrically at 532 nm.

**2.6.2 Glutathione-S-Transferase**

Glutathione-S-transferase activity was estimated based on the conjugation of reduced glutathione with an electrophilic substrate such as 1-chloro-2,4-dinitrobenzene. The reaction was monitored spectrophotometrically at 340 nm.

**2.6.3 Antioxidant Enzymes**

Superoxide dismutase and catalase activities were evaluated as indicators of antioxidant defence. Reduced glutathione was also estimated as an important component of the endogenous antioxidant system.

### *2.7 Neurochemical Evaluation*

Neurotransmitter levels were evaluated to determine the effect of corticosterone and pharmacological treatment on neurochemical alterations associated with depression-like behaviour. Serotonin and other selected neurotransmitter parameters included in the experimental protocol were assessed and compared between groups.

### *2.8 Gastrointestinal Parameters*

Gastrointestinal parameters, including fecal output and fecal water content, were assessed to determine corticosterone-associated gastrointestinal alterations and the effects of Agomelatine, Rifaximin and their combination.

### *2.9 TNF-α Estimation*

Tumor necrosis factor-α (TNF-α) was evaluated as an inflammatory marker associated with corticosterone-induced inflammatory alterations. The levels were compared among the experimental groups.

### *2.10 Evaluation of Gut Microbiota and Gut–Brain Axis*

The effect of corticosterone administration and treatment with Agomelatine, Rifaximin and their combination on intestinal microbiota and gut–brain-axis-related parameters was evaluated according to the experimental protocol. The relationship between intestinal alterations and depression-related Behavioraland biochemical changes was considered in the interpretation of the findings.

### *2.11 Histopathological Evaluation*

Colon and hippocampal tissues were subjected to histopathological examination to assess structural alterations associated with corticosterone exposure and the protective effects of the treatments. Histological changes were evaluated with particular attention to tissue architecture, cellular integrity, inflammatory alterations, and treatment-associated restoration.

### *2.12 Statistical Analysis*

Experimental data were expressed as Mean ± SEM with six animals per group (n = 6). Statistical comparisons were performed using two-way analysis of variance (ANOVA) followed by Tukey's multiple-comparison test. Statistical significance was interpreted according to the significance levels reported in the experimental data, with $p < 0.05$ considered statistically significant.

## 3. Results:

### *3.1 Effect on BehavioralParameters:*

**Table 01: Effect of drugs on Open field test, Sucrose Preference test, Marbel Burying Test:**

| S.NO | GROUPS | distance travelled in meter | Sucrose Preference % | No. of marbles buried |
|---|---|---|---|---|
| 1 | Control | 80.51 ± 0.15 | 90.47 ± 0.09 | 14.22 ± 0.25 |
| 2 | Negative Control | 51.07 ± 0.18 a*** | 40.49 ± 0.176 a*** | 3.966 ± 0.06 a*** |
| 3 | Agomelatin 10mg | 60.64 ± 0.14 a***b*** | 80.90 ± 0.26 a***b*** | 7.646 ± 0.12 a***b*** |
| 4 | Rifaximin 150mg | 66.38 ± 0.24 a***b***c*** | 72.77 ± 0.37 a***b***c*** | 6.406 ± 0.15 a***b***c*** |
| 5 | Combination Therapy | 74.99 ± 0.30 a***b***c*** | 87.97 ± 0.34 a***b***c*** | 10.60 ± 0.085 a***b***c*** |

Values are represented in Mean ± SEM, n=6 ns- Non significant,*p<0.05,
**p<0.01, ***p<0.001, ***p<0.0001, ****p<0.00001
Comparison:
a - Group I vs Group II, Group III, Group IV, Group V

b - Group II vs Group III, Group IV, Group V
c - Group III vs Group IV, Group V ( Two way ANOVA followed by Turkeys test)

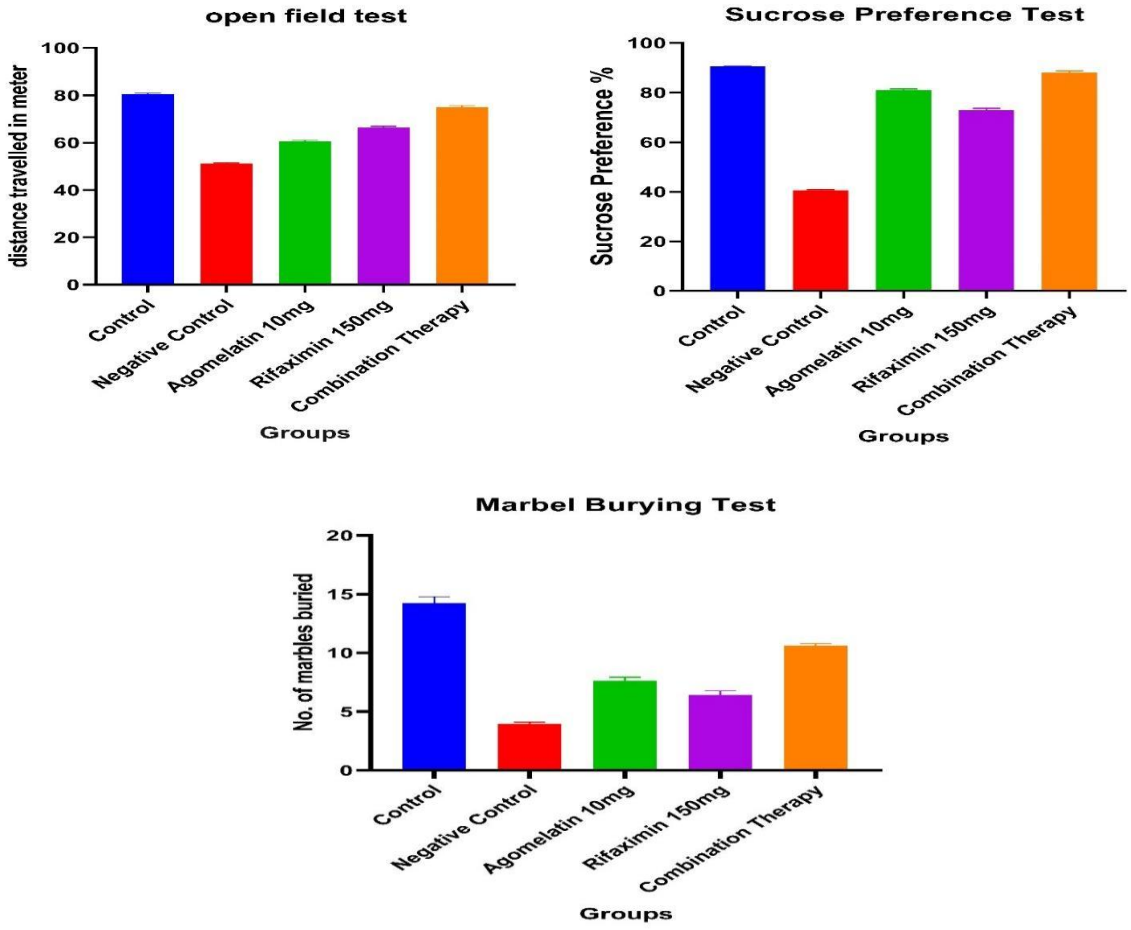



**Fig 01: Effect of drugs on Open field test, Sucrose Preference test, Marbel Burying Test**

| S.NO | GROUPS | Fall of time (in seconds) | | | Latency (in sec.) | |
|---|---|---|---|---|---|---|
| | | WEEK -1 | WEEK-4 | WEEK-21 | Initial Transfer Latency | Retention Transfer Latency |
| 1 | Control | 67 ± 1.095 | 64.6 ± 0.509 | 70.8 ± 1.240 | 17.85 ± 0.21 | 15.48 ± 0.10 |
| 2 | Negative Control | 18.6 ± 0.509 a*** | 11.6 ± 0.509 a*** | 7.8 ± 0.374 a*** | 48.71 ± 0.24 a*** | 52.56 ± 0.11 a*** |
| 3 | Agomelatin 10mg | 45.2 ± 0.374 a***b*** | 57 ± 0.707 a***b*** | 62.6 ± 0.812 a***b*** | 23.58 ± 0.10 a***b*** | 22.56 ± 0.05 a***b*** |
| 4 | Rifaximin 150mg | 27.8 ± 0.860 a***b***c*** | 35.4 ± 0.509 a***b***c*** | 45.8 ± 0.374 a***b***c*** | 21.90 ± 0.16 a***b***c*** | 18.50 ± 0.07 a***b***c*** |
| 5 | Combination Therapy | 42.2 ± 0.663 a***b***c* | 56 ± 0.707 a***b***cns | 61.8 ± 0.663 a***b***cns | 19.72 ± 0.24 a***b***c*** | 14.62 ± 0.14 a***b***c*** |

**Table 02: Effect of drugs on Rotarod & Elevated Plus Maze Test:**

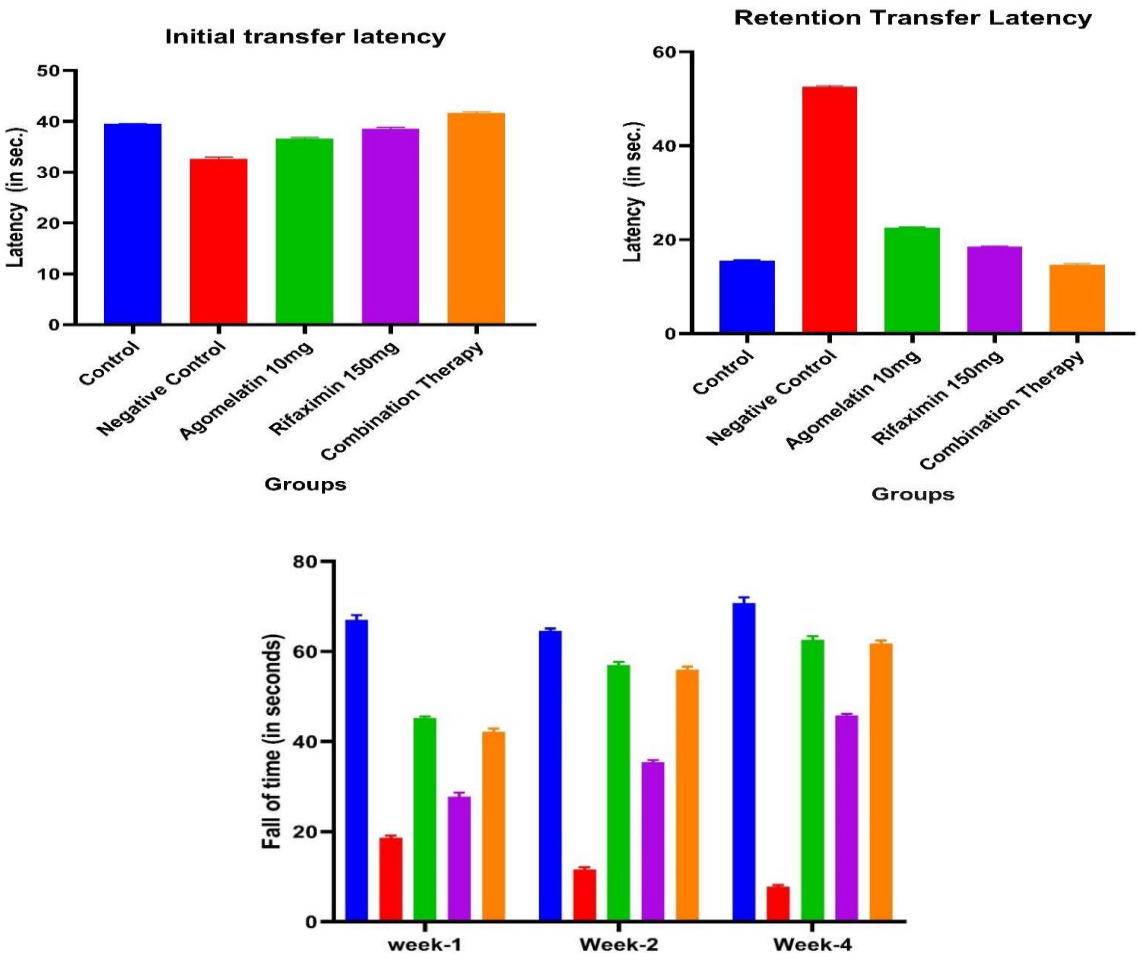



**Fig 02: Effect of drugs on Rotarod & Elevated Plus Maze Test**

**Table 03: Effect of drugs on Lipid Peroxidation, Glutathione-S-Transferase, Superoxide dismutase test:**

| S.NO | GROUPS | LPO (µM) | GST (µmol/g) | SOD (µmol/g) |
|---|---|---|---|---|
| 1 | Control | 18.59 ± 0.11 | 3.798 ± 0.016 | 10.10 ± 0.020 |
| 2 | Negative Control | 43.45 ± 0.46 a*** | 8.208 ± 0.025 a**** | 21.57 ± 0.238 a**** |
| 3 | Agomelatine 10 mg | 37.56 ± 0.12 a***b*** | 7.922 ± 0.022 a*** bns | 14.15 ± 0.238 a*** b*** |
| 4 | Rifaximin 150mg | 27.62 ± 0.10 a***b***c*** | 5.658 ± 0.026 a*** b*** c*** | 15.61 ± 0.101 a*** b*** c*** |
| 5 | Combination Therapy | 24.33 ± 0.14 a***b***c*** | 4.638 ± 0.148 a*** b*** c*** | 20.36 ± 0.038 a*** b*** c*** |

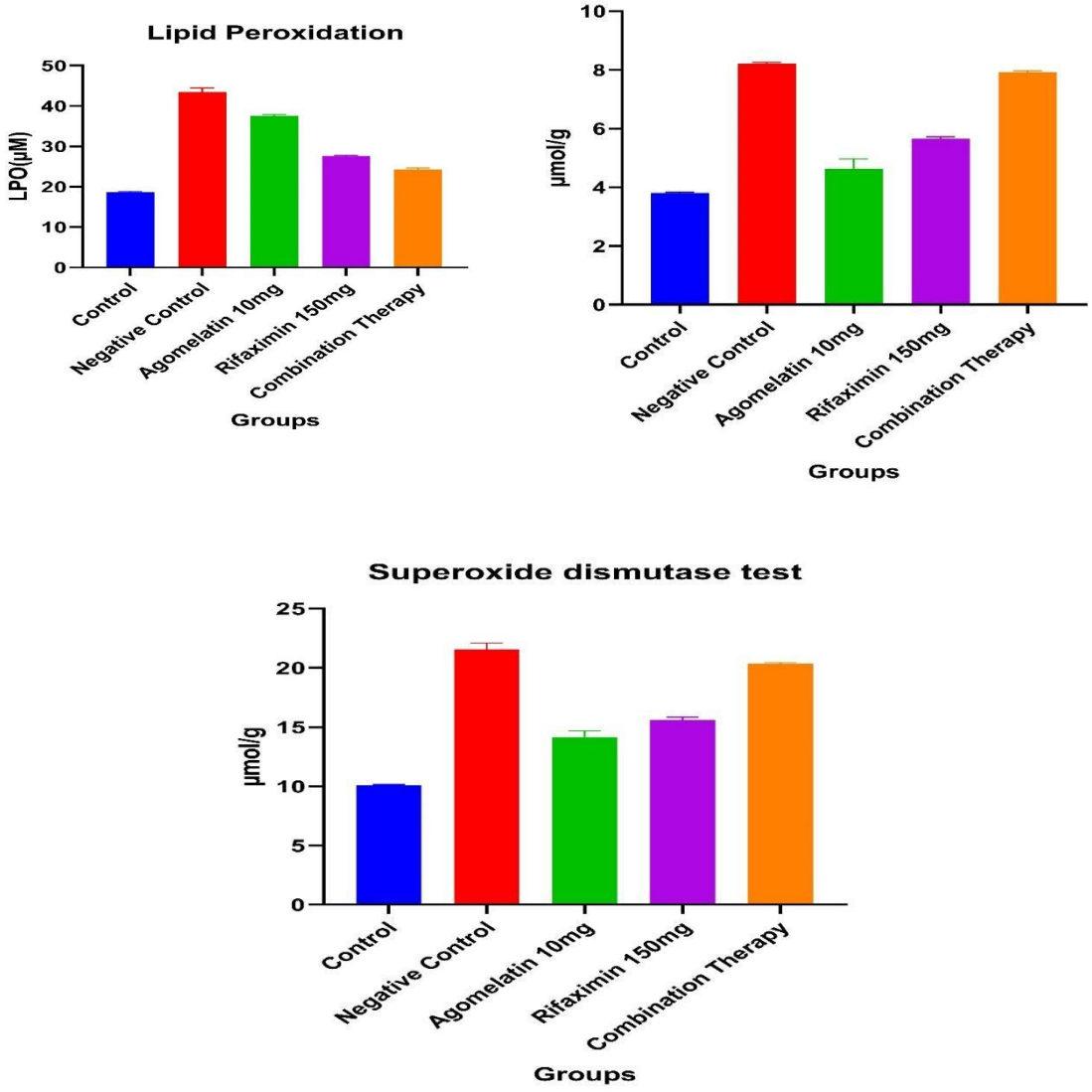



**Fig 03: Effect of drugs on Lipid Peroxidation, Glutathione-S-Transferase, Superoxide dismutase test:**

**Table 04: Effect of drugs on Catalase, Glutathione, Serotonin, Dopamine test:**

| S.NO | GROUPS | CAT µmol/g | GSH (mg/ml) | Serotonin (mg/ml) | Dopamine (mg/ml) |
|---|---|---|---|---|---|
| 1 | Control | 25.40 ± 0.030 | 82.33 ± 0.125 | 18.43 ± 0.06 | 1.794 ± 0.019 |
| 2 | Negative Control | 52.89 ± 0.102 a**** | 56.49 ± 0.567 a**** | 15.37 ± 0.15 a*** | 1.516 ± 0.034 a*** |
| 3 | Agomelatin 10mg | 33.33 ± 0.246 a*** b*** | 79.43 ± 0.369 a** b*** | 16.56 ± 0.10 a*** b*** | 1.562 ± 0.006 a*** bns |
| 4 | Rifaximin 150mg | 38.79 ± 0.033 a*** b*** c*** | 72.57 ± 0.854 a*** b*** c*** | 17.43 ± 0.09 a*** b*** c*** | 1.648 ± 0.011 a*** b*** c* |
| 5 | Combination Therapy | 49.01 ± 0.060 a*** b*** c*** | 79.95 ± 0.698 a* b*** c** | 18.17 ± 0.02 a** b*** c*** | 1.814 ± 0.002 a** b*** c*** |

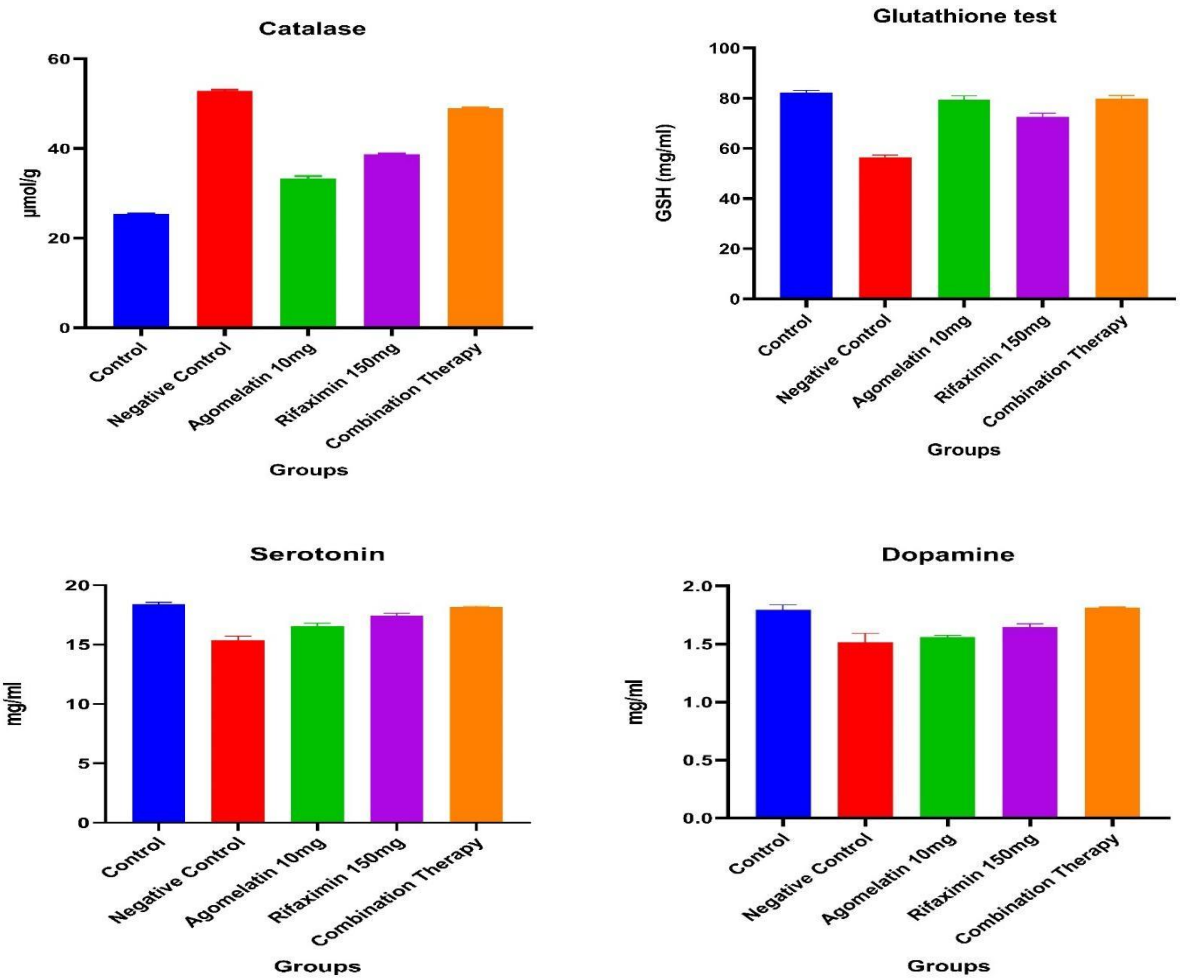



**Fig 04: Effect of drugs on Catalase, Glutathione, Serotonin, Dopamine test**

**Table 05: Effect of drugs on Fecal pellet Output, Fecal Water Content, TNF Alpha:**

| S.NO | GROUPS | No.of.Pellets | percentage | Unit / mg tissue |
|---|---|---|---|---|
| 1 | Control | 1.720 ± 0.06 | 59.88 ± 0.26 | 17.85 ± 0.21 |
| 2 | Negative Control | 10.58 ± 0.14 a*** | 30.17 ± 0.24 a*** | 48.71 ± 0.24 a*** |
| 3 | Agomelatin 10mg | 2.514 ± 0.14 a** b*** | 39.77 ± 0.12 a*** b*** | 23.58 ± 0.10 a*** b*** |
| 4 | Rifaximin 150mg | 2.664 ± 0.13 a*** b**** c** | 37.90 ± 0.29 a*** b*** c*** | 21.90 ± 0.16 a*** b*** c*** |
| 5 | Combination Therapy | 1.632 ± 0.09 a** b*** c** | 35.67 ± 0.08 a*** b*** c*** | 19.72 ± 0.24 a*** b*** c*** |

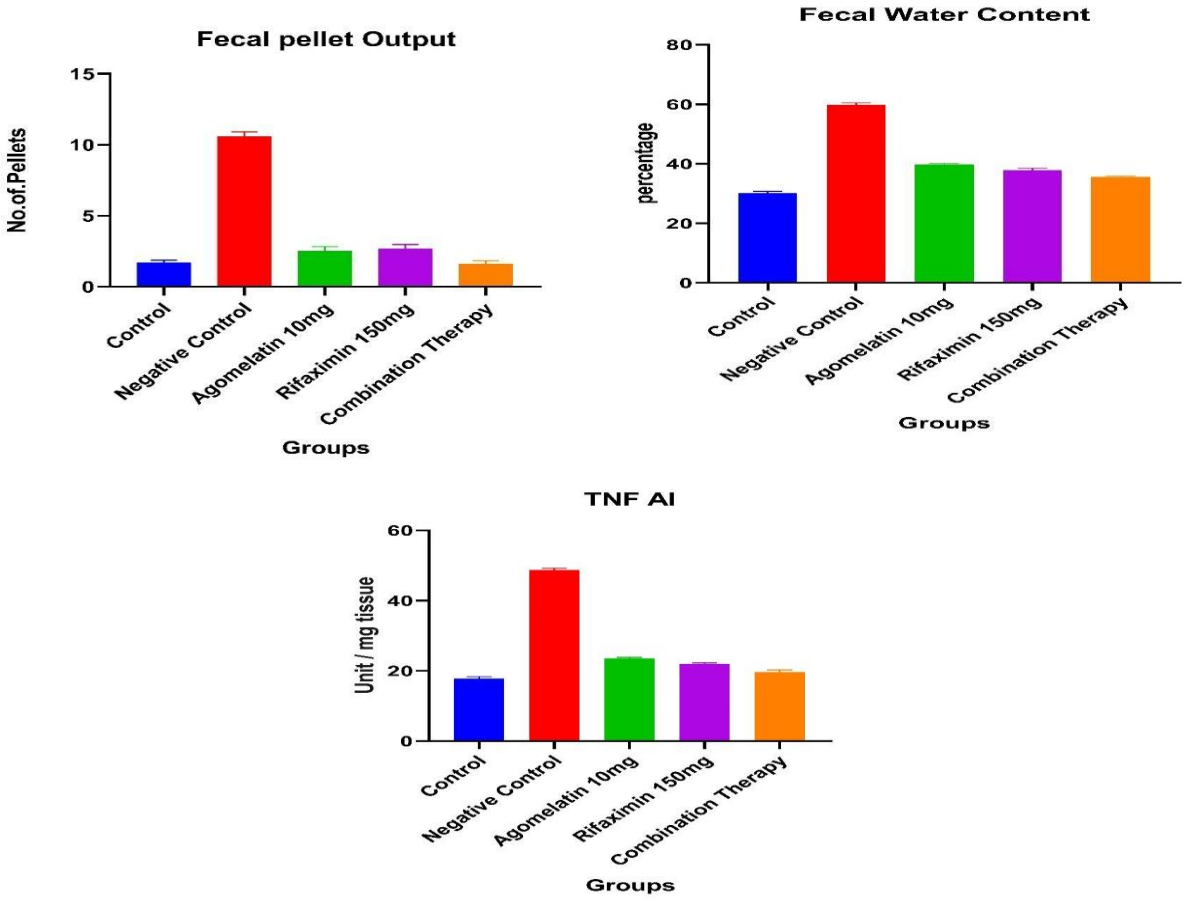



**Fig 05: Effect of drugs on Fecal pellet Output, Fecal Water Content, TNF Alpha**

## 4. Discussion:

The present study evaluated the antidepressant-like effects of Agomelatine and Rifaximin, individually and in combination, in a corticosterone-induced depression model in rats, with particular emphasis on the possible involvement of the microbiota–gut–brain axis. Repeated corticosterone administration produced marked behavioural, oxidative, neurochemical, gastrointestinal, inflammatory and histopathological alterations. A substantial reduction in locomotor activity and sucrose preference was observed in the disease control group, with sucrose preference decreasing from 90.47% in the normal control group to 40.49%, indicating anhedonia and depression-like behaviour. Treatment with Agomelatine and Rifaximin individually improved these alterations, while combination treatment produced comparatively greater improvement, increasing sucrose preference to 87.97% and locomotor activity to 74.99 m. Agomelatine may have contributed to these effects through melatonergic receptor agonism and 5-$HT_2C$ receptor antagonism, whereas Rifaximin may have influenced intestinal microbial and gut-associated pathways. Corticosterone administration also increased lipid peroxidation and altered antioxidant defence parameters, including GST, SOD, catalase and reduced glutathione. Treatment attenuated these oxidative disturbances, with combination therapy reducing lipid peroxidation to 24.33 micromoles per litre. Similarly, serotonin levels decreased from 18.43 milligrams per millilitre in the normal control group to 15.37 milligrams per millilitre in the disease control group, whereas combination treatment restored serotonin levels to 18.17 milligrams per millilitre. Gastrointestinal alterations, including changes in faecal output and faecal water content, were also attenuated by treatment, with the combination showing comparatively greater improvement. Furthermore, TNF-alpha levels increased from 17.85 in the normal control group to 48.71 in the disease control group, while combination treatment reduced the level to 19.72, suggesting attenuation of corticosterone-associated inflammatory activity. Histopathological observations in the colon and hippocampus also indicated comparatively greater tissue protection in the combination treatment group. Overall, these findings suggest that Agomelatine and Rifaximin may exert complementary effects by influencing central antidepressant mechanisms and gut-associated pathways, including oxidative balance, inflammatory signalling, gastrointestinal homeostasis and neurotransmitter regulation. However, since direct microbiome profiling, microbial metabolite analysis and pathway-specific investigations were not performed, the involvement of the microbiota–gut–brain axis remains a possible explanation rather than definitive proof of a causal mechanism. Taken together, the findings indicate that combined Agomelatine and Rifaximin treatment produced broader improvements than either treatment alone in this experimental model, supporting further investigation of combined central and gut-directed therapeutic approaches for depression-like alterations.

## .5. Conclusion:

The present study demonstrated that chronic corticosterone administration produced significant depression-like behavioural changes accompanied by oxidative stress, altered neurotransmitter levels, gastrointestinal disturbances and increased inflammatory signalling in rats. Treatment with Agomelatine and Rifaximin individually attenuated several of these alterations, while the Agomelatine–Rifaximin combination produced a comparatively greater protective effect across behavioural, oxidative, neurochemical, gastrointestinal and inflammatory parameters. The improvement in sucrose preference, locomotor activity, motor performance, oxidative status, serotonin levels, gastrointestinal parameters and TNF-alpha levels following combination treatment indicates greater attenuation of corticosterone-induced alterations. The accompanying improvement in colon and hippocampal histopathological changes further supports the protective effects of the combination. Overall, the findings suggest that simultaneously targeting central antidepressant mechanisms with Agomelatine and gut-associated microbial pathways with Rifaximin may provide a beneficial approach for attenuating corticosterone-induced depression-like changes. The results also support the possible involvement of microbiota–gut–brain-axis modulation in the observed antidepressant-like effects of the combination. However, further mechanistic studies involving detailed microbiota profiling, microbial metabolite analysis and molecular marker evaluation are required to establish the precise contribution of the gut–brain axis to these effects.

**Compliance with ethical standards:**

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**Disclosure of conflict of interest:**
There is no conflict of interest.

**Author Contribution:**
Dr.S.Swarnalatha and Dr.J.Karthi had principal responsibility for the conception and design of the study and drafting of the manuscript. M.Vignesh was responsible for the revision of the manuscript for important intellectual content and contributed towards reviewing of the literature. All authors agreed on the final version of the manuscript.

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