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# Antidepressant-like effects of Schisandrin on lipopolysaccharide-induced mice : Gut microbiota, short chain fatty acid and TLR4/NF-κB signaling pathway

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ABSTRACT

Growing evidence shows that gut microbiota and neuroinflammatory responses play a critical role in the pathogenesis of depression. Our previous study demonstrated that schisandrin (SCH) could reduce proinflammatory factors of depressive mice. Therefore, our present study is to research the potential connection between gut microbial and anti-inflammatory effects of SCH on a depressive mouse model induced by lipopolysaccharide (LPS). We found that SCH pre-treatment could decrease the immobility time of forced swimming test (FST) and tail suspension test (TST). And the results of 16S rRNA demonstrated that SCH pre-administration attenuated the dysbiosis of gut microbiota of depressive mice, along with altered fecal short-chain fatty acids (SCFAs). Furthermore, SCH reduced the levels of proinflammatory factors of depressive mice and the expression of TLR4/NF-κB signaling pathway in the hippocampus. Overall, our study indicated that SCH might recover the gut microbial disorder of depressive mice through suppressing the expression of TLR4/NF-κB signaling pathway.

## 1. Introduction

Depression is a common disease that badly restricts the functions of studying, working and social contact, weakens the quality of life. WHO ranked depression as the third reason of burden of disease worldwide and predicted that the illness will rank first by 2030 [1] Depression is a cumulative functional impairment, and some symptoms are unique to a depressive patient, such as depressed mood, anhedonia, feelings of worthlessness or guilt and suicidal ideation or plan [2]. Indeed, depression is a chronic recurrent disorder so as to complete cure is difficult.

What has become increasingly clear is that inflammation might play a crucial role in a host of psychiatric illnesses [3]. To our knowledge, toll-like receptor 4 (TLR4), as one of the pathogen recognition receptors, has been demonstrated to play a key role in neuroinflammation [4]. TLR4 is a class of membrane-spanning proteins which result in recruitment of the adaptor molecule IκB kinase α (IKKα) followed by the nuclear factor κB (NF-κB) [5,6]. When faced with stress or injury, TLR4 would be activated and so as to induce the production of proinflammatory factors including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [7]. Recently, some meta-analyses have shown that inflammatory marker levels such as IL-6, IL-10 and TNF-α are increased in depressed patients compared with normal individuals [8,9]. These studies indicate that TLR4 may serve as one of antidepressant drug targets.

There are various microorganisms existing in a human gastrointestinal system and keeping their balance is significant for normal physiology and psychology [10,11]. The viewpoint that a dysfunctional

*Abbreviations:* SCH, Schisandrin; LPS, lipopolysaccharide; OFT, open field test; FST, forced swimming test; TST, tail suspension test; SCFAs, short-chain fatty acids; TLR4, toll-like receptor 4; IKKα, IκB kinase α; NF-κB, nuclear factor κB; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1β; IL-6, interleukin-6; BSA, bovine serum albumin; SABC, streptavidin biotin complex; DAB, diaminobenzidine; qRT-PCR, quantitative real-time-PCR; OUT, operational taxonomic unit

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