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ORIGINAL RESEARCH

# Gentianine facilitates proliferation and inhibits inflammation and oxidative stress in caerulein-triggered acute pancreatitis cell model

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## Abstract

Acute pancreatitis (AP) is a life-threatening inflammatory condition of the pancreas. Gentianine (GTN), derived from *Gentiana scabra*, has been demonstrated to suppress inflammation in various diseases. Nonetheless, the specific effects and related pathways through which GTN influences AP progression remain unclear. Herein, we aimed to elucidate the regulatory effects of GTN on AP. Our results confirmed that the reduction in cell proliferation induced by caerulein could be reversed after GTN treatment (25 $\mu$M, 50 $\mu$M and 100 $\mu$M). Moreover, while caerulein treatment increased cell apoptosis, subsequent GTN treatment reduced this effect, as well as the inflammation provoked by caerulein. Furthermore, activation of the Toll-like receptor 4 (TLR4)/nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) pathway induced by caerulein was counteracted by GTN administration. In summary, this research revealed for the first time that GTN promotes cell proliferation and reduces inflammation and oxidative stress in AR42J cells in a caerulein-induced AP cell model, suggesting that GTN holds promise as an effective therapeutic agent for AP.

## Keywords

Gentianine; Acute pancreatitis; Inflammation; Caerulein

## 1. Introduction

Acute pancreatitis (AP) is an inflammatory condition characterized by the activation of digestive proenzymes and leukocytes, infiltration of inflammatory cells, and necrosis of pancreatic acinar cells [1]. The incidence of this disease is rising globally, and while most AP cases are mild and self-limiting, 5–10% of the patients develop severe pancreatitis, often leading to multiple organ failure or complications with a high mortality rate [2]. Thus, identifying effective therapeutic agents for AP is a critical and challenging task.

Many extracts from Chinese herbs have been demonstrated to have an intervention effect on the progression of AP. For instance, calycosin has been shown to mitigate inflammation triggered by high mobility group box 1 (HMGB1), thus alleviating severe AP-induced acute lung injury [3]. On the other hand, Baicalin has been found to modulate miR-15a, offering relief from AP progression [4]. Additionally, irisin has been reported to reduce AP progression in mice by inhibiting the formation of neutrophil extracellular traps [5]. *Gentiana scabra*, a traditional medicinal plant, has been used to treat various diseases, and related research has revealed that its extract, gentianine (GTN), can regulate inflammatory diseases. Specifically, GTN has been shown to decrease the production of pro-inflammatory cytokines in lipopolysaccharide (LPS)-stimulated rats [6] and to reduce TLR4/NLRP3-mediated pyroptosis, thereby improving symptoms of dextran sulfate-induced ulcerative colitis [7]. GTN has also been found to offer protection against arthritis induced by Freund's complete adjuvant [8] and to modulate the TLR4/nuclear factor kappa-B (NF-$\kappa$B) signaling pathway, which helps to alleviate the inflammatory response and reduce ischemic stroke injury [9]. However, the specific role and pathways through which GTN affects AP progression remain poorly understood and warrant further investigation.

In this study, our findings demonstrated that GTN promoted cell proliferation and reduced inflammation and oxidative stress in AR42J cells within a caerulein-induced AP model, thereby providing new insights into the potential therapeutic applications of GTN in AP treatment, which could enhance AP management strategies.

## 2. Materials and methods

### 2.1 Cell culture and treatment

The rat pancreatic acinar AR42J cells (ATCC, Rockville, MD, USA) were cultured in RPMI-1640 medium (31800022, Gibco, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS, 10099-141, Gibco, Grand Island, NY, USA). The cells were maintained at 37 °C in a humidified atmosphere containing 5% $CO_2$.


  

The AR42J cells were treated with 10 nmol/L of caerulein (17650-98-5, Sigma-Aldrich, Taufkirchen, Germany) for 24 h to construct the AP cell model. Subsequently, GTN (25, 50 and 100 $\mu$M; P0566, Shanghai Pureone Biotechnology Co., Ltd, Shanghai, China) was immediately used to treat the AR42J cells for 24 h.

### 2.2 Cell counting kit-8 (CCK-8) assay

AR42J cells were seeded in 96-well plates and cultured for 24 hours. Afterward, 10 $\mu$L of CCK-8 reagent (C0040, Beyotime, Shanghai, China) was added to each well and incubated for 2 hours. The absorbance at 450 nm was measured using a spectrophotometer (ND-ONE-W, Thermo Fisher Scientific, Waltham, MA, USA).

### 2.3 5-Ethynyl-2′-deoxyuridine (EDU) assay

After washing, AR42J cells were treated with EDU reagent (C10310, 50 $\mu$M, RiboBio, Guangzhou, China) for 2 hours. Subsequently, the cells were stained with Apollo and 4′,6-diamidino-2-phenylindole (DAPI), and EDU-positive cells were counted using a fluorescence microscope (DM1000, Leica, Hilden, Germany).

### 2.4 Western blot

Proteins extracted from AR42J cells were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to polyvinylidene fluoride (PVDF) membranes. After blocking with 5% bovine serum albumin (BSA), the membranes were incubated overnight at 4 °C with primary antibodies against Bax (1:1000; ab32503), B-cell lymphoma-2 (BCL-2) (1:1000; ab194583), cleaved caspase-3 (1:500; ab2302), tumor necrosis factor-$\alpha$ (TNF-$\alpha$) (1:1000; ab307164), interleukin (IL)-6 (1 $\mu$g/mL; ab9324), IL-1$\beta$ (1:1000; ab234437), TLR4 (1:1000; ab217274), NLRP3 (1:1000; ab263899) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1:1000; ab8245) (Abcam, Shanghai, China). Subsequently, the membranes were incubated with the goat anti-rabbit IgG secondary antibody (1:2000; ab7090). Protein blots were visualized using a chemiluminescence detection kit (89880, Thermo Fisher Scientific, Inc., Waltham, MA, USA).

### 2.5 Flow cytometry

The FITC Annexin V apoptosis detection Kit (556547, BD Biosciences, Franklin Lakes, NJ, USA) was used for this experiment. After washing, AR42J cells were stained with FITC Annexin V and propidium iodide (PI) in the dark, and cell apoptosis was assessed using flow cytometry (BD Biosciences).

### 2.6 Enzyme-linked immunosorbent assay (ELISA)

The concentrations of IL-1$\beta$, IL-6 and TNF-$\alpha$ in the lysates of AR42J cells were quantified using the TNF-$\alpha$ (ab236712), IL-6 (ab234570) and IL-1$\beta$ (ab255730) ELISA kits (Abcam, Shanghai, China).

### 2.7 Detection of ROS, MDA, SOD and GSH-Px

The levels of reactive oxygen species (ROS), malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were determined using the respective commercial kits: ROS (ab113851), MDA (ab118970), SOD (ab65354) and GSH-Px (ab102530) from Abcam, Shanghai, China.

### 2.8 Statistical analysis

Data analysis was conducted using the SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Each experiment was replicated three times, and the results are presented as mean $\pm$ standard deviations (SD). Differences among groups were evaluated using one-way Analysis of Variance (ANOVA) followed by Tukey's multiple comparisons test. A $p$-value of $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1 GTN promotes the growth of caerulein-triggered AR42J cells

The structural formula of GTN is presented in Fig. 1a. Treatment with caerulein reduced cell viability, which was subsequently restored following treatment with GTN at concentrations of 25 $\mu$M, 50 $\mu$M and 100 $\mu$M (Fig. 1b). Further, the EDU assay results revealed that the decrease in cell proliferation induced by caerulein was reversed with GTN treatment at 50 $\mu$M and 100 $\mu$M (Fig. 1c,d). These findings demonstrate that GTN supports the growth of AR42J cells challenged with caerulein.

### 3.2 GTN reduces apoptosis in caerulein-treated AR42J cells

Next, it was discovered that apoptosis levels were increased following caerulein treatment; however, these effects were mitigated by GTN at doses of 25 $\mu$M, 50 $\mu$M and 100 $\mu$M (Fig. 2a). Furthermore, the increase in Bax and cleaved caspase-3 protein levels and the decrease in BCL-2 protein expression induced by caerulein were all reversed following GTN treatment (Fig. 2b). Collectively, these results indicate that GTN effectively reduces apoptosis in AR42J cells subjected to caerulein treatment.

### 3.3 GTN suppresses inflammation in caerulein-induced AR42J cells

ELISA assays demonstrated that levels of TNF-$\alpha$, IL-6 and IL-1$\beta$ in AR42J cell lysates were elevated following caerulein treatment, but these increases were mitigated by GTN treatment at concentrations of 25 $\mu$M, 50 $\mu$M and 100 $\mu$M (Fig. 3a). Additionally, Western blot analysis revealed that the protein expressions of TNF-$\alpha$, IL-6 and IL-1$\beta$ were intensified after caerulein exposure, but these effects were diminished following GTN treatment (Fig. 3b,c). In summary, GTN effectively reduced inflammation in caerulein-induced AR42J cells.

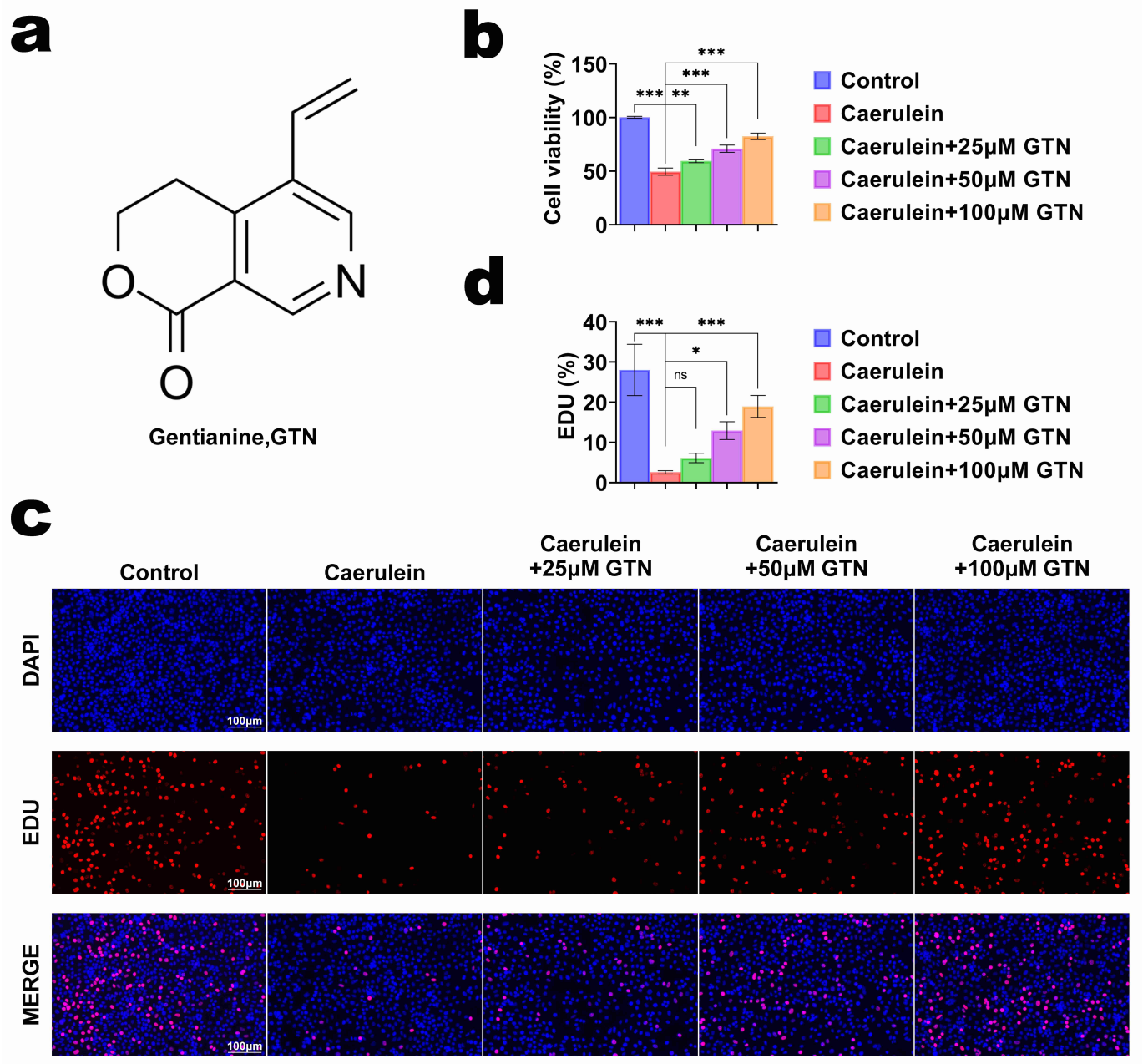


**FIGURE 1. GTN promoted the growth of caerulein-treated AR42J cells.** (a) The chemical structural formula of GTN. (b) Cell viability assessed through CCK-8 assay in the Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100 $\mu$M GTN groups. (c,d) Cell proliferation examined through EDU assay in the Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100 $\mu$M GTN groups. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. GTN: Gentianine; EDU: 5-Ethynyl-2′-deoxyuridine; DAPI: 4′,6-diamidino-2-phenylindole.

### 3.4 GTN alleviates oxidative stress in caerulein-stimulated AR42J cells

Treatment with caerulein increased the ROS level, as indicated by 2′,7′-dichlorofluorescein (DCF) fluorescence intensity; however, this increase was counteracted by GTN treatment at doses of 25 $\mu$M, 50 $\mu$M and 100 $\mu$M (Fig. 4a). Similarly, the reduction in SOD levels caused by caerulein was neutralized following GTN treatment (Fig. 4b). Moreover, the elevation in MDA levels resulting from caerulein exposure was diminished after GTN treatment (Fig. 4c). Additionally, the decrease in glutathione peroxidase (GSH-Px) levels induced by caerulein was reversed with GTN treatment (Fig. 4d). In conclusion, GTN effectively mitigated oxidative stress in AR42J cells stimulated by caerulein.

### 3.5 GTN retarded the TLR4/NLRP3 pathway

Caerulein treatment increased the protein expressions of TLR4 and NLRP3, but these changes were neutralized by GTN treatment at concentrations of 25 $\mu$M, 50 $\mu$M and 100 $\mu$M (Fig. 5), indicating that GTN inhibited the activation of the TLR4/NLRP3 pathway.

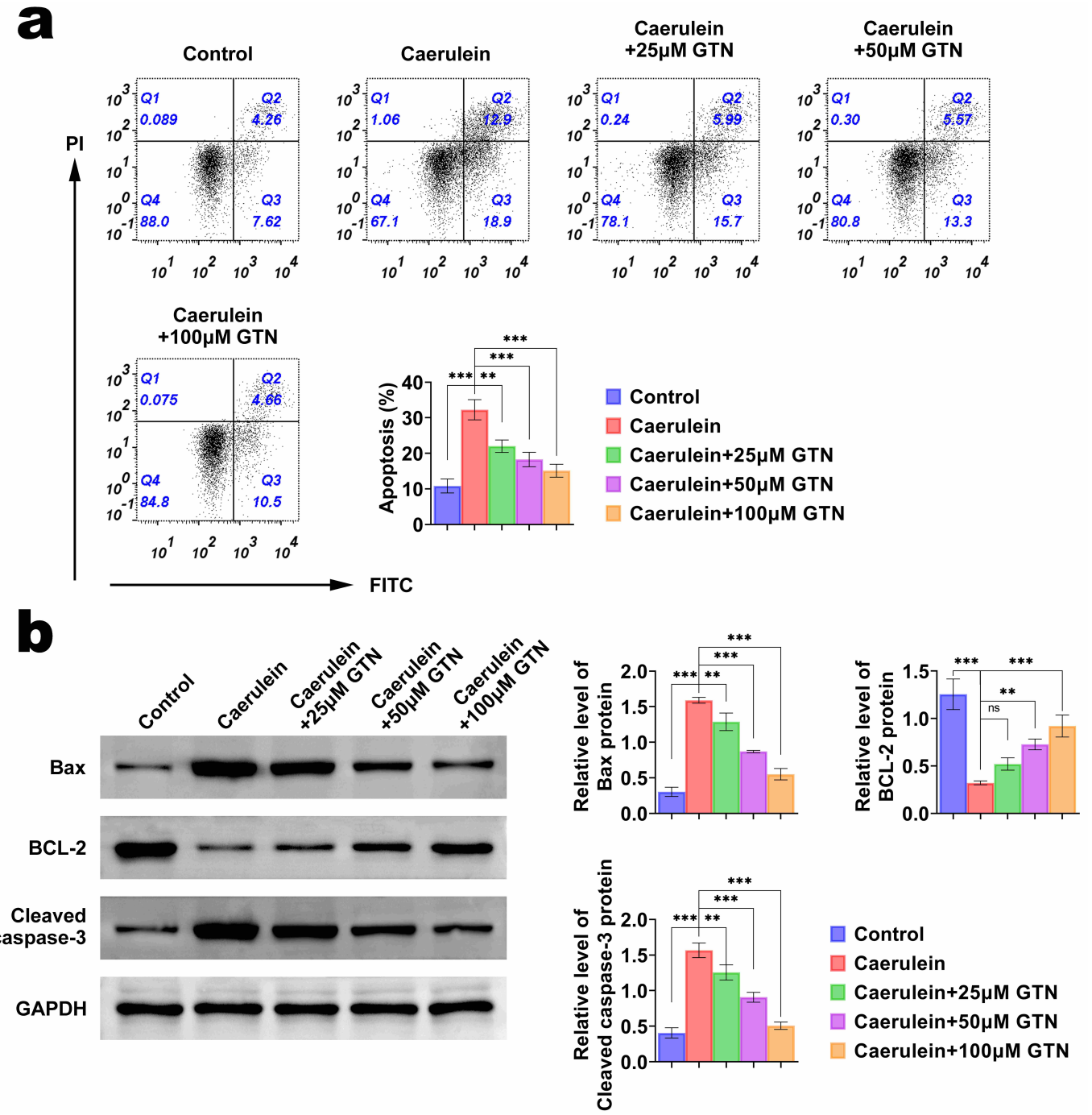


**FIGURE 2. GTN inhibited apoptosis in caerulein-exposed AR42J cells.** Treatment groups: Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100 $\mu$M GTN. (a) Quantification of apoptosis *via* flow cytometry. (b) Western blot analysis of Bax, BCL-2 and Cleaved caspase-3 protein levels. $^{**}p < 0.01$, $^{***}p < 0.001$. GTN: Gentianine, BCL-2: B-cell lymphoma-2; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

## 4. Discussion

Although GTN has been demonstrated to improve the conditions of various diseases [6–9], its regulatory effects on AP progression remained unclear. Consistent with previous studies, our present study research utilized 10 nmol/L caerulein to establish the AP cell model using AR42J cells [10–12]. Amylase levels have been previously adjusted in AR42J cell treatments [13–15]. Our findings revealed that GTN treatment (25 $\mu$M, 50 $\mu$M and 100 $\mu$M) restored the reduced cell proliferation caused by caerulein treatment. Moreover, the increase in cell apoptosis induced by caerulein treatment could be mitigated by GTN treatment.

Damage of the pancreatic parenchyma can generate an inflammatory reaction, but may result into the excessive systemic inflammation and early organ failure [16, 17]. Inflammation is a critical progress in the progression of AP, attracting considerable research aimed at addressing this challenge to ameliorate AP. Notably, miR-5132-5p has been identified to mitigate inflammation in caerulein-induced AP by targeting phospholipase D2 (PLD2) and modulating the nuclear factor

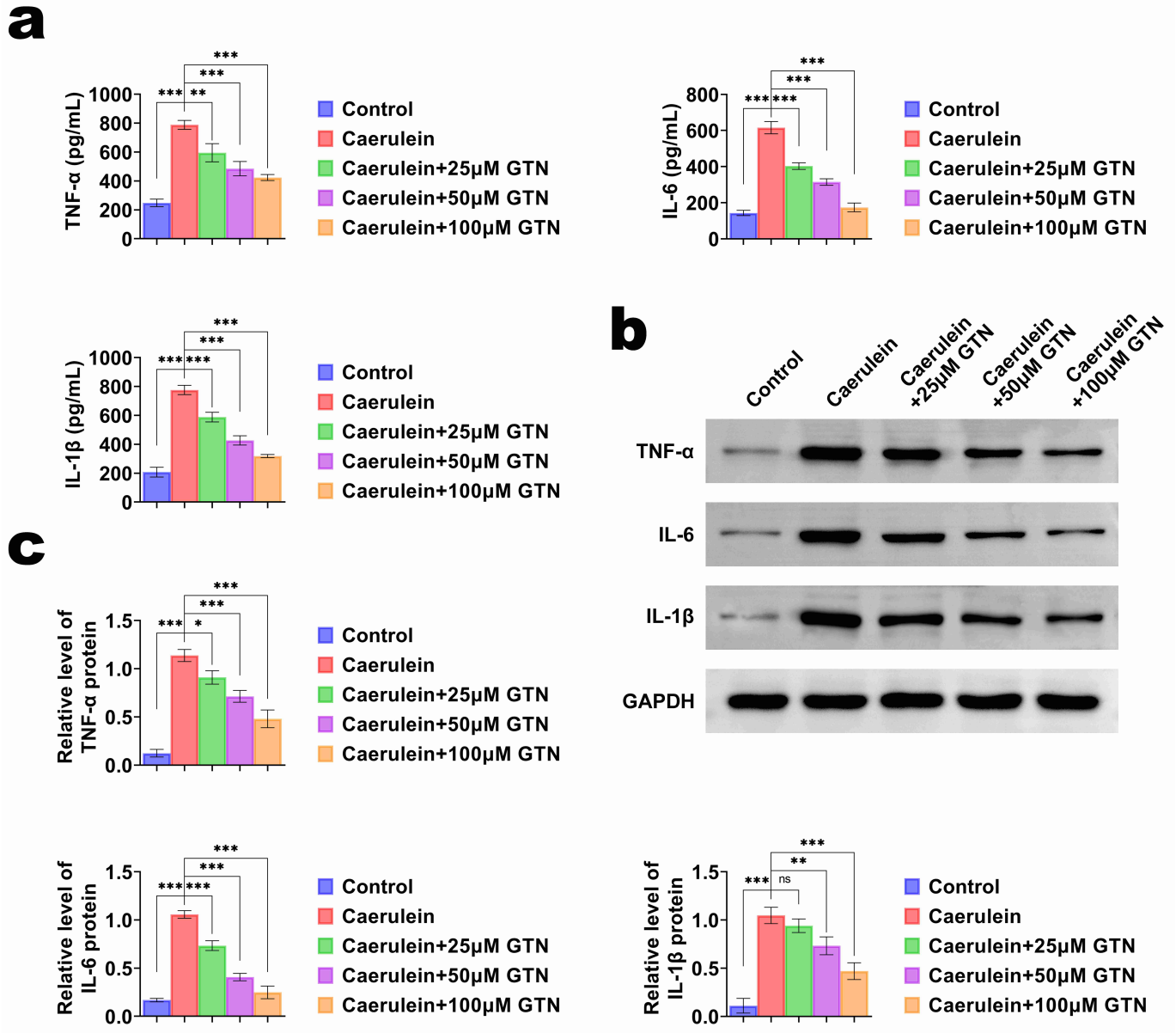


**FIGURE 3. GTN suppressed inflammation in caerulein-induced AR42J cells.** Treatment groups: Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100 $\mu$M GTN. (a) Measurement of TNF-$\alpha$, IL-6 and IL-1$\beta$ levels using ELISA. (b,c) Western blot assessment of TNF-$\alpha$, IL-6 and IL-1$\beta$ protein expressions. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. GTN: Gentianine; TNF-$\alpha$: tumor necrosis factor-$\alpha$; IL: interleukin; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

erythroid 2-related factor 2 (Nrf2)/NF-$\kappa$B pathway [18]. Additionally, botulinum toxin, when administered *via* intraductal injection, has been shown to alleviate inflammation in experimental AP. The compound salidroside enhances pancreatic injury and reduces inflammation in severe AP by affecting the miR-217-5p/YY1-associated factor 2 (YAF2) axis [19]. Moreover, the elimination of protein kinase D (PKD) contributes to AP progression alleviation by decreasing inflammation and necrosis [20]. It is also noted that extracellular adenosine triphosphate (ATP) can intensify systemic inflammation in AP [21]. Despite these insights, the role of GTN in modulating inflammation during AP progression has not been fully elucidated. In this study, we observed that caerulein-induced inflammation was significantly mitigated following treatment with GTN.

Toll-like receptor 4 (TLR4) and nucleotide-binding oligomerization domain-like receptor 3 (NLRP3) inflammasomes are vital molecules in inflammation to induce proinflammatory cytokines, they can affect AP progression through the complex interplay [22, 23]. The TLR4/NLRP3 pathway has been verified to be a pivotal pathway in AP progression, and many researchers have paid more attentions in the regulation of this pathway in AP. For example, chaiqin chengqi decoction was identified as being able to suppress the TLR4/NLRP3 inflammasome pathway to reduce the severity of AP [24]. Similarly, the use of antibiotic combinations has been reported to suppress the TLR4/NLRP3 inflammasome pathway, thereby ameliorating AP progression [25]. Importantly, in the context of ulcerative colitis, GTN has demonstrated efficacy in modulating TLR4/NLRP3-mediated pyroptosis, offering relief from the condition [7]. Nevertheless, the effect of GTN on the TLR4/NLRP3 pathway

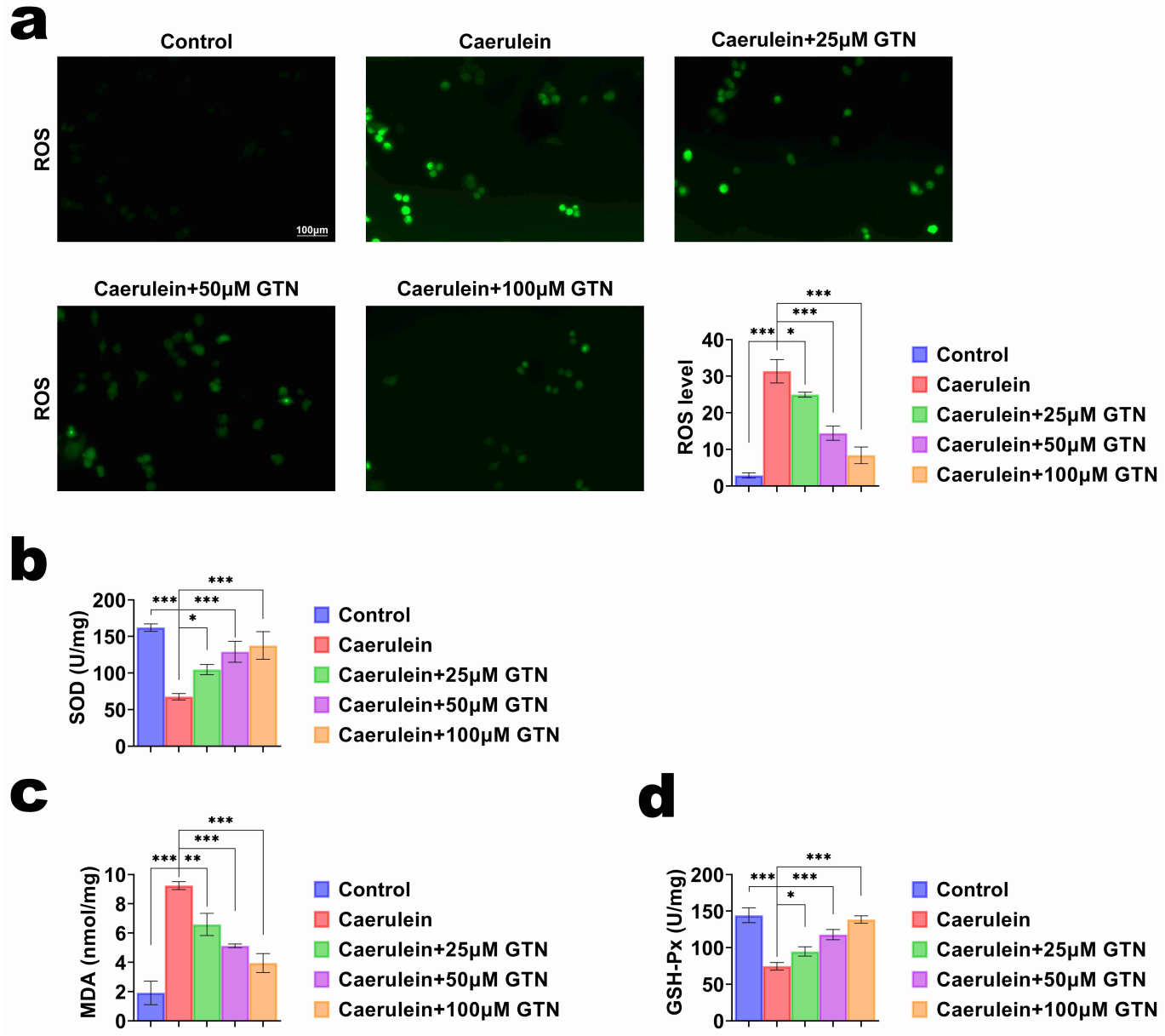


**FIGURE 4. GTN reduced oxidative stress in caerulein-stimulated AR42J cells.** Treatment groups: Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100$\mu$M GTN. (a) ROS levels detected with a ROS assay kit. (b) SOD activity confirmed using an SOD assay kit. (c) MDA levels measured with an MDA assay kit. (d) GSH-Px activity evaluated using a GSH-Px assay kit. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. GTN: Gentianine; ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde; GSH-Px: glutathione peroxidase.

in the context of AP remains insufficiently understood. This study revealed that the activation of the TLR4/NLRP3 pathway induced by caerulein was significantly reduced following GTN treatment, suggesting that GTN effectively inhibits the TLR4/NLRP3 pathway.

## 5. Conclusions

In conclusion, this study presents the first evidence that GTN promotes cell proliferation and reduces both inflammation and oxidative stress in AR42J cells in a caerulein-induced AP model. However, this research has some limitations, including the absence of human samples, animal models, and examinations of other cellular mechanisms. Future investigations are warranted to further elucidate the diverse regulatory roles of GTN in AP progression through more comprehensive experimental approaches.

## AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

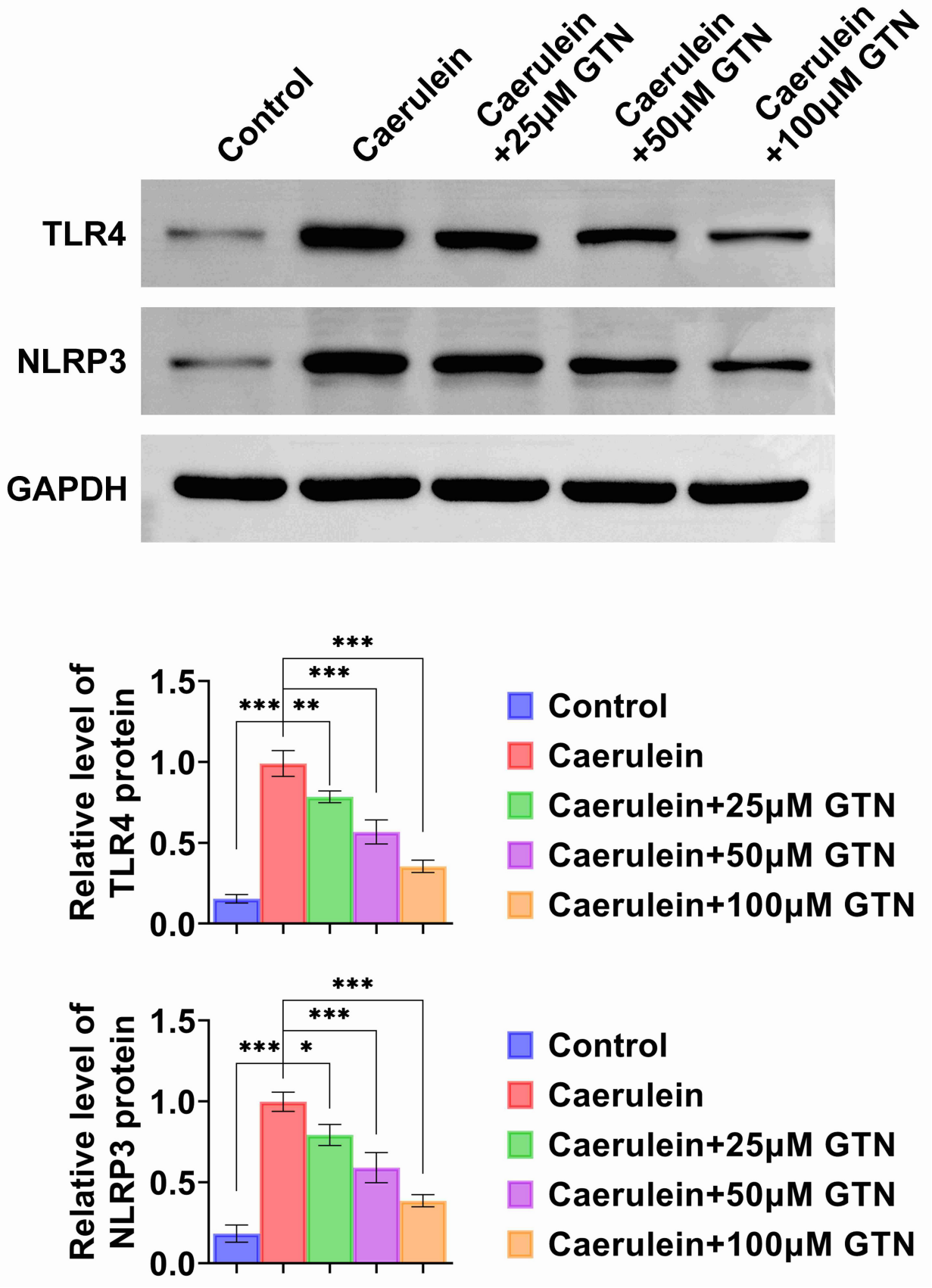


**FIGURE 5. GTN modulates the TLR4/NLRP3 signaling pathway in caerulein-treated AR42J cells.** Treatment groups: Control, Caerulein, Caerulein + 25 $\mu$M GTN, Caerulein + 50 $\mu$M GTN and Caerulein + 100 $\mu$M GTN. Western blot determination of TLR4 and NLRP3 protein expression. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. GTN: Gentianine; TLR4: Toll-like receptor 4; NLRP3: nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

## AUTHOR CONTRIBUTIONS

DBP—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. DBP, HLY, JW and JDM—supervised the data collection, analyzed the data, interpreted the data. All authors have read and approved the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## ACKNOWLEDGMENT

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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