Journal of
Food and Pharmaceutical Sciences

Original article

Figs Fruit Act as Adequate Anti-Inflammatory Agents against Injured Intestines and Memory Impairment of Acute Hypoxia-Induced Rats

Zhafira Naurasarah[1], Andreanyta Meliala[2*], Irwan Supriyanto[3], Yogik Onky Silvana Wijaya[4], Paramita Narwidina[5], Claire Emmanuela Selamat[1], and Rangga Kaila Priandika[1]

[1]International Undergraduate Program in School Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Department of Physiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta , Indonesia.
[3]Department of Psychiatry, FM-PHN, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta , Indonesia.
[4] Departement of Biochemistry, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta , Indonesia
[5]Clinical Nutrition Research Group, Yogyakarta , Indonesia

*Corresponding Author: Andreanyta Meliala | Email: a_meliala@ugm.ac.id

Received: 3 April 2025; Revised: 11 May 2025; Accepted: 26 June 2025; Published: 30 September 2025

Abstract: Figs (*Ficus carica*) possess potential antioxidant, anti-inflammatory, and antidepressant properties. Acute hypoxia (AH) may induce inflammation, increase reactive oxygen species (ROS) production. Nonetheless, limited research has examined the benefits of figs fruit administration in mitigating the impact of AH on mucosal integrity disruption and memory impairment through the gut-brain axis. Therefore, the present study aims to investigate the protective effects of Figs puree (FCP) in rats with AH (10% O_2, 90% N_2, 4h) - induced intestinal injury. This study used a pretest-posttest-control group design. Thirty male Sprague-Dawley rats were divided into 6 groups: NC (negative control, untreated), PC (positive control), VC (vehicle), and FC1, FC2, and FC3 (FC1, 2, and 4 mL of FCP/200g). Histopathological analysis of the ileum, the levels of nitric oxide (NO), and tumor necrosis factor-α (TNF-α) were measured in plasma, and the novel object recognition (NORT) was used as a behavior test. The ileal tissues of FC1, FC2, and FC3 groups showed fewer inflammatory cells and less tissue damage than the NC group. The FCP exhibited non-dose-dependent anti-inflammation activity in TNF-α, NO, IL-6 levels, and histopathological analysis. Rats receiving all doses of FCP spent more time exploring the new object in NORT, suggesting the benefits of the phenolic compounds in FCP as a functional food in alleviating the inflammatory and oxidative impacts of AH-induced intestinal injury.

Keywords: *Ficus carica*; nitric oxide; tumor necrosis factor; intestinal injury

1. INTRODUCTION

Hypoxia and inflammation demonstrate an interdependent relationship; numerous recent studies [1]–[3] indicate that inflammation may be induced by hypoxia, or that inflammation can manifest during hypoxia, contributing to various human disorders. Several inflammatory states and diseases, including chronic arthritis and inflammatory bowel disease, are characterized by the presence of destructive tissue hypoxia. Reduced SpO_2 in acute hypoxia (AH) conditions might hamper cognitive processing for motor execution and diminish neuronal activity in executive functions and motor inhibition. Despite HIF regulating an effective hypoxia response, the HIF cascade synchronizes with nuclear factor-kappa B (NF-kB) [4]. The transcription factor NFκB controls inflammation and regulates immune responses along with tissue homeostasis. Following translocation, NF-kb will promote the transcription of inflammatory genes, such as tumor necrosis factor-ɑ (TNF-ɑ), interleukin-1b (IL-1b), interleukin 6 (IL-6), and mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2)[5]. All of these stated conditions, whether induced by inflammation or hypoxia, saturate into one comprehensive reciprocating condition, hypoxia and inflammation represent an imminent threat of cellular apoptosis[6].

Inflammatory cytokine production due to its ability to initiate a prolonged cascade. TNF-α amplifies lipid signal transduction mediators, including prostaglandins and platelet-activating factors, alongside pro-inflammatory cytokines. Furthermore, TNF-ɑ initiates an autocrine loop that generates IFN-beta at low and persistent levels, resulting in a positive feedback mechanism that contributes to prolonged inflammation. The biological effects of this inflammatory state are linked to heightened cell mortality and tissue necrosis, diminished parenchyma, and augmented tissue stroma [7]. Homeostatic NO is expressed at picomolar levels, making it adequate for remedial physiological processes, whereas exaggerated synthesis of NO mandated by iNOS following hypoxia and inflammation at micromolar levels exhibits pro-inflammatory and devastating properties to neighboring cells[8].

Inflammatory situations are frequently marked by tissue hypoxia or the stability of hypoxia-dependent transcription factors, such as hypoxia-inducible factor (HIF). Intestinal inflammation in inflammatory bowel disease is marked by significant hypoxia at the mucosal surface and concurrent stabilization of HIF. The stabilization of HIF1A during intestinal inflammation may result from alterations in the ratio of metabolic supply to demand, particularly for oxygen, so inducing "inflammatory hypoxia." The gut is a highly regenerative tissue that undergoes complete renewal every 5 to 6 days. The intestinal epithelial cells are essential for digesting, hormone and mucin release, and nutritional absorption. The epithelial cells are regulated by a complex signaling cascade (Notch, BMP, Wnt/β-catenin) that sustains the proliferation and differentiation of epithelial progenitors and the self-renewal ability of intestinal epithelial stem cells. Moreover, cellular oxygen dynamics are essential for preserving intestinal homeostasis [9]. Furthermore, intestinal hypoxia, or oxygen deficiency in the intestines, can significantly result in memory impairment, particularly via the gut-brain axis [10]. Hypoxia disrupts the gut flora, subsequently impacting brain function, particularly memory.

Hypoxia exposure can have detrimental consequences in the hippocampus-prefrontal cortex pathways, which are essential for memory processing [11]. The hippocampus is responsible for memory storage and retrieval; acute hypoxia can cause hippocampal injury and disrupt synaptic plasticity between the hippocampus and prefrontal cortex, leading to cognitive impairment. It is hypothesized that a hypoxic environment adversely affects memory. In animal models, particularly rats, the novel object recognition test (NORT) is utilized to evaluate memory impairment, wherein rats are allowed to explore two similar items for a specified duration [12], [13]. After a delay, the animals are provided with two objects for exploration, one identical to that in the initial trial and the other a novel object [14]

Figs are free of sodium, fat, and cholesterol. Meanwhile, these fruits are rich in beneficial fiber and antioxidant compounds [15]. Several compounds in the fig fruit have anti-inflammatory agents, including apigenin, luteolin, quercetin, hesperetin, and cyanidin. The major antioxidant compounds found in fresh figs include phenolic acids, flavonoids, and carotenoids. Flavonoids exhibit their antioxidant activity via scavenging free radicals, regulating the damaging effects of ROS, chelating metal ions, and inhibiting lipid peroxidation reactions and oxidant enzyme activity in the body while augmenting the beneficial activity of antioxidant enzymes [16]

Acute hypoxia-induced intestinal injury is yet to be thoroughly understood. Accordingly, this study was designed (1) to investigate the role of NO and TNF-α in plasma as an indicator of oxidative stress dan anti-inflammatory index in the pathogenesis of AH-induced intestinal injury in rats, and (2) to evaluate the protective effect of FCP in rats with AH-induced intestinal injury and memory impairment.

2. MATERIALS AND METHODS

2.1. Processing Ficus carica into puree (FCP)

This research utilized whole fig fruits (*Ficus carica* cv Jordan) cultivated in Bandung, West Java. The *Ficus carica* was prepared by cleaning, slicing, crushing, and blending the entire fresh fig fruit, encompassing the peel, pulp, and seeds. Following a 20-minute homogenization at 8033 rpm using an Armfield L4R homogenizer, the resultant FCP was placed in an airtight plastic cup and refrigerated at 2°C in the absence of light. The FCP was prepared every three days to guarantee freshness.

2.2. Experimental design

2.2.1. Animal

There were 30 adult male Sprague-Dawley rats (180-200 g) used as test subjects in the research. Every 2 Sprague-Dawley rats were kept in a standard rat cage (40 x 30 x 20 cm) with a 12-12 hour light-dark cycle, free access to water, and 20 mg of Rat Bio given twice daily. The temperature and humidity of the environment were maintained at 22- 24 °C and 40-60%, respectively. Before the trial, the rats were given 7 days of adaptation, and during the trial, utmost care was enforced to minimize the suffering of the rats. This research activities was carried out two months and cundeucted in the Animal House, Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada after getting the etical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada - Dr. Sardjito General Hospital (approval number: KE/FK/0363/EC/2023, date: 6 March 2023).

2.2.2. Grouping of animals

The rats were divided into 6 groups (n = 5): NC (negative control, untreated), PC (positive control), VC (vehicle, treated with 1 ml corn oil/200g), and FC1, FC2, and FC3 (FC 1; 2; and 4 mL of FCP/200g), respectively. The treatment was given orally through force-feeding every morning at 11.00 a.m., with body weight measurements conducted weekly. After 4 weeks of treatment, blood samples were collected for pre-test measurement, and acute hypoxia (AH) was induced the day after to prevent other variabilities. AH was induced in all groups except NC. The initial number of rats in each group was the same to ensure that the sample size remained within the calculated range according to Federer's formula, if mortality occurs. The formula is as follows: t (r - 1) > 15, t = number of treatments, and r = number of replications (Rukmana *et al*. 2022); 5 (r - 1) > 15; and r > 4.

2.2.3. Acute hypoxia (AH) induction

Rats subjected to AH were situated under an exogenous and normobaric hypoxia stimulation (pressure 760 mmHg, O_2 10%, and N_2 90%) for 4h on a single day AH was induced using a modified version of the procedure published by [17], which involved placing the rats in a 25 cm x 15 cm x 15 cm chamber.

Figure 1. Experimental setting of AH induction

2.3. Biochemical analysis

2.3.1 Plasma collection

After drawing 1 mL of blood from a retro-orbital vein using a hematocrit tube, samples were collected in EDTA-coated vacutainer tubes (BD Biosciences, Franklin Lakes, NJ, USA). The tubes were then centrifuged at 4000 rpm for 15 minutes at 4 ^{o}C to obtain the plasma using Sigma 3K-30.

2.3.2 TNF-α and NO measurement

Plasma TNF-a levels were measured using EliKine Rat TNF-a enzyme-linked immunosorbent assay (ELISA) Kit 96 wells, while CheKine™ Nitric Oxide (NO) Assay Kit 96T (Read OD at 540 NM) was used to determine plasma NO levels. The measurements were performed according to the protocol of each kit.

2.4. Histopathologic analysis

A segment of distal ileum was excised from each rat, preserved in 10% buffered formalin, embedded in paraffin blocks, sectioned at 5 μm, and stained with hematoxylin and eosin (HE) for histological assessment. Histopathological alterations in intestinal architecture were evaluated by a pathologist in a blinded manner and classified as follows: grade 0: no injury (normal histology), grade 1: mild separation of lamina propria (slight inflammatory cell infiltration in the lamina propria), grade 2: moderate separation, grade 3: severe separation and/or edema in the submucosa, grade 4: transmural injury (lots of inflammatory cell infiltration in the lamina propria, some infiltrating the epithelial crypts, some epithelium is degenerating, epithelial thickness is reduced) [18].

2.5. Novel Object Recognition Test (NORT)

NORT was conducted as previously performed [19]. The acclimatization session: the rats autonomously navigated the enclosure for 5 minutes. The training process involved exposing the rats to two similar objects for 5 minutes, during which the duration of their interactions with the objects was documented. The rats were deemed to be exploring when they exhibited behaviours indicative of sniffing and active observation. During the testing session, the rats were exposed to one familiar object and one novel object positioned at opposite corners of the enclosure for 5 minutes, during which the time spent interacting with each object was documented. The testing apparatus was sanitized with alcohol before the subsequent animal trial.

$$\%\ \text{Time} = \frac{a}{a+b} \times 100\%$$

a: duration for rats interacting with the new object (s)
b: duration for rats interacting with the old object (s)

2.6. Statistical analysis

Statistical analysis was conducted utilizing SPSS 20.0 (IBM Corporation, Armonk, NY, USA), with data presented as mean ± SD, where SD denotes standard deviation. Statistical differences across groups were assessed using a one-way analysis of variance. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1. Effect of AH and administration of FCP on body weight

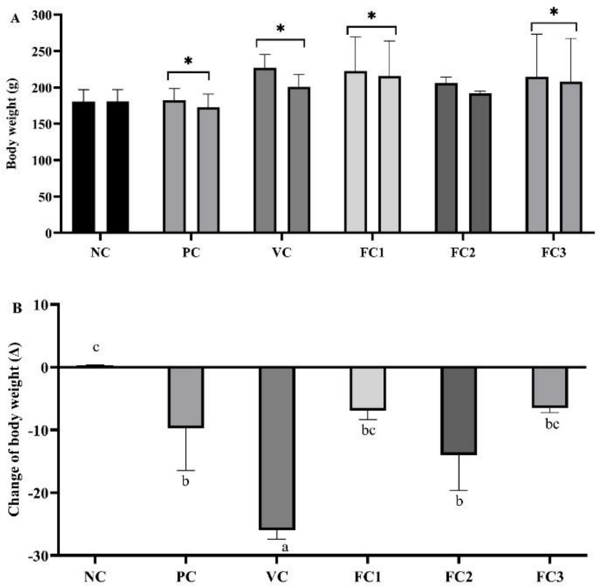

Figure 2. (A). Initial (1st bar) and final (2nd bar) body weight of control and administered rats groups, the sign (*) indicates a significant difference ($p<0.05$, paired sample T-Test) between the initial and final body weight, (B) change of body weight (B), different letters indicate a significant difference between groups ($p<0.5$, one way ANOVA followed by Duncan Multiple Range Test).

When comparing pre- and post-AH exposure, significant weight reduction was observed in the PC, VC, FC1, and FC3 groups (Figure 2.A). All groups subjected to AH had considerable weight reduction, except the FC1 and FC3 groups, which did not differ significantly from the NC group. The VC group exhibited considerable weight loss relative to the other groups (Figure 2.B). The findings of this study align with previous studies, which demonstrated significant weight reduction in the group exposed to hypoxia. However, when the rats were given FC before AH induction, they did not experience significant weight loss. Weight reduction is the body's innate process of enhancing heart function and energy metabolism to counteract cardiac enlargement [20]. FC contains antioxidants and the amino acid tryptophan, which helps counteract the effects of stress and helps maintain a steady body weight [21].

3.2. Protective effect of FCP consumption on inflammatory markers

Plasma TNF-α levels pre and post the intervention exhibited no differences across all groups; however, post intevention of AH exposure, plasma TNF-α levels in the FC1 group were considerably lower ($p<0.05$) than in the PC group and did not differ significantly ($p>0.05$) from the NC, VC, and FC2 groups. This suggests that low and medium doses of FCP possess about equivalent potential in diminishing plasma TNF-α levels. In the assessment of plasma NO levels, the PC group exhibited significantly ($p<0.05$) elevated levels compared to the FC1 group, while the FCP intervention at medium and high dosages showed markedly reduced plasma NO levels relative to the PC group. The study group receiving medium and high dosages of FCP intervention successfully aligned their IL-6 levels with those of the NC group following AH induction (Figure 3).

Ficus carica includes phenolic acids, flavonoids, and carotenoids [22]. The total phenolic and flavonoid constituents in the FCP were 0.0143-0.0150% and 0.2190-0.2201%, respectively [23]. The antioxidant activity of Ficus carica was evaluated using two assays: DPPH and FRAP[24]. The maximum antioxidant value was seen in fresh figs, measuring 21.3 ± 1.2 mM TE/100g for the DPPH assay and 55.5 ± 1.0 mM TE/100g for the FRAP assay. Moreover, an experimental study aimed at quantifying the protective effects of Ficus carica against neuroinflammation in a transgenic mouse model revealed a reduction in pro-inflammatory cytokines, including TNF-α, IL-1β B, IL-2, IL-3, IL-4, IL-6, IL-9, and IL-10. The downregulation of these pro-inflammatory mediators and direct inflammatory chemicals demonstrated the preventive function of Ficus carica against inflammation [25]. Consequently, the Ficus carica possesses significant potential in mitigating oxidative stress and inflammation induced by hypoxia.

Hypoxia is a condition characterized by inadequate oxygen levels in tissues. Cells acclimatize to hypoxia by activating several genes, mostly governed by the production of hypoxia-inducible factors (HIF) and Nuclear Factor kappaβ (NF$\kappa\beta$), which comprises p50 and p60 subunits and remain in an inactive form in the cytoplasm. It can sustain its dormant state owing to the nuclear factor kappa light polypeptide gene enhancer in B cells alpha (I$\kappa\beta$α). In hypoxia, the beta subunit of the IκB kinase complex (IKKb) phosphorylates the inhibitor IκBa, leading to the release of NFκB, which then translocates to the nucleus. After translocation, NFκB will enhance the transcription of inflammatory genes, including TNF-α and HIF. Prolyl Hydroxylases (PHD) and Factors Inhibiting HIF-α (FIH) impede the function of IKKβ, hence obstructing inflammation[4]. TNF-α and additional proinflammatory substances can activate NFκβ pathways in other cells, leading to the expression of more proinflammatory mediators, including TNF-α, IL-1β, IL-6, inducible NOS (iNOS), and intercellular adhesion molecule (ICAM)[26]. iNOS is one of the three isoforms of nitric oxide synthase (NOS) responsible for nitric oxide (NO) production. The remaining two nitric oxide synthases are neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS). The conditions that prompt the synthesis of these isoforms vary, with nNOS and eNOS constitutively produced in cells [27]. iNOS is synthesized in excessive quantities in response to an increase in cytokines, leading to cellular fatigue at the local site of activity. Inflammation regulates the expression of iNOS in immune-competent cells, including macrophages, T cells, and neutrophils. The intrinsic ability of immune-competent cells to express iNOS and subsequently create NO is triggered by standard inflammatory mediators, whether exogenous or endogenous, including IL-1, TNF-α, and IFN-ɣ [28]. In inflammatory conditions, extraordinary quantities of nitric oxide in the form of free radicals are released as part of the immune response, after the production of inducible nitric oxide synthase (iNOS). Multiple routes illustrate how Ficus carica exerts its antioxidative and anti-inflammatory effects. Quercetin, a phenolic component present in FCP, demonstrates anti-inflammatory actions via the NFκβ pathway [5], [29]. Quercetin diminishes the synthesis of TNF-α and C-reactive protein by obstructing the translocation of NFκβ into the nucleus (Shin et al., 2020). Inhibiting TNF-α expression will subsequently reduce the generation of iNOS and NO [30]. Moreover, the bioactive components of Ficus carica have demonstrated inhibitory effects on lipoxygenase enzymes, cyclooxygenase (COX) enzymes, xanthine oxidase, and various other inflammatory mediators. Previous investigations of these compounds yielded empirical evidence of their function in free radical scavenging. The previously described routes validate the ability of Ficus carica figs and their bioactive components to downregulate, diminish, or mitigate the expression of TNF-α levels and excessive NO generation. Antioxidants in Ficus carica may mitigate inflammation and oxidative stress, reducing the overexpression of iNOS and the resultant overproduction of NO. The scavenging of free radicals may diminish the synthesis of superoxides, including ROS and other reactive nitrogen species (RONS). Minimizing inflammation may also hinder the synergy between HIF-1, IL-1b, and IFN-Ɣ, which stimulates nitric oxide synthesis. Ultimately, the excessive synthesis of NO may be reduced, and its harmful cascade leading to the formation of peroxynitrite and N_2O_3 may be further mitigated. This study's results indicate that the consumption of Ficus carica figs may substantially reduce plasma NO levels during inflammation and oxidative stress induced by hypoxia; however, a considerable dosage is necessary to achieve this effect. Moreover, Ficus carica obstructs the translocation of NFκβ pathways, hence diminishing the synthesis of TNF-α in plasma. The findings indicated that the FC1 group receiving a dosage of 1mL/5mL effectively safeguards the body from increased TNF-α production induced by AH. The FC1 group had a modest increase in TNF-α levels relative to the other. These data indicate that the consumption of Ficus carica containing phenolic compounds is advantageous for alleviating AH. Additional research is necessary to assess the acceptability of Ficus carica intake at different dosages.

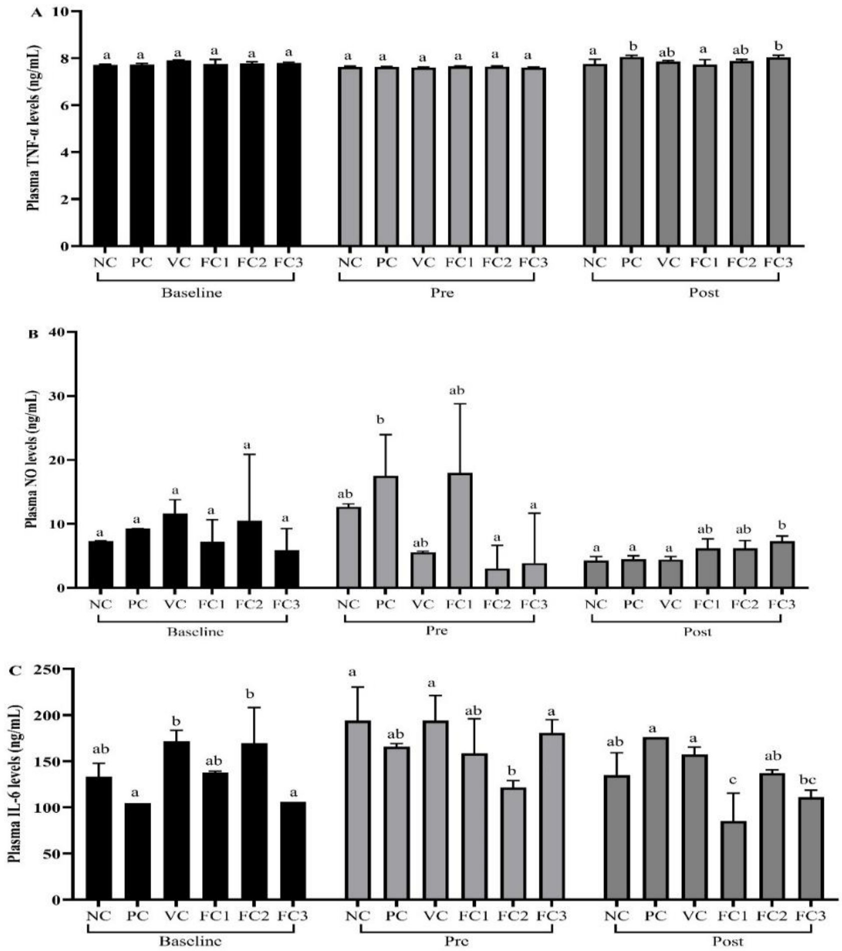

Figure 3. Plasma inflammatory markers of experimental groups before and after acute hypoxia induction. Values are given as mean±SD, and different letters on each bar indicate significant differences ($p<0.05$). Statistical analysis by one-way ANOVA followed by the Duncan Multiple Range Test.

3.3. Effect of FCP on NORT

Figure 4 indicates that treatment with FCP at 1 ml/200g markedly enhanced the duration of NORT by rats compared to the PC and VC groups, consistent with the discrimination index parameters; however, it did not differ significantly from the FC2 and FC3 groups, despite the total exploration time across all groups being statistically similar. Additional research on NORT has demonstrated that two cerebral regions, the perirhinal cortex and the hippocampus, influence the outcomes[19]. The perirhinal cortex detects objects and transmits signals to the hippocampus for memory consolidation. This study assessed whether AH exposure can harm the hippocampus, disrupt hippocampal-prefrontal cortex synaptic plasticity, and subsequently result in cognitive impairment [31]. This results from less activation in the left hemisphere of the dorsolateral prefrontal cortex under hypoxic conditions relative to normoxic conditions, leading to compromised memory ability[32]. Ficus carica includes quercetin, which significantly influences memory deficiencies; moderate dosages might enhance weak memory, while greater doses may promote improved learning capabilities and alter behavior [33].

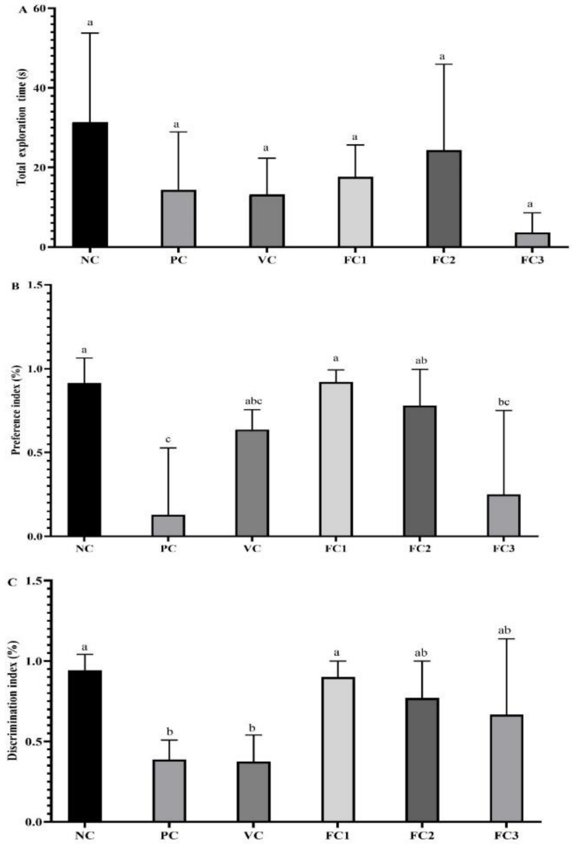

Figure 4. The NOR test was performed to assess the effect of Ficus carica administration on the learning and memory processes of acute hypoxia-induced rats. (A) Total exploration time, (B) Preference index, (C) Discrimination index. Values are given as mean±SD, and different letters on each bar indicate significant differences (p<0.05). Statistical analysis by one-way ANOVA followed by the Duncan Multiple Range Test.

3.4. Effect of FCP on intestinal histology

HE staining was performed to detect inflammatory response and abnormal morphology in the intestines (Figure 5) after AH exposure. In the NC group, HE staining of ileal tissue did not reveal inflammatory cells in the lamina propria (Figure 5A). In the FC1 group, observations indicated minimal infiltration in the lamina propria. In contrast, ileal assessments in the PC, VC, and FC2 (Figure 5B, 5C,and 5D) groups revealed significant inflammatory cell infiltration in the lamina propria (LM) extending to the intestinal lumen, with some infiltrating the epithelial crypts and causing degeneration of certain epithelial cells (EP). In the ileal histology observations of group FC3 (Figure 5E), significant inflammatory cell infiltration was noted in the lamina propria, with some cells infiltrating the epithelial crypts. Additionally, there was degeneration of the epithelium and a reduction in epithelial thickness. Elevated concentrations of inflammatory cytokines induce systemic diseases, particularly affecting the intestines and brain[34]. Polysaccharide components in Ficus carica demonstrate antioxidant and immune-enhancing properties; they protect goblet cells, elevate the expression of tight junction protein claudin-1, and inhibit the production of cytokines such as TNF-α and IL-1β. Furthermore, they significantly modify the gut microbiome by increasing the abundance of Bacteroides and Coprososud while reducing the prevalence of Escherichia and Clostridium at the genus level. Ficus carica may serve as a non-pharmacological technique for alleviating inflammatory bowel illness, with assured microbial health significantly contributing to these advantageous benefits[35]. In this investigation, the administration of high doses of FCP did not demonstrate any advantageous effects. The excessive consumption of Ficus carica likely induces a pendulum effect, whereby excessively high doses might revert the entire system to its origin, triggering intestinal inflammation due to the pro-oxidant effects of antioxidants [36].

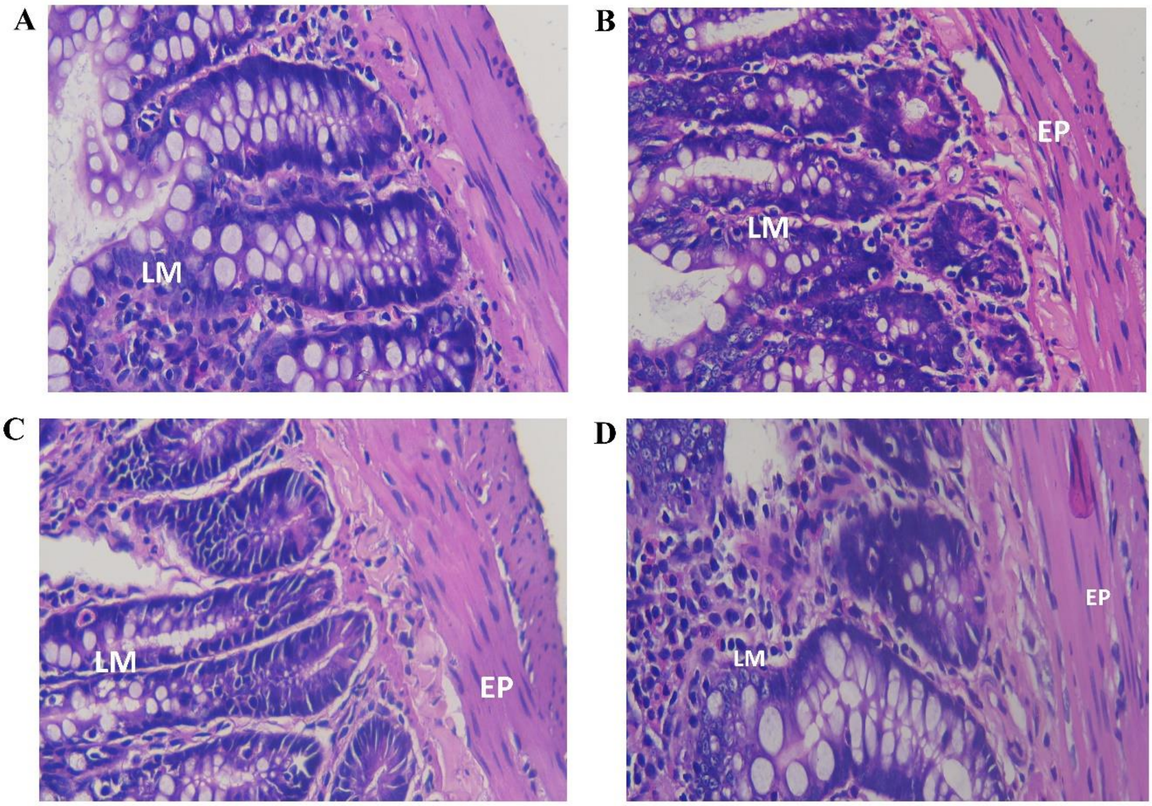

Figure 5. Microscopic characteristics of rat ileum. A Grade 1 injury: normal histological findings (Group NC). B, Grade 2 injury: little inflammatory cell infiltration in the lamina propria (Group FC1). C, Grade 3 injury: Significant infiltration of inflammatory cells in the lamina propria (LM) towards the intestinal lumen, with some penetrating the epithelial crypts, and certain epithelial cells (EP) exhibiting degeneration (Group PC, VC, and FC2). D, Grade 4 injury: Numerous inflammatory cell infiltrations in the lamina propria, with some penetrating the epithelial crypts; degeneration of some epithelium and reduced epithelial thickness (Group FC3). (Hematoxylin and eosin x400)

4. CONCLUSION

The FCP exhibits dose-independent anti-inflammatory effects, as evidenced by assessments of TNF-α, NO, and IL-6 levels, histological analysis, and behavioral tests, wherein rat groups with a modest dose of FCP demonstrated heightened exploration of novel items in the NORT. This shows the advantageous effects of phenolic compounds in FCP as a non-pharmacological approach to mitigate the repercussions of inflammatory and oxidative damage to the intestines induced by AH.

Funding: This research was funded by Dana Masyarakat grant 2023 (Grant Number: 692/UN1/FKKMK/PPKE/PT/2023) provided by the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

Acknowledgments: We are grateful for technical support (equipment and raw materials) belonging to the Department of Physiology and Laboratory technicians in the Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Conflicts of interest: The authors declare no conflict of interest.

Reference

[1] K. Bartels, A. Grenz, and H. K. Eltzschig, "Hypoxia and inflammation are two sides of the same coin," *Proc Natl Acad Sci U S A.*, vol. 110, no. 46, pp. 18351–18352, 2013.

[2] C. Zhang *et al.*, "Mechanism and Basis of Traditional Chinese Medicine Against Obesity: Prevention and Treatment Strategies," vol. 12, p. 615895, 2021, doi: 10.3389/fphar.2021.615895.

[3] D. Kiers *et al.*, "The influence of hypoxia on platelet function and plasmatic coagulation during systemic inflammation in humans in vivo," *Platelets*, vol. 30, no. 7, pp. 927–930, 2019, doi: 10.1080/09537104.2018.1557617.

[4] H. K. Eltzschig and P. Carmeliet, "Hypoxia and inflammation," *N Engl J Med*, vol. 364, no. 7, pp. 656–65, 2011.

[5] L. Rezagholizadeh, M. Aghamohammadian, M. Oloumi, S. Banaei, M. Mazani, and M. Ojarudi, "Inhibitory effects of Ficus carica and Olea europaea on pro-inflammatory cytokines: A review," *Iran. J. Basic Med. Sci*, vol. 25, no. 3, pp. 268–275, 2022, doi: 10.22038/IJBMS.2022.60954.13494.

[6] K. Bartels, A. Grenz, and H. K. Eltzschig, "Hypoxia and inflammation are two sides of the same coin," *Proc Natl Acad Sci*, 2013.

[7] V. A. R. Fernandes, R. O. R. F. Netto, F. Lovaglio, Belozo, and E. J. Caldeira, "Anti-inflammatory and antioxidant effects of using alpha-tocopherol in cell culture of the parotid gland under conditions similar to diabetes mellitus," *Rom J Diabetes Nutr Metab Dis*, vol. 27, no. 3, 2020.

[8] B. N. Gantner, K. M. LaFond, and M. G. Bonini, "Nitric oxide in cellular adaptation and disease," *Redox Biol*, vol. July, no. 34, 2020.

[9] J. Biddlestone, D. Bandarra, and S. Rocha, "The role of hypoxia in inflammatory disease (Review)," *Int J Mol Med*, vol. 35, no. 4, pp. 859–869, 2015, doi: 10.3892/ijmm.2015.2079.

[10] W. Li, Y. Wang, Y. Shi, F. He, and Z. Zhao, "The gut microbiota mediates memory impairment under high-altitude hypoxia via the gut-brain axis in mice," *FEBS J.*, vol. 292, no. 4, pp. 809–826, 2025.

[11] T. Kitamura, S. K. Ogawa, D. S. Roy, T. Okuyama, and M. D. Morrissey, "Engrams and circuits crucial for systems consolidation of a memory," *Science*, vol. 356, no. 6333, pp. 73–78, 2017.

[12] J. Xin *et al.*, "Probiotic alleviate fluoride-induced memory impairment by reconstructing gut microbiota in mice," *Ecotoxicology and Environmental Safety*, vol. 215, p. 112108, 2021, doi: https://doi.org/10.1016/j.ecoenv.2021.112108.

[13] R. Roustazade, M. Radahmadi, and Y. Yazdani, "Therapeutic effects of saffron extract on different memory types, anxiety, and hippocampal BDNF and TNF-α gene expressions in sub-chronically stressed rats," *Nutritional Neuroscience*, vol. 25, no. 1, pp. 192–206, 2022, doi: 10.1080/1028415X.2021.1943138.

[14] L. M. Lueptow, "Novel object recognition test for the investigation of learning and memory

in mice," *Journal of Visualized Experiments*, vol. 2017, no. 126, pp. 1–9, 2017, doi: 10.3791/55718.

[15] O. S. Arvaniti, Y. Samaras, G. Gatidou, N. S. Thomaidis, and A. S. Stasinakis, "Review on fresh and dried figs: Chemical analysis and occurrence of phytochemical compounds, antioxidant capacity and health effects," *Int Food Res*, vol. 119, no. January, pp. 244–267, 2019, doi: 10.1016/j.foodres.2019.01.055.

[16] K. Choudhary *et al.*, "4-Methylesculetin ameliorates LPS-induced depression-like behavior through the inhibition of NLRP3 inflammasome," *Front Pharmacol*, vol. 14, no. February, pp. 1–14, 2023, doi: 10.3389/fphar.2023.1120508.

[17] S. Saxena, I. Agrawal, P. Singh, and S. Jha, "Portable, low-cost hypoxia chamber for simulating hypoxic environments: Development, characterization and applications," *Med Devices Sens*, 2020, doi: 10.1002/mds3.10064.

[18] K. Mohan Kumar *et al.*, "Gut mucosal injury in neonates is marked by macrophage infiltration in contrast to pleomorphic infiltrates in adult: Evidence from an animal model," *Am J Physiol Gastrointest Liver Physiol*, vol. 303, no. 1, pp. 93–102, 2012, doi: 10.1152/ajpgi.00016.2012.

[19] H. H. Nguyen *et al.*, "Effects of Mimosa pudica Linn . Extract on Reducing Seizures , Memory Impairment , and Emotional Disorders in a Mouse Model of Temporal Lobe Epilepsy Induced by Trimethyltin," *Pharm Sci*, vol. 52, no. 1, pp. 110–119, 2025, doi: 10.29090/psa.2025.01.24.2091.

[20] K. Flores, P. Siques, S. Ordenes, and K. Arriaza, "Lower Body Weight in Rats Under Hypobaric Hypoxia Exposure Would Lead to Reduced Right Ventricular Hypertrophy and Increased AMPK Activation," *Front Physiol*, vol. 11, no. 2020, pp. 1–10, 2020.

[21] C. Rabasa, K. Askevik, E. Schéle, M. Hu, and H. Vogel, "Divergent Metabolic Effects of Acute Versus Chronic Repeated Forced Swim Stress in the Rat," *Obes*, vol. 27, no. 3, pp. 427–433, 2019.

[22] A. Solomon *et al.*, "Antioxidant activities and anthocyanin content of fresh fruits of common fig (Ficus carica L.)," *J.Agric.Food.Chem*, vol. 54, no. 20, pp. 7717–23, 2006.

[23] A. Meliala, P. Narwidina, and Y. T. Sumarno, "Antioxidative Parameters Improvements on Nutritional Approach: A Study on Hypoxic Multiple Organs of Sprague-Dawley," *HAYATI J Biosci*, vol. 31, no. 1, pp. 59–70, 2023.

[24] N. Petkova, I. Ivanov, and P. Denev, "Changes in phytochemical compounds and antioxidant potential of fresh, frozen, and processed figs (Ficus carica L.)," *Int Food Res J*, vol. 26, no. 6, pp. 1881–1888, 2019.

[25] M. M. Essa, S. Subash, M. Akbar, S. Al-Adawi, and G. J. Guillemin, "Long-Term Dietary Supplementation of Pomegranates, Figs and Dates Alleviate Neuroinflammation in a Transgenic Mouse Model of Alzheimer's Disease," *PLoS ONE*, vol. 10, no. 3, pp. 1–8, 2015.

[26] R. Singhal and Y. M. Shah, "Oxygen battle in the gut: Hypoxia and hypoxia-inducible factors in metabolic and inflammatory responses in the intestine," *J Biol Chem*, vol. 295, no. 30, pp. 10493–10505, 2020, doi: 10.1074/jbc.REV120.011188.

[27] C. Farah, L. Y. M. Michel, and J.-L. Balligand, "Nitric oxide signalling in cardiovascular health and disease," *Nat Rev Cardiol*, vol. 15, no. 5, pp. 292–316, 2018.

[28] J. N. Sharma, A. Al-Omran, and S. S. Parvathy, "Role of nitric oxide in inflammatory diseases," *Inflammopharmacology*, vol. 15, no. 6, pp. 252–9, 2007.

[29] R. Shobatake, H. Ota, N. Takahashi, S. Ueno, K. Sugie, and S. Takasawa, "Anorexigenic effects of intermittent hypoxia on the gut—brain axis in sleep apnea syndrome," *Int. J. Mol. Sci.*, vol.

23, no. 1, 2022, doi: 10.3390/ijms23010364.

[30] X. Chen, B. T. Andresen, M. Hill, J. Zhang, F. Booth, and C. Zhang, "Role of Reactive Oxygen Species in Tumor Necrosis Factor-alpha Induced Endothelial Dysfunction," *Curr Hypertens Rev.*, vol. 4, no. 4, pp. 245–255, 2008.

[31] M. Jung, I. Brizes, S. Wages, P. Ponce, M. Kang, and P. D. Loprinzi, "Combined effects of acute exercise and hypoxia on memory," *Physiol Int*, vol. 107, no. 2, pp. 337–348, 2020.

[32] Ramírez-delaCruz, M. B.-S. S. I. Alfredo, J. Abián, and P. Abian, "Effects of Acute Hypoxic Exposure in Simulated Altitude in Healthy Adults on Cognitive Performance: A Systematic Review and Meta-Analysis," *Biol*, vol. 13, no. 835, pp. 1–27, 2024.

[33] V. Saxena, R. Gupta, and H. Ahmad, "Memory enhancing effects of Ficus carica leaves in hexane extract on interoceptive behavioral models," *Asian J Pharm Clin Res*, vol. 6, pp. 109–113, 2013.

[34] G. Mukandala, R. Tynan, S. Lanigan, and J. J. O'Connor, "The Effects of Hypoxia and Inflammation on Synaptic Signaling in the CNS," *Brain Sci*, vol. 6, no. 1, pp. 1–14, 2016.

[35] Q. Zou *et al.*, "Ficus carica polysaccharide attenuates DSS-induced ulcerative colitis in C57BL/6 mice," *Food Funct*, vol. 11, no. 7, 2020.

[36] M. Mladenov, L. Lubomirov, O. Grisk, D. Avtanski, and V. Mitrokhin, "Oxidative Stress, Reductive Stress and Antioxidants in Vascular Pathogenesis and Aging," *Antioxidants*, vol. 12, no. 5, pp. 1–29, 2023.