Research Article

# Anxiolytic and neuroinflammatory modulatory effects of *Bacillus clausii* in a physical restraint stress-induced rat model

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**How to cite this article:** Mete SA, Burakle PV, Ande SN. Anxiolytic and neuroinflammatory modulatory effects of *Bacillus clausii* in a physical restraint stress-induced rat model. Innov Pharm Pharmacother 2026;14(3):34-39.

**Source of Support:** Nil.
**Conflicts of Interest:** None declared.

## ABSTRACT

**Introduction:** Anxiety disorders are associated with neurotransmitter imbalance, oxidative stress, hypothalamic–pituitary–adrenal -axis dysregulation, and neuroinflammation. Emerging evidence suggests that psychobiotics may influence emotional behavior through the microbiota–gut–brain axis. *Bacillus clausii*, a spore-forming probiotic, has shown immunomodulatory effects; however, its role in anxiety regulation remains unclear. **Aim**: This study evaluated the anxiolytic potential of *B. clausii* and its effects on neurochemical, oxidative, and inflammatory changes in a restraint stress-induced anxiety model in rats. **Materials and Methods:** Adult Wistar rats were divided into five groups ($n = 5$/group): Control, restraint stress, diazepam-treated, and two *B. clausii* treatment groups (once daily and twice daily). Anxiety was induced by restraint stress for 2 h/day for 14 days. Behavioral changes were assessed using the Elevated Plus Maze, Open Field Test, and Light–Dark Box test. Brain tissues were analyzed for gamma-aminobutyric acid (GABA) levels, oxidative stress markers (malondialdehyde, catalase, and superoxide dismutase), inflammatory markers (tumor necrosis factor-alpha, interleukin-1 beta [IL-1β], interleukin-6, and nuclear factor kappa-B [NF-κB]), and histopathological alterations. **Results:** Restraint stress produced significant anxiety-like behavior, oxidative imbalance, and increased neuroinflammatory markers. *B. clausii* treatment improved anxiety-related behaviors, increased brain GABA levels, enhanced antioxidant defenses, reduced lipid peroxidation, and decreased pro-inflammatory cytokines and NF-κB signaling. Histological analysis showed reduced neuronal degeneration and improved amygdala architecture, with greater effects observed following twice-daily administration. **Conclusion:** *B. clausii* exhibits anxiolytic and neuroprotective effects by modulating GABAergic signaling, oxidative stress, and neuroinflammatory pathways, supporting its potential as a psychobiotic intervention for stress-related anxiety disorders.

**Keywords:** Anxiety, *Bacillus clausii*, neuroinflammation, oxidative stress, psychobiotic, restraint stress

## Introduction

Anxiety disorders are among the most prevalent neuropsychiatric conditions and are characterized by excessive fear, apprehension, emotional disturbances, and behavioral alterations. Globally, anxiety disorders affect an estimated 4–5% of the population at any given time, with approximately 301 million people living with these conditions, making them one of the leading contributors to disability worldwide. Although commonly used pharmacological therapies such as benzodiazepines and selective serotonin reuptake inhibitors provide effective symptomatic relief, their long-term use is associated with adverse effects including tolerance, dependence, sedation, and cognitive impairment. Therefore, the development of safer and more effective therapeutic strategies for anxiety management remains an important area of research.[1,2]

Chronic stress is a major risk factor contributing to anxiety development and causes significant neurobiological alterations through activation of the hypothalamic–pituitary–adrenal (HPA) axis, neurotransmitter imbalance, oxidative stress, and neuroinflammatory responses. Stress-induced activation of inflammatory pathways

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| **Website:** www.innpharmacotherapy.com | **e-ISSN:** 2321-323X |
| **DOI:** 10.31690/ipp.2026.v014i03.005 | **p-ISSN:** 2395-0781 |

increases the production of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). In addition, nuclear factor kappa-B (NF-κB), a key regulator of inflammatory signaling, plays an important role in stress-mediated neuronal dysfunction and emotional regulation.[3,4]

The microbiota–gut–brain axis has emerged as an important regulatory pathway connecting intestinal microorganisms with central nervous system function through neural, immune, endocrine, and metabolic mechanisms. Probiotics capable of influencing brain function through this pathway are termed psychobiotics. These beneficial microorganisms may exert anxiolytic effects by regulating neurotransmitter systems, improving antioxidant defense, reducing inflammatory responses, and maintaining neuronal homeostasis.[5,6]

*Bacillus clausii* is a Gram-positive, spore-forming probiotic known for its stability, gastrointestinal survival, and immunomodulatory properties.[7] Previous studies have suggested that *B. clausii* may influence stress-related behavioral responses and neurochemical pathways; however, its role in restraint stress-induced anxiety and associated neuroinflammatory alterations in brain tissue remains insufficiently investigated.[8]

Therefore, the present study was designed to evaluate the anxiolytic and neuroprotective effects of *B. clausii* in a physical restraint stress-induced anxiety model in rats. The study further investigated its effects on anxiety-related behavior, GABAergic neurotransmission, oxidative stress markers, inflammatory mediators, and histopathological changes in the amygdala.

## Materials and Methods

### Experimental animals

Adult male Wistar rats (200–250 g) were procured from the National Institute of Biosciences, Pune, India. Animals were housed under standard laboratory conditions (22 ± 1°C, 12 h light/dark cycle) with free access to food and water. All experimental procedures were approved by the Institutional Animal Ethics Committee and conducted in accordance with CPCSEA guidelines, Government of India [Figure 1].

### Drugs and treatments

Diazepam (1 mg/kg, i.p.) was used as the standard anxiolytic drug.[9] *B. clausii* was administered orally at two dose levels: $0.5 \times 10^9$ colony-forming units (CFU)/day (once daily [OD]) and $1 \times 10^9$ CFU/day (twice daily [BD]).

The oral dose of *B. clausii* ($1 \times 10^9$ CFU/day) was selected based on previously published preclinical studies and the clinically recommended therapeutic dose used in probiotic formulations. Doses in the range of $10^8$–$10^9$ CFU have consistently demonstrated beneficial effects on gut microbial homeostasis, immune modulation, oxidative stress, and behavioral abnormalities without producing toxicity or adverse effects in experimental animals. A dose of $1 \times 10^9$ CFU/day provides

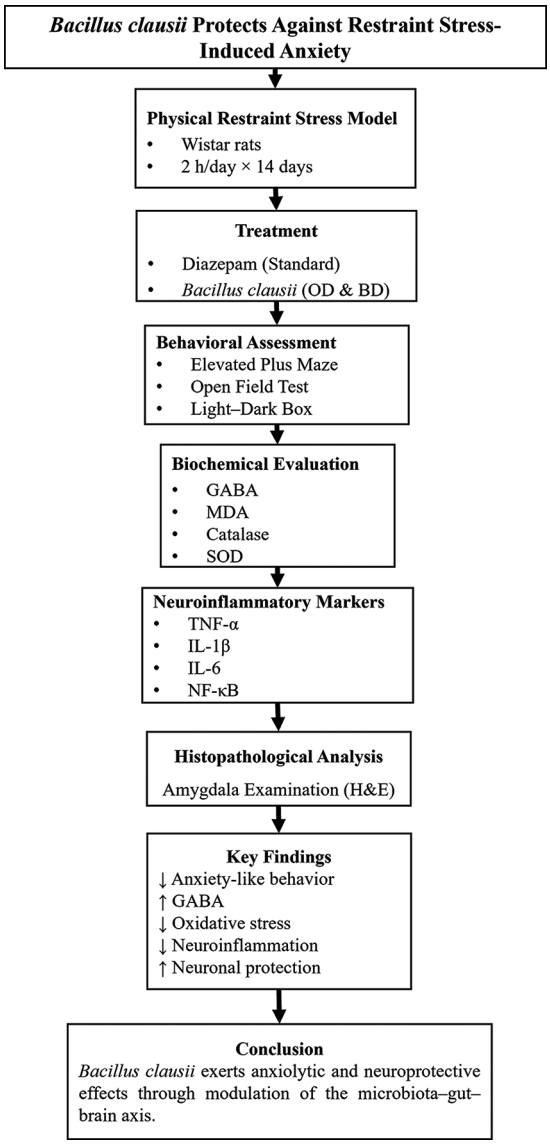


**Figure 1:** Schematic representation of the experimental design and neuroprotective effects of *Bacillus clausii* in a physical restraint stress-induced anxiety model in wistar rats

an adequate number of viable spores capable of surviving gastric acidity, colonizing the intestine, and exerting sustained biological effects through modulation of the microbiota–gut–brain axis. This concentration has been reported to improve neurotransmitter regulation, reduce neuroinflammation, enhance antioxidant defense, and attenuate stress-induced behavioral deficits in rodent models. Therefore, $1 \times 10^9$ CFU/day was considered a biologically relevant dose for evaluating the anxiolytic and neuroprotective effects of *B. clausii* in the present restraint stress-induced anxiety model. The lower dose ($0.5 \times 10^9$ CFU/day) was included to assess dose-dependent efficacy and compare the therapeutic response across two clinically relevant dose levels [Table 1].

### Experimental design

Animals were randomly divided into five groups ($n = 5$/group): [Table 2].

**Table 1: Treatment groups and dosing regimen**

| Treatment | Dose | Route | Frequency |
|---|---|---|---|
| Diazepam | 1 mg/kg | Intraperitoneal | OD |
| *B. clausii* (Low dose) | $0.5\times10^9$ CFU/day | Oral | OD |
| *B. clausii* (High dose) | $1\times10^9$ CFU/day | Oral | BD |

OD: Once daily, BD: Twice daily, CFU: Colony-forming units, *B. clausii*: *Bacillus clausii*

**Table 2: Treatment regimen for the experimental groups**

| Group | Treatment |
|---|---|
| Normal control | Normal saline (1 mL/kg, p.o.) |
| Disease control | Restraint stress (2 h/day) |
| Standard | Restraint stress+Diazepam (1 mg/kg, i.p.) |
| Treatment I | Restraint stress+*B. clausii* OD |
| Treatment II | Restraint stress+*B. clausii* BD |

OD: Once daily, BD: Twice daily, p.o: Per oral (oral administration), i.p: Intraperitoneal, *B. clausii*: *Bacillus clausii*

Anxiety was induced by physical restraint stress for 2 h/day for 14 consecutive days. Behavioral assessments were performed on day 15, followed by biochemical and histopathological analyses on day 16 [Figure 2].

## Behavioral assessment[8]

Anxiety-like behavior was evaluated using the Elevated Plus Maze (EPM), Open Field Test (OFT), and Light-Dark Box (LDB) test.

### *EPM*

The EPM consisted of two open and two closed arms elevated 45 cm above the floor. The number of arm entries and time spent in open and closed arms were recorded over a 10-min period.

### *OFT*

Animals were placed individually in the center of a 60 × 60 cm open-field arena and allowed to explore freely for 5 min. Time spent in central and peripheral zones was recorded.

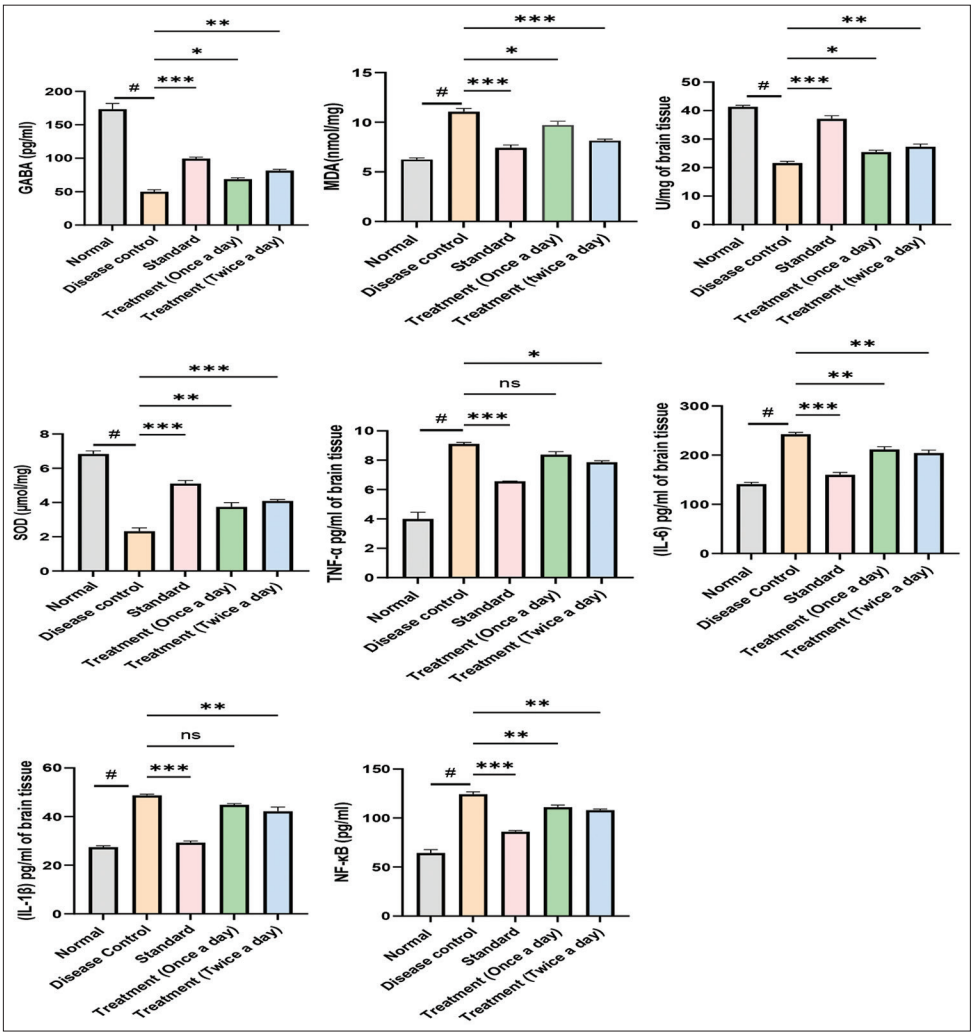


**Figure 2:** Effect of *Bacillus clausii* on the levels of biochemical and inflammatory biomarkers. Data are presented as mean ± standard error of the mean ($n$ = 5/group). (Statistical analysis was performed using one-way analysis of variance followed by Bonferroni's multiple comparison test. Statistical significance is indicated as $^{\#}P < 0.001$ versus the normal control group; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{*}P < 0.001^{**}$ versus the disease control group; ns, not significant)

### *LDB test*

The apparatus consisted of illuminated and dark compartments. Animals were allowed to explore for 5 min, and the time spent in each compartment was recorded.

## Biochemical analysis[10]

Following behavioral testing, rats were euthanized, and brain tissues were collected. Tissue homogenates (10% w/v) were prepared in phosphate buffer (pH 7.4) and centrifuged at 10,000 × g for 15 min at 4°C. Supernatants were used for biochemical analyses.

### *Neurotransmitter estimation*

Brain gamma-aminobutyric acid (GABA) levels were estimated and expressed as pg/mL.

### *Oxidative stress markers*

1. Oxidative stress was assessed by measuring:
2. Malondialdehyde (MDA) as an index of lipid peroxidation.
3. Catalase activity.
4. Superoxide dismutase (SOD) activity.

### *Neuroinflammatory markers*

Brain levels of TNF-α, IL-1β, IL-6, and NF-κB were quantified using enzyme-linked immunosorbent assay kits according to the manufacturer's instructions.

## Histopathological examination

Brain tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 4 μm thickness. Sections were stained with hematoxylin and eosin and Nissl stain. Histopathological evaluation of the amygdala was performed under light microscopy (×40 magnification).

## Statistical analysis

Data were expressed as mean ± standard error of the mean ($n = 5$). Statistical analysis was performed using one-way analysis of variance followed by Dunnett's or Bonferroni *post hoc* tests. $P < 0.05$ was considered statistically significant.

# Results

Table 3 summarizes the effects of *B. clausii* on behavioral, neurochemical, oxidative stress, and neuroinflammatory parameters in rats subjected to chronic physical restraint stress. Compared with the normal control group, the disease control group exhibited pronounced anxiety-like behavior, characterized by increased closed-arm entries and reduced open-arm entries in the EPM, decreased time spent in the central zone with increased peripheral zone exploration in the OFT, and prolonged time spent in the dark compartment in the LDB Test. Chronic restraint stress also markedly reduced brain GABA concentration, increased lipid peroxidation (MDA), decreased antioxidant enzyme activities (catalase and SOD), and significantly elevated the pro-inflammatory mediators TNF-α, IL-6, IL-1β, and NF-κB. Diazepam effectively reversed these stress-induced alterations across all measured parameters. Similarly, B. clausii treatment attenuated anxiety-like behavior, restored brain GABA concentration, reduced oxidative stress, improved endogenous antioxidant defense, and suppressed neuroinflammatory responses. Among the two treatment regimens, the BD administration consistently produced greater improvement than the OD regimen, demonstrating superior anxiolytic, antioxidant, neuroprotective, and anti-inflammatory effects and yielding responses closer to those observed with diazepam.

## Histopathological findings

Microscopic analysis of the amygdala revealed marked neuronal alterations following restraint stress. The normal control group showed intact neuronal architecture with organized cells and preserved nuclei, whereas the disease control group exhibited neuronal degeneration, pyknotic nuclei, cellular shrinkage, and vacuolization. Diazepam treatment reduced these degenerative changes. *B. clausii* administration improved neuronal organization and reduced cellular damage, with greater neuroprotective effects observed in the BD treatment group [Figure 3].

# Discussion

The present study demonstrates that B. clausii exhibits significant anxiolytic and neuroprotective effects in a restraint stress-induced

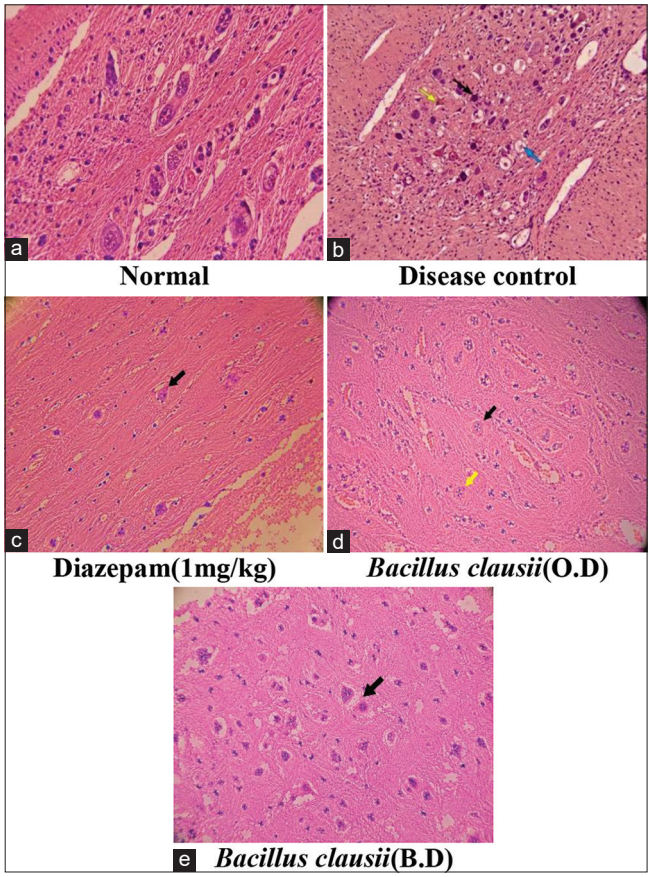


**Figure 3:** Histopathological evaluation of brain tissue. (a) Normal, (b) disease control, (c) diazepam (1 mg/kg), (d) *Bacillus clausii* (OD), and (e) *Bacillus clausii* (B.D)

**Table 3: Effect of *B. clausii* on behavioral, neurochemical, oxidative stress, and neuroinflammatory parameters in restraint stress-induced anxiety model (*n*=5/group)**

| Parameter (Unit) | Normal control | Disease control | Diazepam | *B. clausii* OD | *B. clausii* BD |
|---|---|---|---|---|---|
| Behavioral parameters | | | | | |
| Elevated plus maze | | | | | |
| Closed arm entries (No.) | 2.75±0.23 | 6.25±0.37 | 2.50±0.32 | 3.50±0.32 | 3.25±0.31 |
| Open arm entries (No.) | 2.25±0.12 | 1.50±0.14 | 2.75±0.12 | 1.75±0.12 | 2.50±0.14 |
| Open field test | | | | | |
| Time spent in central zone (sec) | 22.29±0.32 | 13.90±0.29 | 25.15±0.29 | 16.97±0.23 | 22.45±0.31 |
| Time spent in peripheral zone (sec) | 117.88±1.24 | 246.82±1.89 | 135.35±1.59 | 187.75±2.46 | 182.20±1.53 |
| Light-dark box test | | | | | |
| Time spent in dark compartment (sec) | 129.90±2.79 | 171.61±1.10 | 137.85±1.26 | 156.93±1.46 | 139.47±1.35 |
| Neurochemical parameter | | | | | |
| GABA (pg/mL) | 173.4±4.8 | 49.9±1.7 | 99.4±1.21 | 68.79±1.08 | 81.60±1.12 |
| Oxidative stress parameters | | | | | |
| MDA (nmol/mg) | 6.2±0.10 | 11.6±0.18 | 7.4±0.15 | 9.7±0.23 | 8.1±0.17 |
| Catalase (U/mg) | 41.3±0.30 | 21.6±0.33 | 37.1±0.61 | 25.4±0.38 | 27.3±0.56 |
| SOD (U/mg) | 6.83±0.10 | 2.31±0.11 | 5.10±0.10 | 3.74±0.14 | 4.09±0.04 |
| Neuroinflammatory parameters | | | | | |
| TNF-α (pg/mL) | 3.90±0.26 | 9.11±0.06 | 6.56±0.01 | 8.37±0.11 | 7.86±0.05 |
| IL-6 (pg/mL) | 141.11±2.06 | 242.62±2.22 | 160.14±2.86 | 211.66±3.25 | 204.31±3.51 |
| IL-1β (pg/mL) | 27.4±0.31 | 48.7±0.27 | 29.28±0.37 | 44.82±0.28 | 42.16±1.01 |
| Inflammatory signaling marker | | | | | |
| NF-κB (pg/mL) | 64.3±1.95 | 124.3±1.34 | 86.0±0.66 | 111.0±1.33 | 108.0±0.66 |

Values are expressed as mean±SEM (*n*=5 animals per group). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test. OD: Once daily, BD: Twice daily, GABA: Gamma-aminobutyric acid, MDA: Malondialdehyde, SOD: Superoxide dismutase, TNF-α: Tumor necrosis factor-alpha, IL-6: Interleukin-6, IL-1β: Interleukin-1 beta, NF-κB: Nuclear factor-kappa B, SEM: Standard error of the mean, ANOVA: Analysis of variance, *B. clausii*: *Bacillus clausii*

anxiety model in rats. B. clausii effectively attenuated stress-induced anxiety-like behaviors, with BD administration producing greater efficacy than OD treatment.

Recent evidence suggests that psychobiotics regulate emotional behavior through the microbiota–gut–brain axis by influencing neurotransmitter balance, immune responses, oxidative stress, and HPA axis activity. Likewise, Jafari *et al*. and Barrio *et al*. demonstrated that probiotic supplementation alleviates anxiety-like behavior through modulation of neurochemical signaling. Consistent with these observations, the anxiolytic effects of B. clausii observed in the present study are likely attributable to its ability to modulate microbiota–gut–brain communication and restore neurophysiological homeostasis.[11,12]

Stress-induced anxiety is associated with impaired GABAergic neurotransmission. In the present study, restraint stress significantly reduced brain GABA levels, whereas *B. clausii* administration restored GABA concentrations, indicating recovery of inhibitory neurotransmission. Supporting these findings, Rehman *et al*. demonstrated that *B. clausii* and Lactobacillus fermentum ameliorated stress-induced behavioral deficits through modulation of neurotransmitter systems and enhancement of monoaminergic signaling. Likewise, Oroojzadeh *et al*. and Le Morvan de Sequeira *et al*. reported that psychobiotic interventions regulate GABA-related pathways and strengthen gut–brain communication, thereby improving behavioral outcomes under stress. Collectively, these findings suggest that restoration of GABAergic neurotransmission is a key mechanism underlying the anxiolytic effects of B. clausii.[8,13,14]

Oxidative stress and neuroinflammation are major contributors to neuronal dysfunction associated with chronic stress.[15] In the present study, restraint stress significantly increased MDA levels while reducing the activities of the antioxidant enzymes catalase and SOD, indicating enhanced lipid peroxidation and impaired antioxidant defense. *B. clausii* treatment effectively reversed these alterations by reducing MDA levels and restoring endogenous antioxidant enzyme activities. Furthermore, probiotic administration significantly suppressed the stress-induced elevation of TNF-α, IL-1β, IL-6, and NF-κB, demonstrating attenuation of neuroinflammatory responses. Supporting these findings, Rehman *et al*. reported that *B. clausii* exerts neuroprotective effects through modulation of stress-associated molecular pathways, while Wiegers *et al*. highlighted the antioxidant and anti-inflammatory properties of psychobiotics mediated through the microbiota–gut–brain axis. Collectively, these findings indicate that B. clausii confers neuroprotection by restoring redox homeostasis and suppressing inflammatory signaling, thereby mitigating stress-induced neuronal damage.[8,16]

Histopathological evaluation further confirmed the neuroprotective activity of *B. clausii*. Restraint stress caused neuronal degeneration and structural alterations in the amygdala, whereas probiotic treatment preserved neuronal architecture and reduced cellular damage. Compared with diazepam, which produces anxiolytic effects mainly through direct GABA-A receptor activation, *B. clausii* may provide broader and safer effects by regulating neurotransmission, oxidative balance, immune responses, and microbiota-mediated pathways.

Collectively, the present findings suggest that *B. clausii* exerts anxiolytic and neuroprotective effects through multiple complementary mechanisms, including restoration of GABAergic neurotransmission, enhancement of endogenous antioxidant defenses, suppression of oxidative stress and neuroinflammatory signaling, preservation of neuronal integrity, and modulation of the microbiota–gut–brain axis. The observed effects are consistent with improved redox homeostasis, which may involve Nrf2-mediated antioxidant pathways and reduced reactive oxygen species generation, as well as attenuation of inflammatory signaling that may involve the TLR4/NF-κB pathway, although these mechanisms were not directly investigated in the present study. The superior efficacy observed with the BD regimen may be attributed to prolonged transient intestinal colonization, sustained immunomodulatory activity, and continuous production of beneficial microbial metabolites, resulting in more persistent regulation of gut–brain communication. Collectively, these integrated pharmacological effects attenuated oxidative stress and neuroinflammation, preserved neuronal architecture, and improved anxiety-related behavioral outcomes. These findings support the therapeutic potential of *B. clausii* as a promising psychobiotic for the management of stress-related anxiety disorders; however, further mechanistic studies and clinical investigations are warranted to confirm the underlying pathways and therapeutic efficacy.

## Conclusion

The present study demonstrates that *B. clausii* exhibits anxiolytic and neuroprotective effects in a restraint stress-induced anxiety model by improving behavioral responses, restoring GABA levels, reducing oxidative stress, suppressing neuroinflammatory pathways, and preserving neuronal integrity. The observed effects may involve modulation of the microbiota–gut–brain axis, although this mechanism was not directly investigated in the present study. These findings support the potential of *B. clausii* as a psychobiotic candidate for the management of stress-related anxiety. Further mechanistic investigations and clinical studies are warranted to confirm its therapeutic efficacy and elucidate the underlying mechanisms.

## Acknowledgments

The authors would like to thank the management of Dr. Rajendra Gode Institute of Pharmacy, Amravati, for their administrative support, continuous encouragement, and for providing the necessary facilities to conduct this study.

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