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# Hyperoside inhibits lipopolysaccharide-induced inflammatory responses in microglial cells via p38 and NFκB pathways

Hui-Hui Fan[a,b], Lan-Bing Zhu[a], Ting Li[a], Hui Zhu[a], Ya-Nan Wang[b], Xiao-Li Ren[d], Bei-Lei Hu[a], Chen-Ping Huang[b], Jian-Hong Zhu[a,b,c,*], Xiong Zhang[a,b,**]

[a] Department of Geriatrics and Neurology, The Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China
[b] Department of Preventive Medicine, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China
[c] Key Laboratory of Watershed Science and Health of Zhejiang Province, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China
[d] Laboratory Animal Center, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China

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ABSTRACT

Hyperoside (quercetin-3-O-β-D-galactoside) is an active compound isolated from herbs. Neuroinflammation is a key mechanism involved in neurodegenerative disorders including Parkinson's disease. In this study, we aimed to investigate the potentiality of hyperoside in inhibiting microglia-mediated neuroinflammation. BV2 microglial cells were pretreated with hyperoside and stimulated with lipopolysaccharide (LPS). The results showed that hyperoside significantly inhibited LPS-induced production of nitric oxide and pro-inflammatory cytokines including IL-1β and TNF-α, as well as the expression of inducible nitric oxide synthase. Similar results were observed in primary microglial cells isolated from neonatal mice. Analyses in MAPK and NFκB signaling combined with specific inhibitors suggested that hyperoside attenuated the LPS-induced inflammatory responses via p38 and NFκB pathways. Furthermore, hyperoside suppressed reactive microglia-mediated neurotoxicity as evidenced by conditioned media culture, but had no direct impact on $MPP^+$-induced toxicity in SH-SY5Y neuroblastoma cells. Collectively, our data suggest that hyperoside may serve as a protective agent by alleviating microglia activation in disorders such as Parkinson's disease.

## 1. Introduction

Microglia are the key cells of the immune system in brain and participate in the modulation of neuroinflammation [1,2]. Neuroinflammation plays a vital role in initiation and progression of neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease, amyotrophic lateral sclerosis, and frontotemporal lobar dementia [3]. For instance, β-amyloid peptide-induced neurotoxicity in cortical and mesencephalic neurons is promoted by microglia activation via the production of reactive oxygen species (ROS) [4]. An excessive activation and proliferation of microglia has been found in postmortem brains of PD patients [5], and its released inflammatory mediators such as interleukin 1β (IL-1β), tumor necrosis factor alpha (TNF-α) and nitric oxide (NO) are involved in PD pathogenesis [6].

Herbal medicines, including *Acanthopanax senticosus* and *Hypericum perforatum*, have been reported to protect against PD [7]. Their extracts prevent the loss of dopaminergic neurons in the substantia nigra of chemical-induced PD rodents [8–11], potentially by inhibiting the inflammatory responses in the brain [10,11]. However, the molecular compound and the involved pathways, which is responsible for the neuroprotective effects of the herbal extracts, remains unclear. Hyperoside (quercetin3-O-β-D-galactoside), an active compound isolated from the above herbs, has been suggested in prevention or protection against several types of disorders in cellular or animal models. For examples, it protects against liver damage [12], cerebral ischemia [13], infection [14], tumor progression [15], and plays a role in analgesia [16]. Potential mechanisms include modulation of intracellular calcium signaling [17], inhibiting nuclear factor κB (NFκB) signaling [12], as well as suppression of ROS by inactivating glycogen synthase kinase 3β (GSK-3β) and the subsequent nuclear factor erythroid 2-related factor 2 and antioxidant responsive element (Nrf2-ARE) signaling [18].

Previous studies have shown an anti-inflammatory role of hyperoside in human endothelial cells and murine peritoneal macrophages [19–21]. However, it remains elusive whether hyperoside suppresses microglia-mediated neuroinflammation and thereby contributes to the protection of the herbs against PD. In this study we aimed to understand

* Correspondence to: J.-H. Zhu, Department of Preventive Medicine, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China.
** Correspondence to: X. Zhang, Department of Geriatrics and Neurology, The Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou, Zhejiang 325000, China.
*E-mail addresses:* jhzhu@wmu.edu.cn (J.-H. Zhu), zhangxiong98@gmail.com (X. Zhang).

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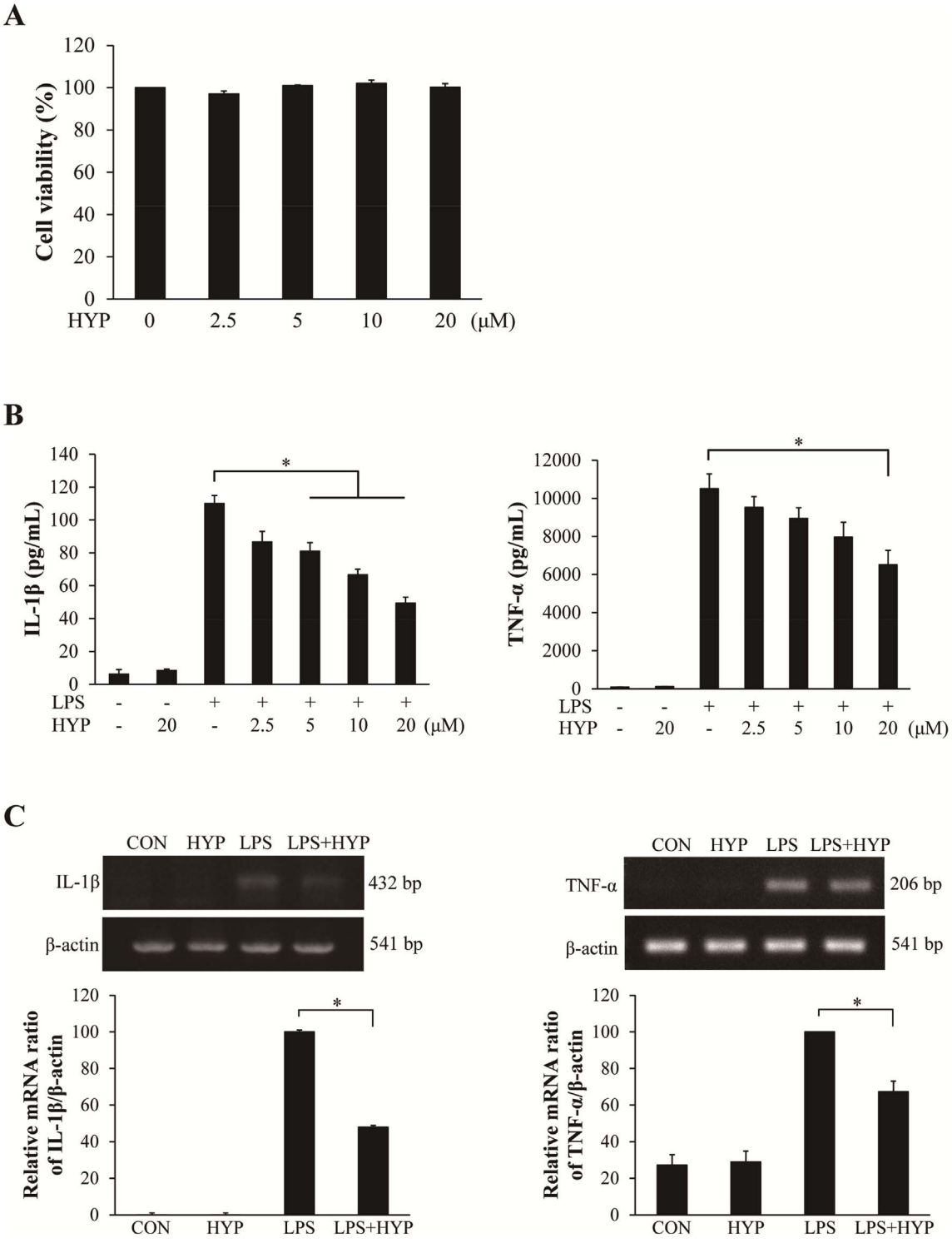


**Fig. 1.** Effect of hyperoside on the production of inflammatory cytokines in BV2 cells. (A) Effect of hyperoside on BV2 cell viability. Cells were treated with 0, 2.5, 5, 10 or 20 μM of hyperoside for 24 h. (B) Hyperoside attenuates LPS-induced production of IL-1β and TNF-α. Cells were pretreated with hyperoside at 0, 2.5, 5, 10 or 20 μM for 30 min before exposure to LPS (100 ng/mL) for 24 h. (C) Effect of hyperoside on mRNA expression of IL-1β and TNF-α. Cells were pretreated with 20 μM hyperoside for 30 min, then exposed to LPS (100 ng/mL) for 4 h. Values are mean ± SE from three independent experiments. CON, control; HYP, hyperoside. *$P < 0.05$ between the indicated groups.