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TRA-017, A Derivative of Tranilast, Protects against Hepatic Inflammation Induced by Lipopolysaccharide Administration

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ABSTRACT

Background: Liver is considered as the main detoxification organ of human body. Hepatic inflammation is a key mechanism under many liver diseases. The present study suggested that TRA-017, a tranilast derivative, protective effects against hepatic inflammation in animal model. Therefore, TRA-017 is potential chemical or drugs treating liver diseases such as hepatitis and cirrhosis.

Methods: The study was performed on *Swiss albino* mice brought from Pasteur Institute in Ho Chi Minh City, Vietnam. Mice were randomly divided into 4 groups: Veh, TRA-17, LPS and Treatment. To investigate the effects of TRA-017 on hepatic inflammation, we injected mice with LPS (2.5 mg/kg) every day for 5 consecutive days to induce hepatic inflammation model. TRA-017 (20 mg/kg, s.c.) was administered 1h prior to every LPS treatment. After that, we evaluated TRA-017-induced amelioration effects *via* investigating biochemical markers (AST, ALT, cytokines and XOD activity levels) oxidative stress markers (ROS) and H and E histopathological characteristics.

Result: Our results suggested that LPS significantly increase AST, ALT, cytokines (IL-6, TNF-α, IL-1β and IFN-γ) and XOD activity levels ($p<0.01$ vs. corresponding Veh) and that pre-treament with TRA-017 significantly attenuated LPS-induced increase of AST, ALT, cytokines (IL-6, TNF-α, IL-1β and IFN-γ) and XOD activity levels ($p<0.01$ vs. corresponding LPS group). LPS also remarkably increased ROS formation ($p<0.01$ vs. corresponding Veh). Pre-treatment with TRA-017 significantly attenuated LPS-induced oxidative stress burden in the liver ($p<0.01$ vs. corresponding LPS group). Administration with LPS induced remarkably changes on histopathology of mouse liver. Pre-treatment with TRA-017 showed counteractive effects against LPS-induced histopathological changes. In conclusion, treatment with TRA-017 attenuated LPS-induced hepatic inflammation.

Key words: Hepatic inflammation, Inflammatory cytokines, Lipopolysaccharide, Reactive oxygen species, Tranilast derivative, Xanthine oxidase.

INTRODUCTION

Liver diseases are a major global health concern, causing about two million deaths yearly (Devarbhavi *et al*., 2023). While these diseases have various causes, hepatic inflammation is a key mechanism that dictates disease severity in conditions like hepatitis and cirrhosis (Zhou *et al*., 2022). This inflammation can result from viral infections, various poisons (industrial, plant, or fungal), or sterile stressors exacerbated by metabolic changes, leading to acute or chronic disease (Robinson *et al*., 2025). Although inflammation's initial role is protective, excessive inflammation can cause irreversible damage and worsen liver conditions. Inflammation is present at all stages of liver disease and dampening pro-inflammatory pathways while boosting anti-inflammatory ones can slow or halt progression. Conversely, untreated inflammation can advance to fibrosis, cirrhosis and eventually hepatocellular carcinoma (Li *et al*., 2022; Zhou *et al*., 2022).

Bacterial lipopolysaccharides (LPS) are critical cofactors in liver injury pathogenesis (Su, 2002). LPS triggers Toll-like receptor 4 (TLR4) signaling. This leads to endotoxemia, where LPS from bacteria enters the bloodstream and activates TLR4 (Pimentel-Nunes *et al*., 2010; Soares *et al*., 2010). Because LPS/TLR4 signaling drives the clinical symptoms of endotoxemia, administering LPS to rodents is a reliable way to experimentally model endotoxemia, septic shock and hepatic inflammation (Hamesch *et al*., 2015).

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Tranilast is an medication that possesses anti-allergic property. It's currently approved in Japan and the Republic of Korea to treat asthma and keloid and hypertrophic scars. The drug works by several mechanisms: it slows cell proliferation, blocks the release of inflammatory substances from mast cells and inhibits collagen production, growth factor signaling and the transformation of fibroblasts into myofibroblasts (Chuang *et al*., 2023). As having strong bioactive potential, tranilast have been used as the foundational molecule for creating new chemical medicines (Ismail *et al*., 2020; Phan *et al*., 2024).

In this study, we investigated the administration of LPS on liver inflammatory changes and tested the effects of TRA-017, a tranilast derivative, on LPS-induced hepatotoxicity.

MATERIALS AND METHODS

Animals

Swiss albino mice were purchased from Pasteur Institute in Ho Chi Minh City, Vietnam. The male mice used for the experiments were 8-week-old. The average body weight of the mice was about 24 g. All mice were fed *ad libitum* in an air-conditioned room at 23±1°C and 55±5% relative humidity with a standard 12 h light and 12 h dark cycle. All experiments were accepted by The Animal Research Ethics Committee of Ton Duc Thang University (TDTU-AEC). Decision No. 08/HĐTVĐĐ. All experiments were carried out at Ton Duc Thang University.

Synthesis

TRA-017 was synthesized according to the previously described protocol (Nguyen *et al*., 2025). Briefly, 3 mmol of anthranilic acid derivative (1a-i), 3.1 mmol of Meldrum's acid (2) and 6 mL of toluene were added into a 50 mL RB flasks. The reaction mixture was refluxed at 110°C and surveilled every 30 minutes by thin layer chromatography ultilzing ethanol-dichloromethane (2:1) and hexane-ethyl acetate (1:1) solvent systems. After the reaction was completed, the mixture was filtered under reduced pressure and washed with 10 mL of cold toluene during the filtration process. After that, the crude product was dissolved in 10 mL of saturated $NaHCO_3$ solution and slowly added 10% HCl while stirring until pH of the solution equaled 2. The precipitate was filtered and dried at 60°C to obtain the pure product.

A mixture of 3 mmol of derivatives 3a-i, 3.1 mmol of 3,4,5-trimethoxybenzaldehyde (4), 0.5 mL of 10% piperidine solution in toluene was added to a 50 mL round-bottom flask. The reaction mixture was refluxed at 110°C and monitored by TLC using dichloromethane-hexane (1:1) and dichloromethane-ethanol-acetic acid (20:1:0.1) solvent system. The obtained mixture was then concentrated in vacuum to remove toluene. The crude product was dissolved in 10 mL of saturated $NaHCO_3$ solution, followed by adding 10% HCl dropwise until pH = 2. The resulting precipitate was then filtered and dried at 60°C to obtain pure product (Fig 1).

Experimental design

Mice were acclimated for 7 days, then were randomly separated into 4 groups, with each experimental group containing six animals.

- **Veh:** Administration with saline.
- **TRA-017:** Administration with saline + TRA-017.
- **LPS:** Administration with LPS (2.5 mg/kg/day).
- **Treatment:** Administration with LPS + TRA-017.

For the LPS administration, mice were injected subcutaneously (s.c.) with LPS (2.5 mg/kg) every day for 5 consecutive days. Saline solution (0.9% NaCl) were chosen as control. TRA-017 (20 mg/kg, s.c.) was dissolved in saline and injected 1 h prior to every LPS treatment. 2 h after the final LPS dose, mice were sacrificed by cervical dislocation technique. Serum and liver tissue was collected for further biological and pathological investigation.

Evaluation of alanine transaminase (ALT) and aspartate aminotransferase (AST), TNF-α, IL-6, IL-1β and IFN-γ levels

Mouse serum ALT and AST levels were investigated using the Erba ALT test kit (Cat No: BLT00080) and the Erba AST

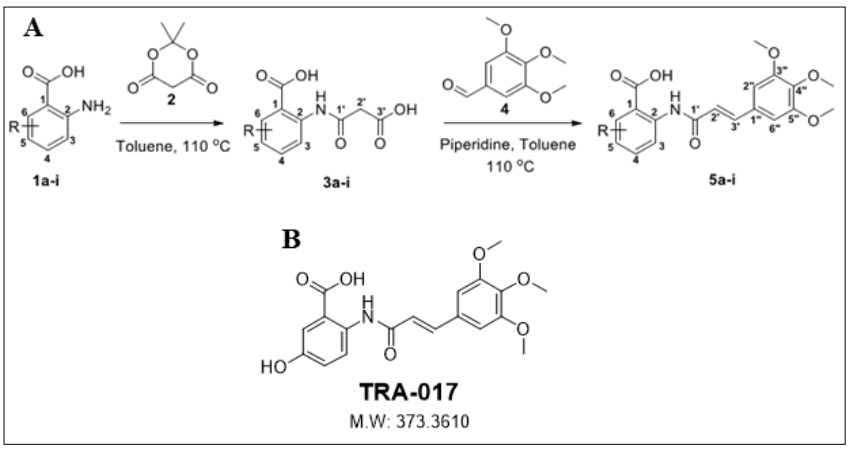


Fig 1: (A) Synthetic scheme of N- (3,4,5-trimethoxycinnamoyl) anthranilic acid derivatives (5a-i). (B) TRA-017 molecular structure.

test kit (Cat No: BLT00051). Results are calculated automatically by Semi Automated Biochemistry Analyzer. Cytokines (IL-6, TNF-α, IL-1β and IFN-γ) were investigated using enzyme-linked immunosorbent assay kit (ELISA) (Elabscience) according to manufacturer protocol.

Evaluation of reactive oxygen species (ROS) levels

The ROS formation in the liver was assessed by measuring the conversion from 22 ,72 -dichlorofluorescin diacetate (DCFH-DA) to dichlorofluorescin (DCF) (Pham *et al*., 2025). Liver homogenates were added to a tube containing 2 mL of PBS with 10 nmol of DCFH-DA, dissolved in methanol. The mixture was incubated at 37°C for 3 h and then fluorescence was measured at 488 nm excitation and 525 nm emission. DCF was used as a standard.

Evaluation of xanthine oxidase activity levels

The levels of serum XOD activity were measured using commercial kits (Cat. NO. E-BC-K805-M, Elabscience).

Histopathological analysis

The liver was carefully removed from the animals of all groups and fixed in buffered formal saline for further histological analysis, following haematoxylin-eosin (H/E) staining protocol. The tissues were then dehydrated with graded alcohol, cleared in xylene before embedding in paraffin wax (melting point 56.0°C). Serial sections of 5 µm thickness were cut in rotary microtome and then passed through xylene followed by absolute alcohol and water. The sections were stained with haematoxylin, dehydrated with graded alcohol, counter-stained with eosin, cleared in xylene and mounted in mounting solution (Sigma). The slides were left to air dry for 24 h before observation under the microscope (Thermo EVOS FL Fluorescence Microscope).

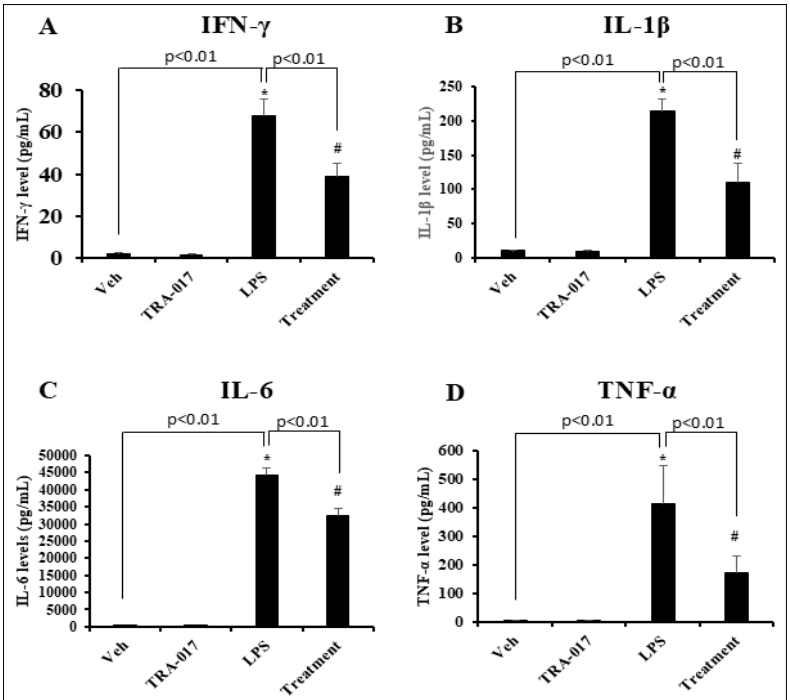
Statistical analysis

All data were presented in terms of MEAN ± SEM (n = 6). Data were analyzed with IBM SPSS version 22.0. One-way analysis of variance (ANOVA) was used to compare groups. Tukey's (HSD) post-hoc tests was performed to determine which specific groups differed. Results with a p-value less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Effects of TRA-017 on the changes of cytokines (IL-6, TNF-α, IL-1β and IFN-γ) induced by LPS

To investigate the effects of TRA-017 on LPS induced inflammatory reaction, we evaluated the changes of serum cytokines levels of mice. As shown in Fig 2, administration with LPS significantly induced increase in IFN-γ, IL-1β, IL-6 and TNF-α levels (IFN-γ, p<0.01 vs. corresponding Veh; IL-1β, p<0.01 vs. corresponding Veh; IL-6, p<0.01 vs. corresponding Veh; TNF-α, p<0.01 vs. corresponding Veh) and pre-treament with TRA-017 attenuated the increase of these cytokine levels induced by LPS (IFN-γ, p<0.01 vs.



Each value is presented as Mean ± S.E.M. of 6 mice. *p<0.01 vs. corresponding veh group, #p<0.01 vs corresponding LPS group (one-way ANOVA followed by Tukey's HSD pair-wise comparisons).

Fig 2: Effects of TRA-017 on the changes of IFN-γ (A), IL-1β (B), IL-6 (C) and TNF-α (D) levels induced by LPS.

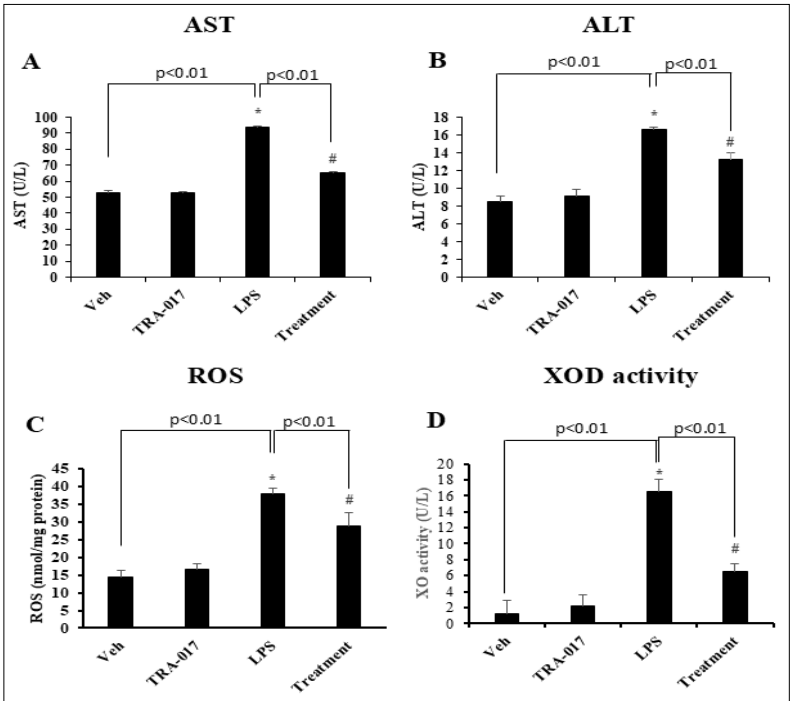
corresponding LPS group; IL-1β, p<0.01 vs. corresponding LPS group; IL-6, p<0.01 vs. corresponding LPS group; TNF-α, p<0.01 vs. corresponding LPS group). LPS-induced TLR4 signaling activates nuclear factor-κB (NF-κB), which then moves to the nucleus to trigger the rapid production and release of inflammatory signaling molecules or cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β from immune cells like neutrophils, macrophages and Kupffer cells (Gali *et al*., 2024; Luedde and Schwabe, 2011; Robinson *et al*., 2025; Zhong *et al*., 2019). Bacterial infection could induce the production of antiviral cytokines such as type I IFNs, IL-1β and IL-6, which directly slow down viral replication (Nie *et al*., 2025; Varughese *et al*., 2019). However, excessive up-regulation of cytokines could result in cytokine storm which cause liver tissue dysfunctions and damages. Here, TRA-017 exerted a counteractive effect against LPS-induced pro-inflammatory cytokines up-regulation. Therefore, our results suggested that TRA-017 attenuate LPS-induced hepatic inflammation *via* a cellular signaling that suppress TLR4 signaling pathway.

Effects of TRA-017 on the changes of AST, ALT levels induced by LPS

LPS induced hepatotoxicity has been reported to be associated with increased AST and ALT levels (Sayed *et al*., 2021). Serum ALT and AST increase feasibly due to hepatocytic degeneration (Mai *et al*., 2019). As depicted in Fig 3A and Fig 3B, administration with LPS significantly increased AST and ALT levels (AST, p<0.01 vs. corresponding Veh; ALT, p<0.01 vs. corresponding Veh) and pre-treatment with TRA-017 attenuated the increase of AST and ALT levels induced by LPS (AST, p<0.01 vs. corresponding LPS group; ALT, p<0.01 vs. corresponding LPS group). Therefore, in here, we demonstrated that TRA-017 attenuated hepatocytic degeneration.

Effects of TRA-017 on the changes of ROS formation induced by LPS

Previous researches have demonstrated that LPS induced liver injury, increases in serum ALT and AST levels in line with increases in oxidative burdens (Mai *et al*., 2019; Zhang *et al*., 2019). In this study, we investigated ROS formation after injecting LPS to clarify the role of ROS in the effects of TRA-017 on LPS-induced hepatotoxicity. As shown in Fig 3C, administration with LPS induced significant increase of ROS formation (p<0.01 vs. corresponding Veh). Pre-treatment with TRA-017 attenuated ROS formation after injection with LPS (p<0.01 vs. corresponding LPS group). Thus, our results suggested that TRA-017 attenuated liver injury *via* reducing ROS formation.



Each value is presented as Mean ± S.E.M. of 6 mice. *p<0.01 vs. corresponding Veh group, #p<0.01 vs corresponding LPS group (one-way ANOVA followed by Tukey's HSD pair-wise comparisons).

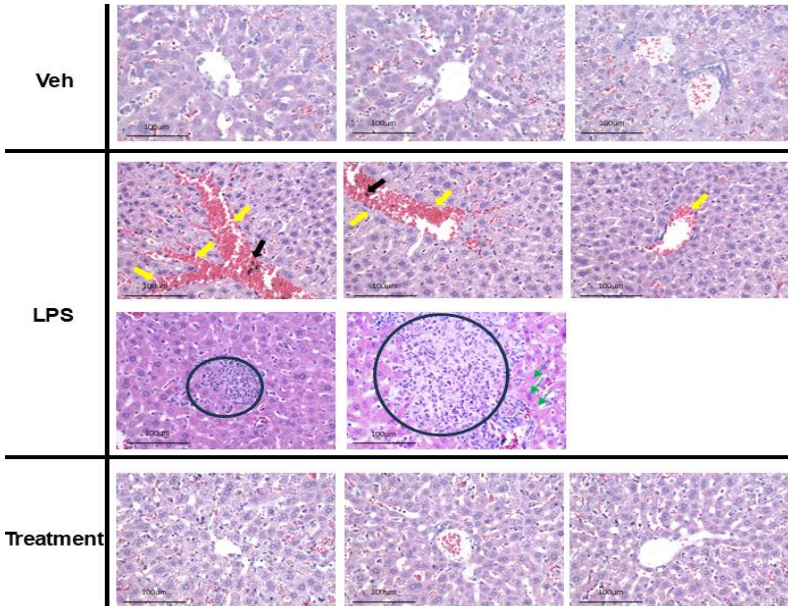
Fig 3: Effects of TRA-017 on the changes of AST (A), ALT (B), reactive oxygen species (C) and xanthine oxidase activities (D) levels induced by LPS.

Effects of TRA-017 on the changes of serum XOD activity level induced by LPS

Since acute hepatotoxicity induced by LPS has been reported to be associated with the increase of serum XOD activity and xanthine oxidase inhibitor such as febuxostat has been reported to have protective effects on hepatotoxicity (Abdelrahman and Abdelmageed, 2024; Nishikawa *et al*., 2020). Here, we evaluated the effects of TRA-017 on the changes of serum XOD activity after administration with LPS. As shown in Fig 3D, LPS injection significantly increase XOD activity in the serum of mice and pre-treatment with TRA-017 attenuated LPS-induced XOD activity increase. These results are consistent with the study of Abooali *et al*. (2014) that stimulation with TLR4 ligand such as LPS could lead to XOD activity increase (Abooali *et al*., 2014). Nishikawa *et al*. (2020) also reported that inhibiting XOD activity could reduce apoptosis, inflammation and oxidative stress induced by LPS administration (Nishikawa *et al*., 2020). For that reason, it is plausible that TRA-017 could protect–mouse liver *via* down-regulation of XOD activity. In this study, we did not measure the *in vitro* inhibitory effect of TRA-017 on XOD activity. Therefore, we do not exclude the hypothesis that TRA-017 could exert its liver protective effects as an xanthine oxidase inhibitor as febuxostat did (Nishikawa *et al*., 2020). However, since TRA-017 has been demonstrated as an TGF-β inhibitor in our previous study (Nguyen *et al*., 2025), in here, we will focus on discussing the mechanism of TRA-017 as an TGF-β inhibitor. XOD is an enzyme critical to the breakdown of purines, conversion of hypoxanthine to xanthine and then to uric acid. XOD can activate pro-inflammatory signals (Abooali *et al*., 2014). In addition, XO elevation correlated with pathophysiological development induced by excessive ROS formation (Chen *et al*., 2017; Chung and Yu, 2000; Yoshida *et al*., 2020). Many studies have indicated the relationship between XOD and TGF-β signaling pathway. XOD derived ROS increased TGF-β1 production. ROS can activate TGF-β1 that activates Smads and eventually induce cellular toxicity (Alruhaimi *et al*., 2024). Increases of macrophage XOD activity could also induces macrophage adventitial infiltration and generates ROS-induced TGF-β1 secretion (Cicalese *et al*., 2019). Therefore, the inhibitory effects of TRA-017 on TGF-β signaling might be related to the attenuation of XOD elevation after LPS administration. More experiments have to be conducted to clarify the exact mechanism under the interaction between XOD and TGF-β mediated by TRA-017.

Effects of TRA-017 on histopathological alterations in liver tissues

As biochemical resutls indicated that TRA-017 protects mouse liver from hepatic inflammation. We confirmed these findings by conducting liver histopathological study. In Fig 4,



Normal features were observed in the liver of the Veh group. The central veins are enlarged in the liver of the LPS group with perivenular necrosis (green arrow), hemorrhage, dilatation and congestion of central vein (CV) (yellow arrow), foamy macrophage infiltrate (circle) and infiltration of inflammatory cells (black arrow). TRA-017 pre-treatment protected against the histopathological changes on the liver of the treament group. Hepatic morphology of mice in the treament group was similar to that of Veh group. Scale bar: 100 μm.

Fig 4: Haematoxylin and eosin stained hepatic tissue sections from different groups of mice at high magnification (×400).

there was no pathological changes observed in the absence of LPS. Administration with LPS induced histopathological changes including perivenular necrosis (green arrow), hemorrhage, dilatation and congestion of central vein (CV) (yellow arrow), foamy macrophage infiltrate (circle) and infiltration of inflammatory cells (black arrow) in mice. Pre-treatment with TRA-017 significantly attenuated inflammatory histopathological pattern in mouse liver sections. One of the mechanism of action of tranilast involves the down-regulation of chemical mediators from mast cells/monocytes/macrophages (Rogosnitzky *et al*., 2012). In a healthy liver, Kupffer cells (KCs), endothelial cells (ECs) and hepatic stellate cells (HSCs) are responsible for monitoring and maintaining the tissue. When the liver is injured, damage signals activate KCs, causing them to release inflammatory chemokines and cytokines. Notably, KCs produce TGF-β, which activates HSCs. This inflammatory environment-driven by various chemokines and then attracts different types of immune cells, including neutrophils, monocytes, T helper cells and natural killer T cells. The sustained activation of HSCs by these immune signals is what ultimately causes hepatic inflammation (Cao *et al*., 2021). Accumulating researches indicated that tranilast inhibit TGF-β-mediated signaling and TGF-β secretion (Chakrabarti *et al*., 2009; Platten *et al*., 2001). The previous study also demonstrasted the TGF-β inhibitor effects of TRA-017 (Nguyen *et al*., 2025). Therefore, TRA-017 could inhibit KCs-induced TGF-β secretion and rescue mouse liver from histopathological changes due to hepatic inflammation caused by LPS administration.

CONCLUSION

Taken together, we proposed a mechanism of action of TRA-017 against hepatic inflammation induced by LPS administration as follows:

- TRA-017 inhibits TGF-β and attenuate the activation of inflammatory cytokines through blocking the release of chemical mediators from mast cells/monocytes/macrophages.
- TRA-017 binds to TGF-β and reduced oxidative stress damages induced by LPS administration in the liver tissue, at least partly, *via* down-regulation of xanthine oxidase activity levels.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the The Animal Research Ethics Committee of Ton Duc Thang University (TDTU-AEC).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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