Raspberry ketone ameliorates LPS-induced depression-like behavior in mice by inhibiting TLR-4/NF-κB signaling pathway via the gut-brain axis

覆盆子酮通过肠-脑轴抑制TLR-4/NF-κB信号通路改善LPS诱导的小鼠抑郁样行为

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Abstract

Presently, there is an urgent need to unearth non-toxic and effective compounds from the realm of medicinal plants to enhance depression treatment. This study was aimed to investigate the impact of raspberry ketone (RK) on lipopolysaccharides (LPS)-induced depression in mice and explore its potential mechanisms. The present study demonstrated that RK has significant improvement in LPS-induced depressed mice by regulating the TLR-4/NF-κB inflammatory pathway to reduce neuroinflammation and upregulating neurotrophic factor and synapse-associated proteins to enhance synaptic function. Moreover, RK mitigated the intestinal inflammatory response and prevented the penetration of LPS into circulation by inhibiting the TLR-4/NF-κB signaling pathway, regulating the intestinal microbiota composition and restoring the integrity of the intestinal barrier. In addition, RK increased the secretion of bacterial metabolite short-chain fatty acids, which can alleviate depression-like behavior. This study fills a research gap in the field of antidepressants in the medicinal food plant raspberry.

Introduction

- Depression is expected to become the leading contributor to the global burden of disease by 2030. To date, classical antidepressants developed in accordance with the monoamine hypothesis have inherent limitations. Hence, exploring the potential of bioactive compounds from the realm of medicinal plants with potent efficacy and minimal toxic side effects offers a novel approach to tackle the challenges associated with treating depression.
- This study investigated the efficacy of RK in alleviating depression-like behavior induced by LPS. By analyzing its impact on intestinal flora homeostasis, gut microbiota-derived metabolites, intestinal immunity and inflammatory factors in colon and brain tissues, we aimed to uncover the mechanisms from the perspective of the gut-brain axis. These novel findings not only introduced a fresh therapeutic avenue for enhancing depression but also uncovered the medicinal potential of raspberry ketone in the context of the gut-brain axis.

Objectives

- To explore the efficacy of RK in alleviating depression-like behaviors induced by LPS
- To explore the potential mechanisms involved by linking the regulatory effects of RK on intestinal homeostasis and neuroinflammation response in LPS-induced depressed mice.

Materials and Methods

- Materials: raspberry ketone, Escherichia coli 055: B5-derived lipopolysaccharide.
- Methods: Behavioral tests (EPM, OFT, TST), Histological staining (Hematoxylin and Eosin staining, Alcian blue staining, Immunohistochemical staining), Elisa kits, 16S rRNA, qRT-PCR, WB, gas chromatography-mass spectrometry.

Mice Feeding Schedule

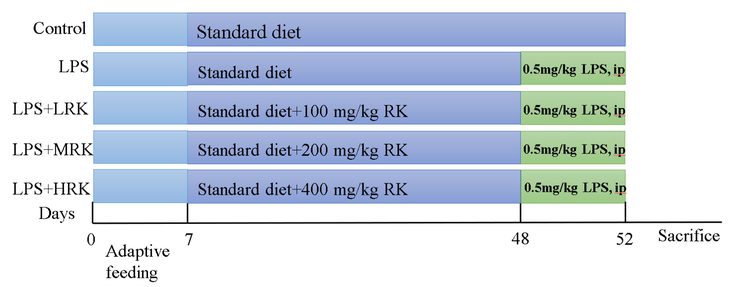


Fig. 1. Mice feeding schedule.

Results and Discussion

Cognitive and Behavioral Performance

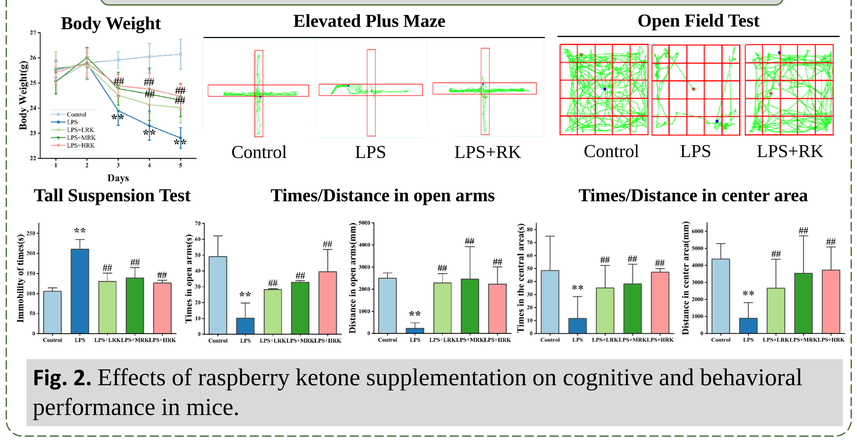


Fig. 2. Effects of raspberry ketone supplementation on cognitive and behavioral performance in mice.

Colon & Blood Inflammation

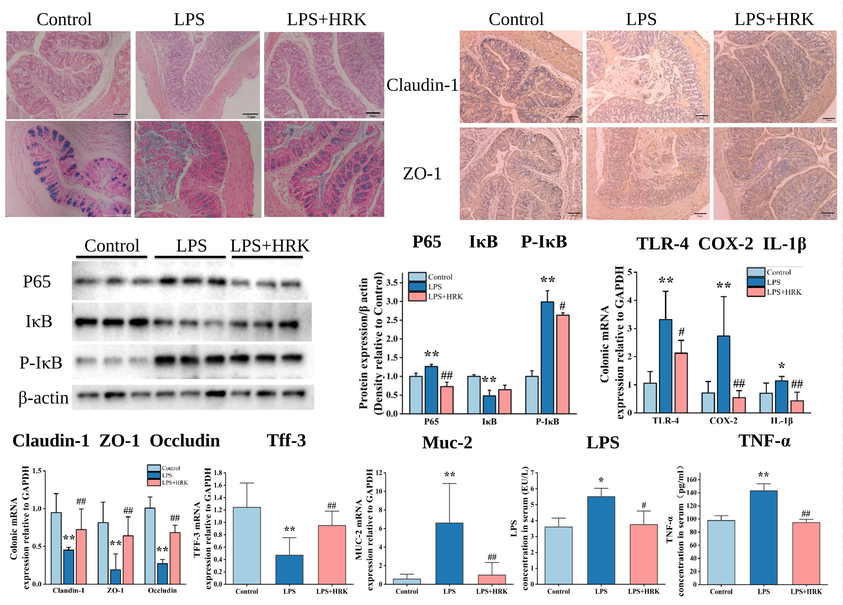


Fig. 3. Effect of supplementing raspberry ketone on colonic pathology and blood biochemical indicators in LPS-induced depressed mice.

Intestinal Microbiota & Metabolites

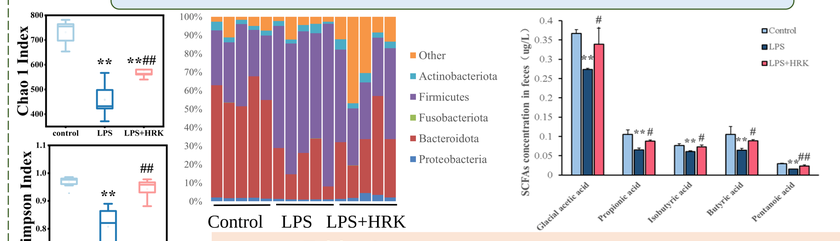


Table. 1. Relative abundance of bacterial genus (%)

Relative abundance (%)	Control	LPS	LPS+HRK
Muribaculaceae	43.82±7.04	10.95±6.39**	25.76±8.30#
Enterorhabdus	0.61±0.28	2.04±0.57**	0.67±0.38##
Akkermansia	7.85±2.72	0.51±0.10*	10.60±3.26##
Lachnospiraceae	13.86±5.81	1.49±0.85*	11.41±3.95#

Fig. 4. Effects of raspberry ketone supplementation on intestinal flora and its metabolites (SCFAs) in LPS-induced depressed mice.

Neuroinflammation

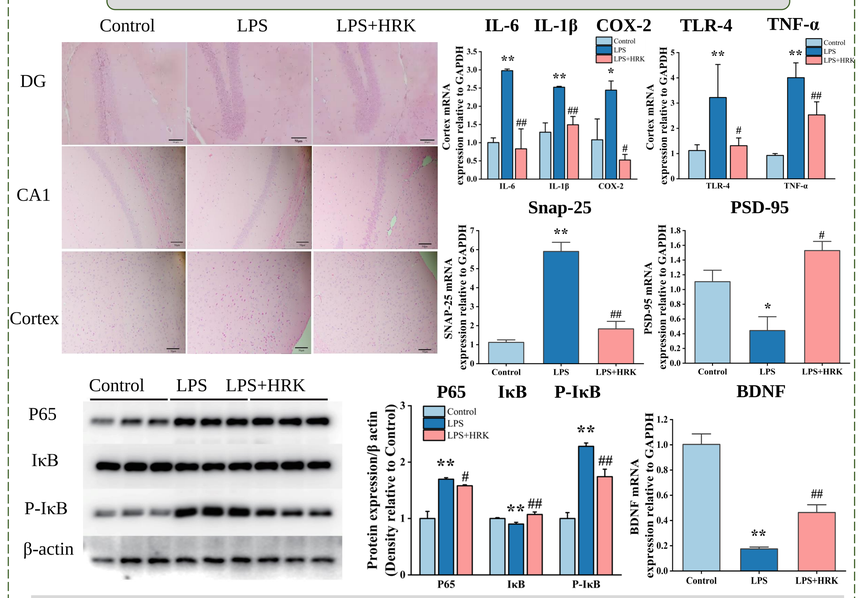
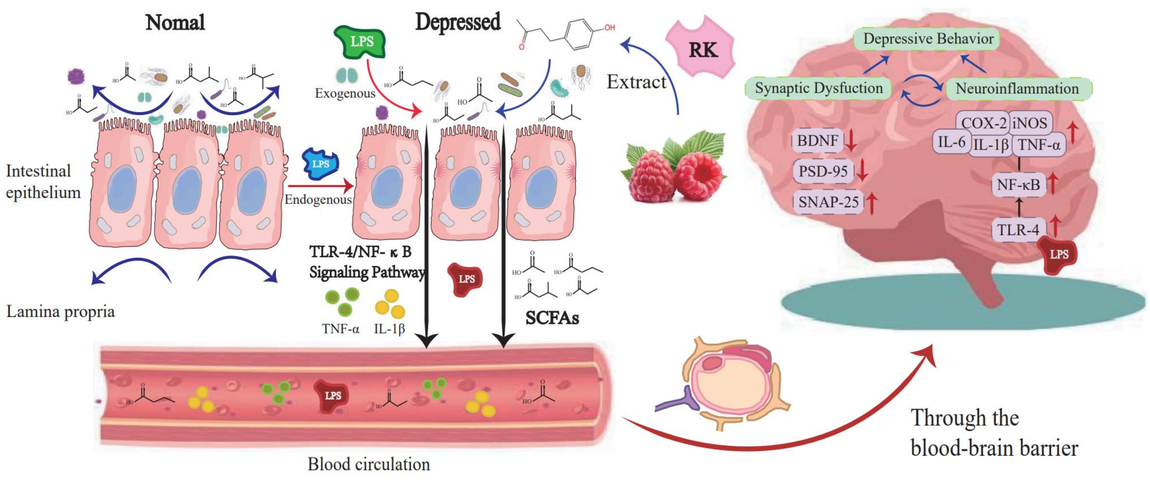


Fig. 5. Effects of raspberry ketone supplementation on synapse-associated proteins and brain inflammatory responses in LPS-induced depressed mice.

Conclusions

- RK suppressed the activation of the TLR-4/NF-κB signaling pathway in the colon and reduced the subsequent release of inflammatory factors by effectively repairing the structural integrity of colonic tissues.
- RK significantly reduced neuroinflammation and mitigated depressive symptoms by regulating the structural balance of gut microbiota, increasing the secretion of SCFAs, and modulating the TLR-4/NF-κB signaling pathway in the brain.

Graphical Abstract



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