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# ANTI-INFLAMMATORY EFFECT OF SCHIZANDRISIDE ISOLATED FROM *Memecylon scutellatum* Lour IN LIPOPOLYSACCHARIDE-STIMULATED RAW 264.7 MURINE MACROPHAGES

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## ABSTRACT

Inflammation plays a key role in increasing the risk of chronic diseases such as diabetes, rheumatoid arthritis, and cancer. The *Memecylon* genus is known for its antioxidant, antidiabetic, anticancer, and antimicrobial properties. However, the anti-inflammatory activity of the *Memecylon scutellatum* Lour remains poorly understood. Therefore, this study aimed to explore the anti-inflammatory effects of schizandriside, a compound isolated from the leaves of *M. scutellatum* in lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophages. Nitric oxide (NO) production was measured using the Griess assay, TNF-α and IL-6 secretion were quantified through Elisa and iNOS, COX-2 protein level was analyzed by Western blotting. The results demonstrated that schizandriside reduced the production of NO, TNF-α and IL-6 production and strongly inhibited iNOS, COX-2 protein expression in LPS-stimulated RAW 264.7 cells. This data suggested that schizandriside has strong potential as an anti-inflammatory agent for treating inflammatory diseases.

**Keywords:** Anti-inflammation, *Memecylon scutellatum* Lour, schizandriside.

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## INTRODUCTION

Inflammation functions as a protective response in tissues to external agents, including physical or chemical factors, or the invasion of foreign substances like bacteria or viruses, that help regulate homeostasis in the human body (Dinarello, 2010; Olefsky et al., 2010). Inflammation occurs in two forms: acute and chronic inflammation. The immune system triggers and regulates acute inflammation. In contrast, chronic inflammation persists for extended periods and may lead to progressive cell damage (Scrivo et al., 2011). In inflammation, macrophages are key contributors to the inflammatory process. Activated macrophages exhibit increased production of various bioactive molecules and pro-inflammatory cytokines such as nitric oxide (NO), prostaglandin 2 (PGE2), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Valledor et al., 2010; Scheller et al., 2011). NO is generated by a family of P450 mono-oxygenase-like enzymes called nitric oxide synthases (NOS). Overproduction of NO can exacerbate the deleterious effects, such as septic shock and inflammatory diseases (Jung et al., 2014). Previous studies have highlighted the significant role of COX-2 in inflammation. In many inflammatory cells, including macrophages, COX-2 is induced by cytokines and stimulators like lipopolysaccharide (LPS), resulting in the abundant production of PGE2 at the inflammation site (Zeilhofer & Brune, 2006; Jachak, 2007; Murakami & Ohigashi, 2007).

The genus *Memecylon* has been harnessed for healing in Asia-Pacific countries (Jussieu & Usteri, 1791). It is employed to treat various conditions, including dermatological issues, gastrointestinal ailments, chickenpox, polyuria, excessive menstrual bleeding, dysentery, bacterial infections, diabetes, and inflammation (Kshirsagar & Singh, 2001; Prakasha et al., 2010; Tumkur Ramasetty et al., 2016). The *Memecylon scutellatum*, a species within the *Memecylon* genus, has been reported in diverse habitats, including tropical rainforests with varying rainfall levels, rocky mountain regions and regions with a temperature range (Bremer, 1981; Stone, 2012, 2014). This plant is abundant in tropical environments such as India, Cambodia, China, Southeast, Laos, Malaysia, Myanmar, Thailand, and Vietnam (Bremer, 1981; LaFrankie, 2010). *M. scutellatum* has also been utilized in traditional Chinese medial treatment for its properties in detoxification, decreasing swelling and treating sore, carbuncle and pyogenic infections (Tumkur Ramasetty et al., 2016). Tran et al. (2024) identified schizandiside as one of 15 isolated compounds from *M. scutellatum*. The study showed that schizandiside significantly inhibited NO production with $IC_{50}$ 88.92 ± 1.42 μM in LPS-stimulated RAW 264.7 cells.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed to manage various inflammatory disorders by targeting COX-2 and inhibiting prostaglandin synthesis. However, NSAIDs is use to associated with adverse side effects and a raised risk of heart attack (Ren et al., 2019). This has led to expanding interest in new bioactive molecules derived from biological sources as safer alternatives for long-term management of pain and inflammation. Therefore, this study aims to evaluate the anti-inflammatory impact of schizandiside, a compound isolated from the leaves of *M. scutellatum* in LPS-induced RAW 264.7 cells.

## MATERIALS AND METHODS

### Plant material and schizandriside isolation

The leaves of *M. scutellatum* were harvested at Phuc Yen, Vinh Phuc, Vietnam in September 2022 and identified by Nguyen The Cuong, Institute of Biology (IB), Vietnam Academy of Science and Technology (VAST A voucher specimen (USTH-MS01) was deposited at IB, VAST).

A total of 12.5 mg of schizandriside (Fig. 1) was isolated as shown in our previous study (Tran et al., 2024). The NMR and MS data of schizandriside were compared with those reported in the literature and found to

match. The purity of the compound was confirmed by HPLC analysis (purity > 95%, data not shown). After verifying the data, schizandriside was used to study the anti-inflammatory mechanism in LPS-stimulated RAW 264.7 cells. The structure of schizandriside was shown in Figure 1.

**Cell culture**

RAW 264.7 macrophages were purchased from American Type Culture Collection (ATCC, Virginia, USA) and grown in Dulbecco's Modified Essential Medium (DMEM, Gibco, USA) medium supplemented with 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin solution (Gibco, USA) in a humidified atmosphere containing 5% $CO_2$ at 37 $^oC$.

**Cell viability assay**

Cell viability was determined by a 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. Briefly, RAW 264.7 cells at a density of $10^5$ cells/well were seeded into 96-well plates and cultured in a 37 $^oC$, 5% $CO_2$ incubator for 24 hours. The cells were treated with samples at various concentrations. After 24 hours, the cells were incubated with 20 µL of MTT solution (5 mg/mL) for an additional 3-4 h. The formation of formazan was measured by reading absorbance at a wavelength of 570 nm in a spectrometer (Biotek, USA).

**Western blotting**

RAW 264.7 cells were cultured in six-well plates at a density of $10^5$ cells/well in an incubator at 37 $^oC$, 5% $CO_2$ for 24 hours. Cells were then treated with various concentrations of the tested samples for 30 min, followed by subsequent incubation with LPS at 1 µg/mL for 24 hours. The protein content was determined with the BSA assay kit (Thermo Fisher Scientific Inc.). The protein samples were electrophoresed through 10% or 12% SDS-PAGE and then transferred onto nitrocellulose membranes. The membrane was then blocked with 5% skim milk for 2 h, followed by incubating with the primary antibodies overnight at 4 $^oC$. After washing 3 times for 10 min with phosphate-buffered saline Tween-20 (PBST) and the membrane was incubated with secondary antibodies for 2 h at room temperature. After washing 3 times for 10 min with PBST buffer, the proteins were visualized using PierceTM enhanced chemiluminescent (ECL) Western blotting substrate solution (Thermo Fisher Scientific) and imaged using the Azure system c300.

**ELISA assay**

RAW 264.7 cells were cultured at a density of $10^5$ cells/well in a 6-well plate overnight. The cells were pre-incubated for 30 min with various concentrations of schizandriside and stimulated for 24 hours with 1 µg/mL LPS. The cell culture supernatants were harvested and centrifuged at 1,000 × g for 5 minutes to eliminate particulate matter. IL-6 and TNF-α levels were measured using an ELISA kit following the manufacturer's guidelines.

**Statistical analysis**

Experiments were conducted a minimum of three times, and all data are presented as mean ± SD. Statistical analysis was performed using t-tests and one-way ANOVAs, with $p < 0.05$ deemed statistically significant.

## RESULTS

### Schizandriside suppressed the protein expression level of iNOS and COX-2 in LPS-stimulated RAW 264.7 cells

In the context of infectious and proinflammatory factors, iNOS protein is strongly upregulated, leading to the production of NO at micromolar levels (Murakami & Ohigashi, 2007). Furthermore, NO plays a critical role in sustaining extended COX-2 gene expression (Perkins & Kniss, 1999). Su et al. identified schizandriside as a newly discovered compound extracted from the roots of *Capparis tenera* (Su et al., 2017). Moreover, Tran et al. reported the chemical composition of *M. scutellatum*, which includes memeloside (a newly identified compound), schizandriside (Fig. 1), and 13

other known compounds. Schizandriside has been shown to exhibit inhibitory effects on NO production in LPS-stimulated RAW 264.7 cells (Tran et al., 2024). In this study, we evaluated iNOS and COX-2 protein levels using Western blot analysis. We reassessed the viability of schizandriside at concentrations of 10–100 μM in RAW 264.7 cells over 24 hours. Our results confirmed that schizandriside did not exhibit cytotoxic effects at these concentrations (Supplemental data 1).

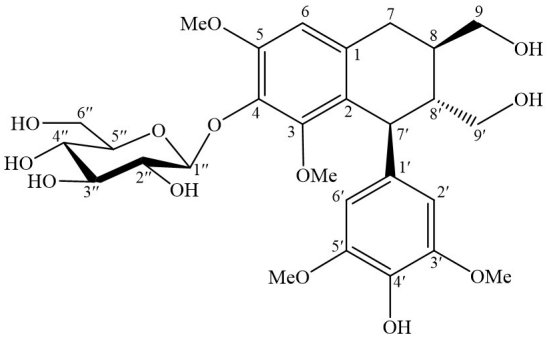


*Figure 1*. Structure of schizandriside

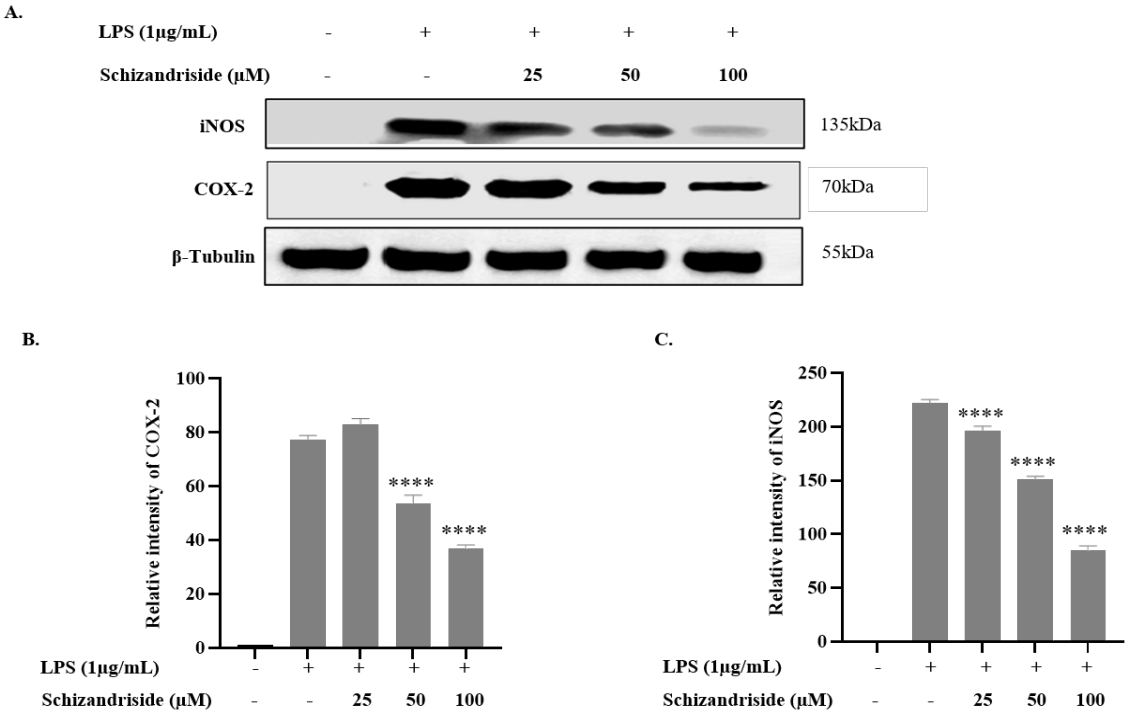


*Figure 2*. Impact of schizandriside on COX-2 and iNOS protein expression in LPS-stimulated RAW 264.7 cells. Cells were exposed to LPS (1 μg/mL) for 30 minutes, followed by treatment with schizandriside for 24 hours. Western blot analysis anti-COX-2, anti-iNOS, and anti-β-tubulin antibodies (A). Blot quantification was conducted using ImageJ software, normalized to the respective β-tubulin band intensity, and presented as the relative expression levels of COX-2 and iNOS (B, C) compared to LPS group. Data are expressed as mean ± SD (n = 3). ****indicates significant difference ($p < 0.0001$)

Furthermore, the data revealed that schizandriside significantly reduced the expression of iNOS and COX-2 proteins within 24 h ($p < 0.0001$) (Fig. 2A). Notably, at a concentration of 100 μM, schizandriside suppressed iNOS and COX-2 protein levels by 2.5-fold and 2.1-fold, respectively, compared to the LPS-stimulated group ($p < 0.0001$) (Figs. 2B, C). These results indicate that schizandriside possessed anti-inflammatory properties by suppressing iNOS and COX-2 protein expression, highlighting its capability

as an effective therapeutic candidate for managing inflammatory conditions.

**Schizandriside inhibited TNF-α and IL-6 secretion in LPS-stimulated murine macrophage RAW 264.7 cells**

Activation of macrophages by LPS through toll-like receptors (TLRs) initiates a series of downstream signalling pathways, leading to increased production of inflammatory mediators such as NO, iNOS, and COX-2, along with pro-inflammatory cytokines like TNF-α and IL-6 (Fang et al., 2004). Figure 3 presents the TNF-α and IL-6 levels determined by the ELISA assay. The results show that schizandriside, at a concentration of 100 μM, significantly reduced 3.5-fold and 2.2-fold the concentration of TNF-α and IL-6 secretion, respectively. Taken together, the data indicate that schizandriside effectively suppressed the release of inflammatory mediators in LPS-stimulated RAW 264.7 cells.

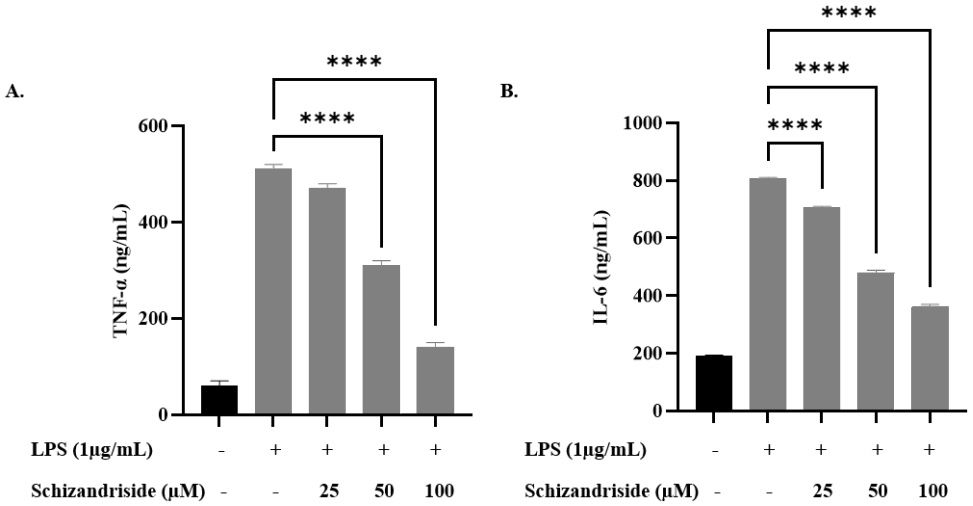


*Figure 3.* Effects of schizandriside on the TNF-α and IL-6 secretion in LPS - murine macrophage RAW 264.7 cells. Cells were pre-treated with different concentration of schizandriside (25, 50 and 100 μM) in 30 min, then stimulated with LPS (1 μg/mL) for 24 h. (A, B) TNF-α and IL-6 level in the supernatant were measured by ELISA. Each bar shows mean ± SD of three independent experiments performed in triplicate (****$p < 0.0001$, compared with LPS)

## DISCUSSION

This study focused on assessing the anti-inflammatory effects of schizandriside, a compound isolated from *M. scutellatum.* The findings revealed that schizandriside effectively suppressed LPS-induced inflammation in RAW 264.7 murine macrophages by decreasing iNOS and COX-2 protein expression and suppressing the TNF-α and IL-6 production.

The *Memecylon* genus has been intensively studied for its chemical constituents and bioactivities, including anti-inflammatory and other therapeutic effects. Puratchikody & Nagalakshmi (2007) demonstrated that the alcohol-derived extract from *M. umbellatum* Burm leaves produced a significant wound-healing response in comparison to the reference medication nitrofurazone ointment (0.2% w/w). The ethanol-based extract of *M. umbellatum* exhibited dose-dependent anti-inflammatory activity in acute and sub-acute rat models, specifically through carrageenan-induced rat paw edema and cotton pellet-induced granuloma (Joshi et al., 2009). Moreover, the ethyl acetate extract from the leaves of *Memecylon edule* was shown to significantly stimulate interleukin -10 production and inhibit the response in both the ethylphenylpropiolate (EPP)-induced mouse

ear edema model and the writhing test in mice (Nualkaew et al., 2009). A methanol extract of *Memecylon talbotianum* exhibited the strong inhibition of xanthine oxidase ($IC_{50}$ of 12.56 mg/mL) and 15-lipoxygenase ($IC_{50}$ of 1 mg/mL) related to gout and inflammatory diseases (Tumkur Ramasetty et al., 2014). Furthermore, Joshi et al. reported that the ethanol extract of *M. umbellatum* exhibited antispasmodic activity in isolated rat ileum preparations. Phytochemical analysis of this plant has identified alkaloids, triterpenes, flavonoids, and saponins in the chloroform and ethyl acetate seed extracts (Elavazhagan et al., 2010). Moreover, extracts of *Memecylon terminale* were found to contain notable concentrations of alkaloids and flavonoids, along with intermediate levels of steroids, tannins, and phenols (Padukone, 2013). Recently, Tran et al. identified chemical constituents isolated from *M. scutellatum* and screened their anti-inflammatory activity in LPS-stimulated RAW 264.7 murine macrophages (Tran et al., 2024; Phuong, 2023). Our study is the first to further investigate the anti-inflammatory effects of a pure compound extracted from this plant, highlighting its potential therapeutic applications.

Macrophages, found throughout the human body, are crucial in inflammatory responses by offering immediate protection against pathogens before leukocyte migration occurs. Stimulation with LPS triggers the release of inflammatory regulators, including interleukins, TNF-α, iNOS, and COX-2 (Alexander & Rietschel, 2001). LPS is known to drive the release of pro-inflammatory cytokines via the TLR4-NF-κB signalling pathway (Chanput et al., 2010). Among these cytokines, TNF-α has been shown to further activate NF-κB and AP-1 transcription factors, which are involved in various inflammatory pathways in macrophages (Liu et al., 2000). Moreover, mounting evidence suggests that MAPKs play significant roles in inflammatory processes by inducing phosphorylation of key signalling pathways, including NF-κB, AP-1, and STATs (Feng et al., 2010). LPS-induced activation of MAPKs controls inflammatory molecules, such as iNOS and COX-2, by modulating NF-κB activation (Jung et al., 2014). In our study, schizandriside demonstrated anti-inflammatory activity by inhibiting iNOS and COX-2 protein levels and reducing the production of TNF-α and IL-6. However, further studies exploring its effects on signaling pathways, such as NF-κB and MAPKs, would provide valuable insights into its precise mechanism of action and warranty to explore these mechanisms in greater detail.

## CONCLUSION

This study underscores the anti-inflammatory effects of schizandriside, a compound shown to significantly inhibit the production of key inflammatory enzymes and mediators, including iNOS, COX-2, IL-6, and TNF-α, at the protein level in LPS-stimulated RAW 264.7 macrophages. By targeting these crucial markers of inflammation, schizandriside appears to effectively modulate inflammatory responses at both the cellular and molecular levels. Given its efficacy in reducing these pro-inflammatory markers, schizandriside demonstrates potential as a novel therapeutic agent for managing a broad range of inflammatory conditions. This compound could initiate the development process of more effective and safer anti-inflammatory therapies.

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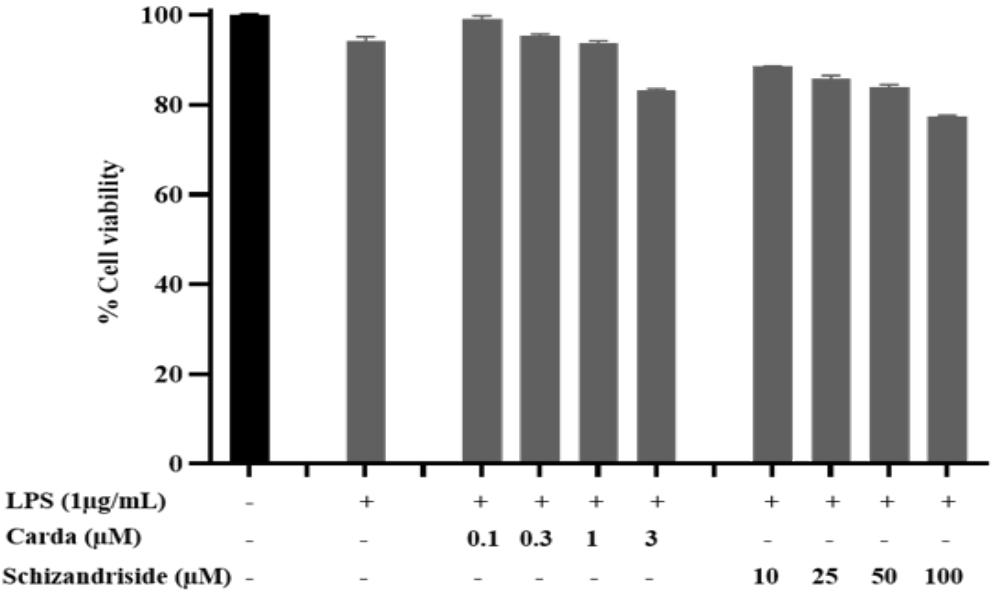


*Supplementary data 1.* Cell viability of schizandriside in RAW 264.7 cells stimulated by LPS. After treatment with schizandriside (10−100 μM) for 30 min, cells were stimulated for 24 hours with LPS (1 μg/ml). MTT assay was used to determine cell viability. Cardamonin was used as a positive control. Data represent means ± SD of three independent experiments