Assessments of *Akkermansia muciniphila* in depression and cognitive behaviors in rats

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ABSTRACT

This study investigated the effects of ***Akkermansia muciniphila*** (AKK) on depressive behavior and cognitive functions in rats subjected to Chronic Mild Stress (CMS). Thirty-two male Sprague Dawley rats were divided into four groups: No CMS/ Phosphate Buffered Saline (PBS), No CMS/AKK, CMS/PBS, and CMS/AKK, and underwent a 28-day AKK treatment. Behavioral assessments included the Forced Swim Test, Open Field Test, and Novel Object Recognition Test. The study also measured corticosterone levels and analyzed the expression of c-Fos and IL-1β in the medial prefrontal cortex, hippocampus, and amygdala. Results showed AKK significantly reduced depressive behaviors and enhanced cognitive abilities, particularly in learning and memory, in CMS rats. AKK also lowered corticosterone levels and modulated c-Fos and IL-1β expression in key brain regions. These findings suggest ***Akkermansia muciniphila*** has potential as a therapeutic agent for depression, ameliorating depressive behaviors and cognitive functions.

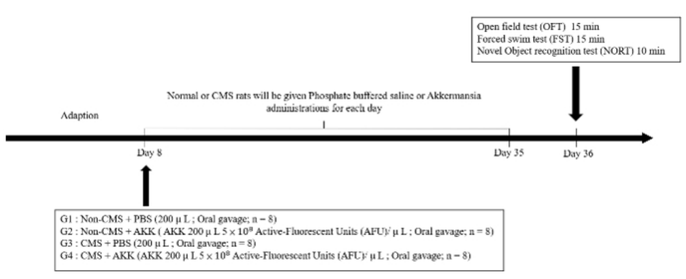
METHODS

Animals

In this study, we utilized 32 male Sprague Dawley rats weighing between 150-200g. These rats were subjected to a 7-day acclimation period in a controlled environment with a temperature of 23 ± 2℃ and a 12/12-hour light/dark cycle. The rats had ad libitum access to food and water. Following the acclimation period, the rats were divided into four groups, including No CMS/ PBS, No CMS/AKK, CMS/PBS, and CMS/AKK group. All rats were given AKK administrations for 28-day.

Experiments procedure

In this experiment, 32 rats were divided into four groups, each consisting of 8 rats. The groups included No CMS/ PBS, No CMS/AKK, CMS/PBS, and CMS/AKK group. The no CMS groups were not subjected to CMS induction, while the CMS groups underwent chronic mild stress for 4 weeks. The AKK group received AKK treatment for 28 days, with rats drinking 200 μL (5 × 108 colony-forming unit (AFU)/μL) of AKK daily, while the no AKK group received 200 μL of PBS. After 28 days of treatment, behavioral tests, including the novel object recognition test (NORT), open field test (OFT), and forced swim test (FST), were conducted on all groups within one day. Following the behavioral tests, we assessed biomarkers such as c-Fos, IL-1β in the mPFC, hippocampus, amygdala, and corticosterone in serum of the depression animal model underlying AKK treatment.



RESULTS

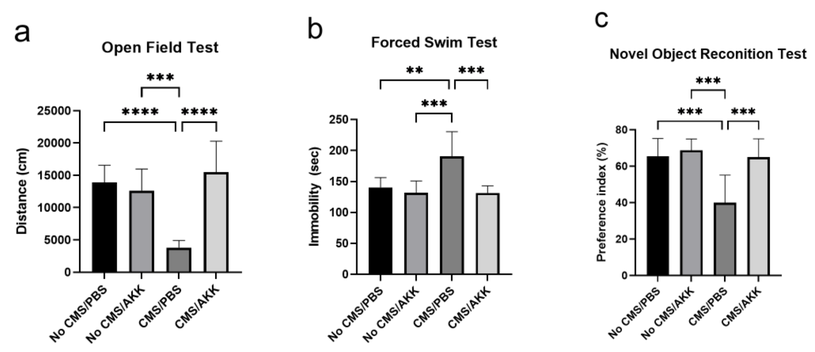


Figure 1. Differential Behavioral Responses to CMS and AKK Treatment in Rats.

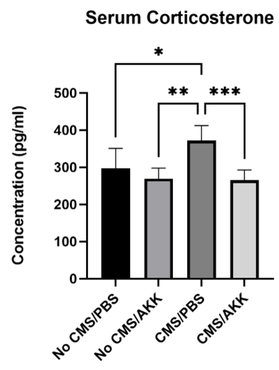


Figure 2. Serum Corticosterone Alterations Induced by CMS and Modulation by AKK

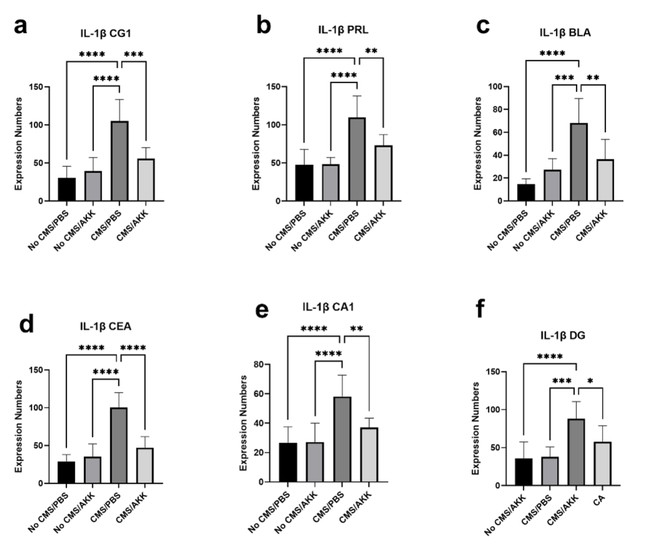


Figure 3. CMS and AKK Modulate IL-1β Expression in Brain Regions

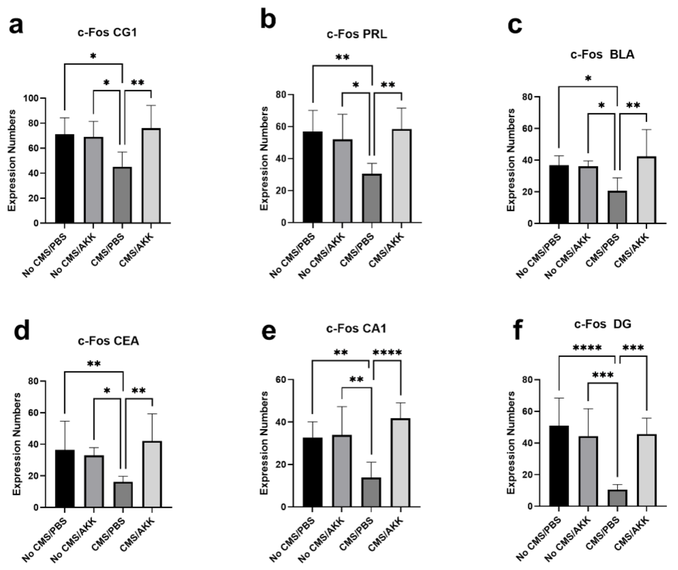


Figure 4. Effects of CMS and AKK Treatment on c-Fos Expression

Datas are presented as mean ± 95% CI, with n = 8 per group.
*Statistical analyses were initially conducted using a two-way ANOVA, followed by a one-way ANOVA, and subsequently by Tukey's multiple comparisons test to determine significance levels. The levels of significance are denoted as: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.*

Under chronic stress, rats exhibited depressive-like behaviors with reduced locomotion in the Open Field Test (Figure 1a), heightened despair in the Forced Swim Test (Figure 1b), and diminished cognitive function in the Novel Object Recognition Test (Figure 1c). Elevated corticosterone levels in these rats (Figure 2) confirmed a physiological response to stress. In contrast, rats treated with AKK under the same conditions showed significant behavioral and physiological improvements, with corticosterone levels akin to non-stressed controls, suggesting AKK's potential in mitigating stress effects. Molecular analysis revealed upregulated IL-1β expression across several brain regions involved in stress response (Figure 3a-f), indicating an inflammatory response to stress. This was accompanied by altered c-Fos expression (Figure 4a-f), signifying changes in neural activity. AKK treatment effectively reduced IL-1β levels and normalized c-Fos expression, highlighting its anti-inflammatory and neuroprotective properties in stress conditions.

DISCUSSION

This study presents compelling evidence for AKK's potential as a therapeutic agent in mitigating depressive behaviors and cognitive impairments induced by chronic mild stress (CMS) in rats. Chronic stress, known to trigger physiological and behavioral changes akin to human depression symptoms, led to decreased locomotion, increased despair, and elevated corticosterone levels in our CMS model. Remarkably, AKK treatment reversed these adverse effects, suggesting its capability to modulate the stress response, potentially by dampening the hypothalamic-pituitary-adrenal (HPA) axis overactivity, as indicated by the normalization of corticosterone levels. Further insights were gained at the molecular level, where AKK treatment significantly reduced IL-1β expression, a marker of inflammation, in key brain regions associated with stress and emotion. This reduction points to an anti-inflammatory effect of AKK, a crucial finding considering the established link between inflammation and depression. Additionally, the normalization of c-Fos expression, indicative of neural activity, suggests AKK's ability to recalibrate neural circuits disrupted by chronic stress. These findings enrich the domain of psychobiotics, positioning AKK as a promising candidate for depression treatment, particularly by targeting the intricate interplay between the gut-brain axis and the immune system. The cognitive restoration observed with AKK treatment, particularly in areas compromised by stress, underscores its potential to enhance memory and other cognitive functions affected in depressive disorders. This cognitive benefit might stem from AKK's anti-inflammatory actions, fostering an environment favorable for neuronal repair and synaptic plasticity. Given the pivotal role of the gut-brain axis in neuropsychiatric health, this study advocates for further exploration into AKK's therapeutic mechanisms. Understanding how AKK modulates gut microbiota, exerts direct anti-inflammatory effects within the brain, and influences brain function through its metabolic products could unveil novel strategies for managing depression and other stress-related neuropsychiatric conditions.

CONCLUSIONS

Our study highlights the therapeutic potential of AKK in mitigating the behavioral and physiological impacts of chronic stress, which are known contributors to depression. The results pave the way for future investigations into psychobiotics as a novel and promising avenue for depression treatment, with the potential for integration into holistic treatment strategies.