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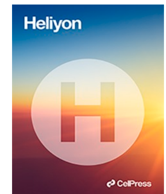

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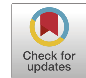

Anti-inflammatory effect of glycyrrhetinic acid in IL-1β-induced SW982 cells and adjuvant-induced arthritis

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ABSTRACT

Influences of Glycyrrhetinic acid on expression of inflammatory factors in interleukin (IL)-1β-induced SW982 cells and its anti-inflammatory effects were discussed in this study. MTT results showed that Glycyrrhetinic acid (≤80 μmol·L−1) almost has no toxicity on SW982 cells. The results of ELISA and real-time PCR showed that Glycyrrhetinic acid (10, 20 and 40 μmol · L-1) can significantly inhibit the expression of inflammatory factors such as IL-6, IL-8 and matrix metalloproteinase-1 (MMP-1). Western blot analysis showed that Glycyrrhetinic acid remarkably blocked the NF-κB signaling pathway *in vitro*. Molecule docking showed that Glycyrrhetinic acid could bind to the active site (NLS Polypeptide) of NF-κB p65. Furthermore, observation of rat foot swelling proved that Glycyrrhetinic acid had a significant therapeutic effect on adjuvant-induced arthritis (AIA) in rats *in vivo*. Collectively, all these findings suggested that Glycyrrhetinic acid might be a promising lead compound worthy of further pursuit as anti-inflammation agent.

1. Introduction

Rheumatoid arthritis (RA) is chronic autoimmune disease centered at synovitis. Inflammatory reasons, joint pains, swelling, synovial membrane and pannus formation are major pathological features, accompanied with damages cartilage and bones [1]. In addition, rheumatoid arthritis influences about 0.7% ~ 1% of adults and the morbidity of women is twice that of men [2]. Human synoviocytes are the main source of inflammatory cells and matrix metalloproteinase (MMP), such as IL-1β, IL-6, IL-8 and MMP-1 [3]. These inflammatory mediators play the key role in pathophysiology of RA. Given pathologic conditions, overproduction of inflammatory factors may cause cytokines imbalance, inflammatory damages and even bone erosion, distortion and joint damages [4]. Therefore, studies concerning treatment on RA mainly concentrate in inhibiting expression of inflammatory factors.

In the past two decades, extensive studies on medical compounds of plants have disclosed that pentacyclic triterpenoid has extremely important pharmacological activity. Pentacyclic triterpenoid has extensive sources, including fruits, vegetables, grains, beans, plants and medicinal plants. It has attracted great attentions due to its strong anti-inflammatory and anti-cancer activity [5,6].

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Glycyrrhetinic acid is a kind of pentacyclic triterpenoid (Fig. 1A), which has extensive distribution in food and medicinal plants. It not only is relatively non-toxic and can protect livers, but also shows good anti-tumor and anti-inflammatory characteristics [7,8]. Although anti-inflammatory effect of Glycyrrhetinic acid has been proved through abundant studies, no study of Glycyrrhetinic acid in human synovial cells (SW982) has not been reported yet. SW982 cell is a useful tool to study expressions of inflammatory cytokines or MMP in RA [9]. Therefore, this study mainly discusses the relevant molecular mechanism of anti-inflammatory effect of Glycyrrhetinic acid in SW982 cells, and further to explore a meliorate inflammation in a adjuvant-induced arthritis (AIA) rats.

2. Materials and methods

2.1. Materials

SW982 cells were bought from the Shanghai Cell Library of Chinese Academy of Sciences. Glycyrrhetinic acid was purchased from ALADDIN Co. Ltd (Shanghai, China). IL-1β, DMEM medium, MTT were purchased from Sigma-AldrichCo. Ltd (St. Louis, MO, USA). All antibodies purchased from Cell Signaling Technology Co. Ltd (Danvers, MA, USA).Enzyme-linked immunosorbent assay (ELISA) kits for IL-6, IL-8 and MMP-1 were purchased from Shanghai Biovol Technologies Company (Shanghai, China).

2.2. MTT assay

SW982 cells in logarithmic phase were collected and incubated into the 96-hole plate (1×10^5 cells/well). And then treated with Glycyrrhetinic acid (5, 10, 20, 40, 60, 80 and 100 μmol L^{-1}) for 24 h after stimulation with 10 ng/mL IL-1β for 24 h. Then, 15 μL MTT (0.5 mg/mL) was added in each hole and cultured by 4 h continuously. The supernate was abandoned and DMSO solution was added. The mixture was incubated by 30 min under 37 °C incubator and OD value at 490 nm was tested by the ELISA. The cell viability (CV) was calculated according to the following formula: CV = [(OD490 of the experimental group − OD490 of the blank group)/(OD490 of the control group − OD490 of the blank group)] × 100%.

2.3. Detection of pro-inflammatory cytokine IL-6, IL-8 and MMP-1

The SW982 cells were stimulated with IL-1β (10 ng mL^{-1}) for 24 h and then treated with Glycyrrhetinic acid (10, 20 and 40 μmol L^{-1}) for 24 h. IL-6, IL-8 and MMP-1 levels in the culture media were measured by ELISA. All measurements were obtained in triplicate.

2.4. Real-time PCR assay

The SW982 cells were stimulated with IL-1β (10 ng mL^{-1}) for 24 h and then treated with Glycyrrhetinic acid (10, 20 and 40 μmol L^{-1}) for 24 h. Follow the kit instructions and use Trizol reagent to extract total cellular RNA. Real-time PCR was employed to detect the expression changes of IL-6, IL-8 and MMP-1 genes. The primer sequence was shown in Table 1. The reaction was incubated in a thermal cycler as follows: 95 °C for 5 min and 40 cycles of 95 °C for 30 s, 95 °C for 1 s, and 64 °C for 30 s.GAPDH as an internal reference.

2.5. Western blot assay

The SW982 cells were stimulated with IL-1β (10 ng mL^{-1}) for 24 h and then treated with Glycyrrhetinic acid (10, 20 and 40 μmol L^{-1}) for 24 h. Cells were lysed with RIPA lysate to extract total protein. Bradford was used to determine the concentration of total protein. The total protein was separated by polyacrylamide gel electrophoresis (SDS-PAGE), and was transferred on PVDF membranes. The membranes were blocked with 5% dehydrated skim milk in TBST for 2 h at room temperature. The blots were washed thrice in

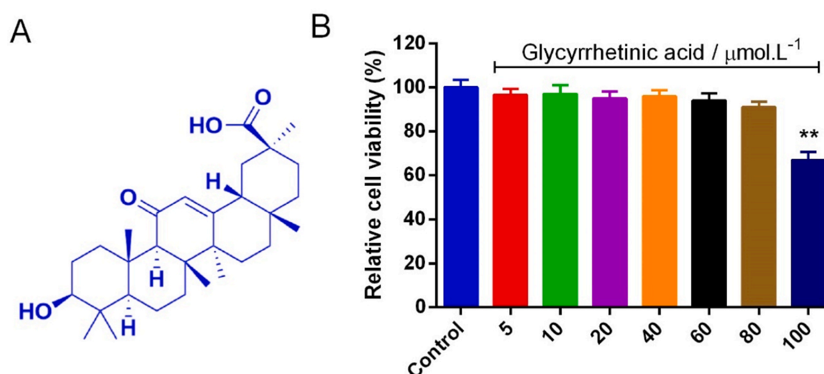

Fig. 1. (A). The structure of Glycyrrhetinic acid. (B). MTT assay was performed to assess the cytotoxicity of Glycyrrhetinic acid on SW982 cells. $^{**}P < 0.001$ vs Control group. All experiments were repeated three times.

Table 1
Primer sequences used for real-time PCR.

Gene	Primer	Sequence (5′-3′)	Product size (bp)
IL-6	Forward	TACATCCTCGACGGCATCTCA	165
	Reverse	CACCAGGCAAGTCTCCTCATTG	
IL-8	Forward	TCTTGGCAGCCTTCCTGATT	152
	Reverse	TGGTCCACTCTCAATCACTCTCAGT	
MMP-1	Forward	GGCTGAAAGTGACTGGGAAAC	162
	Reverse	GGCAAATCTGGCGTGTAA	
GAPDH	Forward	TGCCCTCAACGACCACTTTG	105
	Reverse	TACTCCTTGGAGGCCATGTG	

TBST buffer and were incubated overnight at 4 °C with primary antibodies. Then, rinse three times with TBST, incubate the secondary antibody at room temperature for 40 min, wash the membrane and use it ECL luminous fluid and automatic exposure instrument exposure. Scan the protein bands with Image J software to quantitatively analyze the expression changes of the corresponding protein.

2.6. Molecule docking

The X-ray crystal structure of NF-κB p65 (PDB: 1MY5) complexed with the inhibitor was obtained from the RCSB Protein Data Bank. Vin a docking encoded in DISCOVERY STUDIO 2017 software was employed to identify the potential binding of Glycyrrhetinic acid to NF-κB p65. Docking parameters were set to default values. All docked poses of Glycyrrhetinic acid were clustered using a tolerance of 2 Å for RMSD and were ranked on the basis of the binding docking energies. The lowest energy conformation in the most populated cluster was selected for subsequent study [10].

2.7. Induction of adjuvant-arthritis

The rats were injected with 0.1 mL Freund's complete adjuvant (FCA) intracutaneously into the left hind feet to cause inflammation. Male SD rats were purchased from the Experimental Animal Center of Anhui Medical University. The rats were housed under specific pathogen-free conditions, with free access to water and food. The protocols were approved by the Ethical Committee on Animal Research at the School of Pharmacy of Anhui Medical University, in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (No. 8023, revised 1978). The rats in the normal group were injected with the same amount of physiological saline at the same site. The rats were randomly divided into four groups after 10 days of FCA injection. One group was treated with compound Glycyrrhetinic acid (15 and 30 mg/kg) for 14 days, and the rats in the positive control group were treated with indometacin (10 mg/kg) for 14 days. Take indometacin solid from the refrigerator at 4 °C. According to the 1 mL dose of each rat, indometacin was dissolved in 5% CMC-Na solution after weighing, and then administered by gavage. All animal experiments were conducted in accordance with the guidelines of National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Laboratory Animal Ethics Committee of the Anhui Medical University.

2.8. Histologic assessment

On day 27, all rats were anesthetized by slow subcutaneously administration of Ketamine/xylazine (50/5 mg/kg) and sacrificed by dislocating the cervical spine. Foot pads were dissected, fixed in 10% formalin, decalcified and dehydrated, then embedded in paraffin. Samples were serially sectioned at 5 μm and stained with H&E. The histological changes were photographed under microscope.

2.9. Statistical analysis

Results are expressed as mean ± SD standard deviation. Statistical comparisons were performed using one-way ANOVA followed by the least significant difference test. The minimum level of significance was $P < 0.05$.

3. Results

3.1. Cytotoxicity of Glycyrrhetinic acid on SW982 cells

SW982 cells were treated by different concentrations of Glycyrrhetinic acid for 24 h after stimulation with 10 ng mL^{-1} IL-1β for 24 h (Fig. 1B). Compared with the control group, the low-concentration Glycyrrhetinic acid (≤80 μmol L^{-1}) hardly cause toxicity to SW982 cells. However, Glycyrrhetinic acid causes significant toxicity on cells when its concentration is increased to 100 μmol L^{-1}. In a word, low-concentration Glycyrrhetinic acid almost has no toxicity on SW982 cells, whereas high-concentration Glycyrrhetinic acid can inhibit survival rate of cells significantly ($P < 0.05$).

3.2. Glycyrrhetinic acid downregulate contents of inflammatory factors in IL-1β-induced SW982 cells

According to ELISA results, contents of IL-6 (Fig. 2A), IL-8 (Fig. 2B) and MMP-1 (Fig. 2C) under stimulation of 10 ng mL^{-1} IL-1β are significantly higher compared with those in the blank control group. Contents of IL-6, IL-8 and MMP-1 decrease accordingly after different concentrations of Glycyrrhetinic acid (10, 20 and 40 μmol L^{-1}) are added in. To sum up, Glycyrrhetinic acid can inhibit production of inflammatory factors in IL-1β-induced SW982 cells.

3.3. Glycyrrhetinic acid inhibits mRNA expression of inflammatory factors in IL-1β-induced SW982 cells

It can be seen from real-time PCR results that expressions of IL-6 (Fig. 3A), IL-8 (Fig. 3B) and MMP-1 (Fig. 3C) after 10 ng mL^{-1} IL-1β is added in are upregulated significantly compared to the control group. The expressions of mRNA in inflammatory factors after different concentrations of Glycyrrhetinic acid (10, 20 and 40 μmol L^{-1}) are added in decrease significantly. Therefore, Glycyrrhetinic acid can inhibit expression of inflammatory factors on the mRNA level (Fig. 3).

3.4. Effects of Glycyrrhetinic acid on NF-κB signal pathways in IL-1β-induced SW982 cells

According to Western Blot (Fig. 4A), NF-κB signal pathways are activated significantly under the simulation of 10 ng mL^{-1} IL-1β compared to the blank control group. Glycyrrhetinic acid can inhibited the phosphorylation and degradation of IL-1β-induced IκB to prevent the activation of IκB kinase. And it also remarkably decreased the phosphorylation of p65, and certain downstream signaling molecules, such as iNOS and COX-2, were also inhibited (Fig. 4B). Further analysis of the results were conducted by molecule docking. The protein crystal structure of NF-κB p65 (PDB: 1MY5) was used. As shown in Fig. 5A, a typical docking pose demonstrated that Glycyrrhetinic acid could bind to the active site (NLS Polypeptide) of NF-κB p65. Three hydrogen bonds interacted between Glycyrrhetinic acid and NF-κB p65 NLS Polypeptide: two was between the carboxyl and residue of ASP294, ARG295, and the other was between the ketone group with ARG295. The steroid core of Glycyrrhetinic acid was inserted into the active site deeply. Additionally, certain weak interactions, including pi-alkyl and van der Waals, contributed tothe binding affinity of Glycyrrhetinic acid with NF-κB p65 (Fig. 5B). These results demonstrate that Glycyrrhetinic acid can significantly inhibit NF-κB signal pathways that are activated by IL-1β.

3.5. Anti-inflammatory effects of Glycyrrhetinic acid in AIA model

AIA rat model is similar to human RA in histopathology and clinical features. This model is an ideal experimental animal model commonly used in preclinical research and evaluation of potential anti-arthritis drugs. In this study, the AIA rat model was established by intradermal injection of FCA into the plantar of rats. And the anti-inflammatory activity was proved *in vivo* by using Glycyrrhetinic acid (15 and 30 mg/kg) and indometacin in the treatment of AIA model rats. The dose of positive drug indometacin is 10 mg/kg [11–13]. The potential effect of Glycyrrhetinic acid on AIA rats was evaluated by measuring the changes of claw volume and arthritis index in the inflammatory stage. As shown in Fig. 6, compared with the model group, the drug group reduced rat foot swelling in a concentration dependent manner (Fig. 6A-B). From the 10 t h day to the 24 t h day, the arthritis index of rats in the model group increased significantly, while 30 mg/kg Glycyrrhetinic acid significantly decreased the arthritis index (Fig. 6C). The change of animal body weight has been used as one of the parameters to evaluate the course of inflammatory diseases and the response to drug treatment. Compared with the model group, the body weight of the drug treatment group increased significantly (Fig. 6D).

HE staining section of knee joint showed the effect of Glycyrrhetinic acid on joint pathological injury in AIA rats. As shown in Fig. 7A, the articular cartilage of rats in the normal group has smooth surface, complete layers, and no inflammation and bone destruction. However, the knee sections of model group showed many typical pathological features similar to RA, such as synovial hyperplasia and inflammatory cell infiltration (Fig. 7B). Treatment with Glycyrrhetinic acid (15 and 30 mg/kg) and indometacin (10 mg/kg) reduced these pathological changes in AIA rats to varying degrees (Fig. 7C–E).

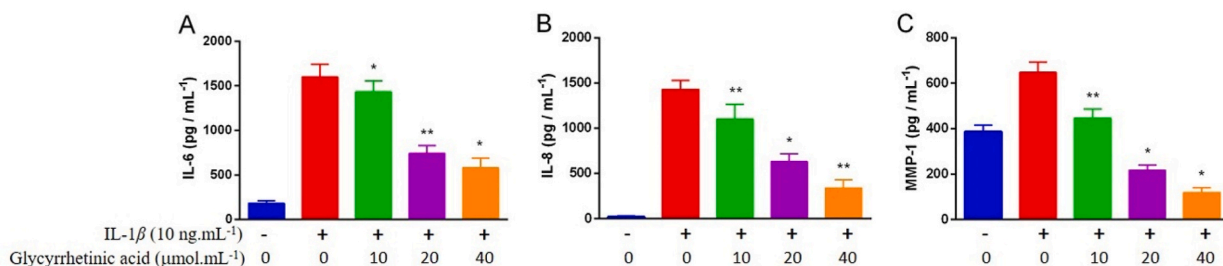

Fig. 2. Effects of Glycyrrhetinic acid on IL-6 (A), IL-8 (B) and MMP-1 (C) in IL-1β-induced SW982 cells.$^{*}P < 0.05$, $^{**}P < 0.001$ vs IL-1β without Glycyrrhetinic acid. Values are presented as mean ± SD (n = 3).

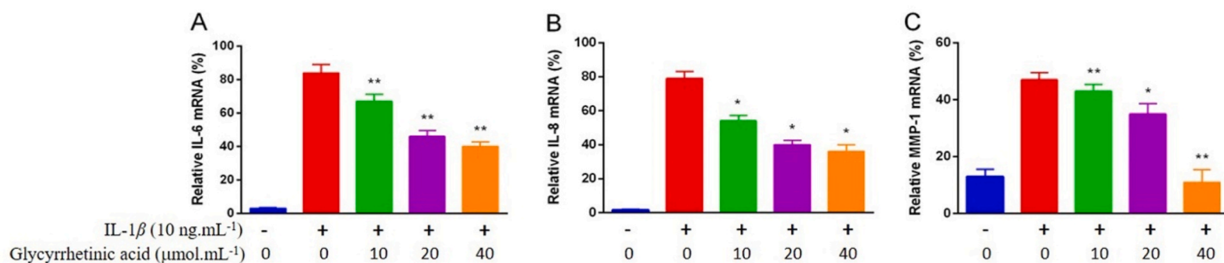

Fig. 3. Effects of Glycyrrhetinic acid on mRNA expression of IL-6 (A), IL-8 (B) and MMP-1(C) in IL-1β-induced SW982 cells. *$P < 0.05$, **$P < 0.001$ vs IL-1β without Glycyrrhetinic acid. Values are presented as mean ± SD (n = 3).

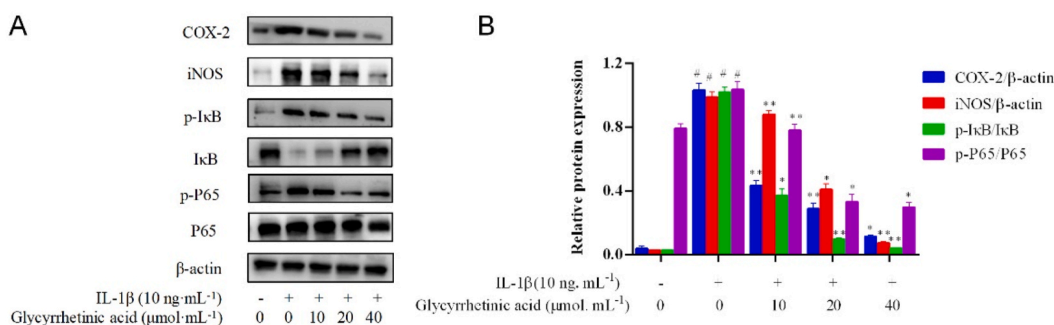

Fig. 4. Glycyrrhetinic acid inhibited the activation of NF-κB signaling pathway in IL-1β-activated SW982 cells. Western blot (A) analysis and quantitative data of protein (B). $^{\#}P < 0.05$ compared with the negative control group.*$P < 0.05$, **$P < 0.001$ vs IL-1β without Glycyrrhetinic acid. Values are presented as mean ± SD.

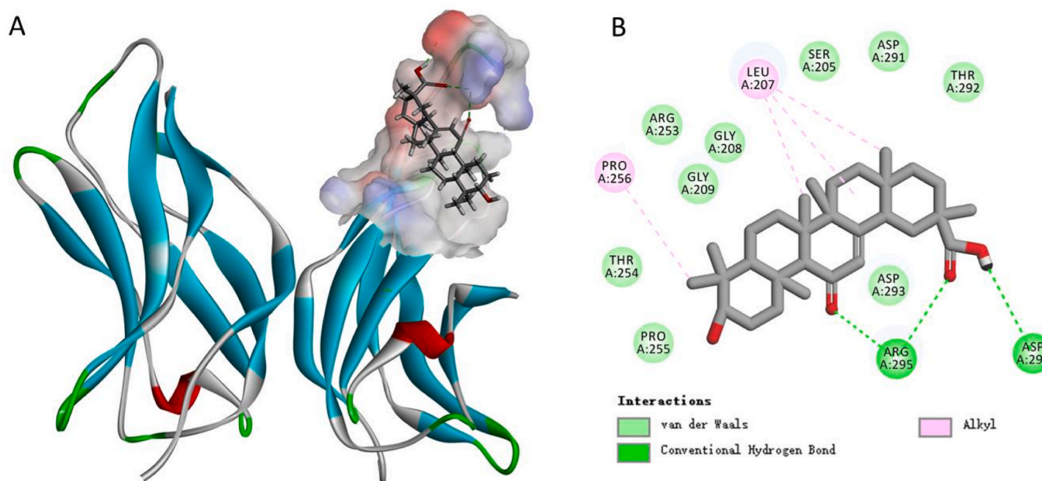

Fig. 5. 3D (A) and 2D (B)model of the interaction between Glycyrrhetinic acid with the active site of NF-κB p65.

4. Discussions

Many studies have demonstrated that sapon in compounds of pentacyclic triterpene parent nucleus have anti-inflammation effect and they have been applied to clinics [14]. Influences of pentacyclic triterpenoid saponins on inflammation activity might be related with structural changes. Some studies have demonstrated that oxidization of pentacyclic triterpenoid and their analogue C-3 has strong inhibiting effect on inflammation occurrences of 5-lipoxidase [15]. Betulinic acid and its derivatives influence occurrence of inflammation by inhibiting activity of phospholipase A2 (PLA2) [16]. In treatment experiment of tissue-type polypeptide antigen-induced inflammation reactions, corosolic acids also present better anti-inflammation activity than indometacin, an

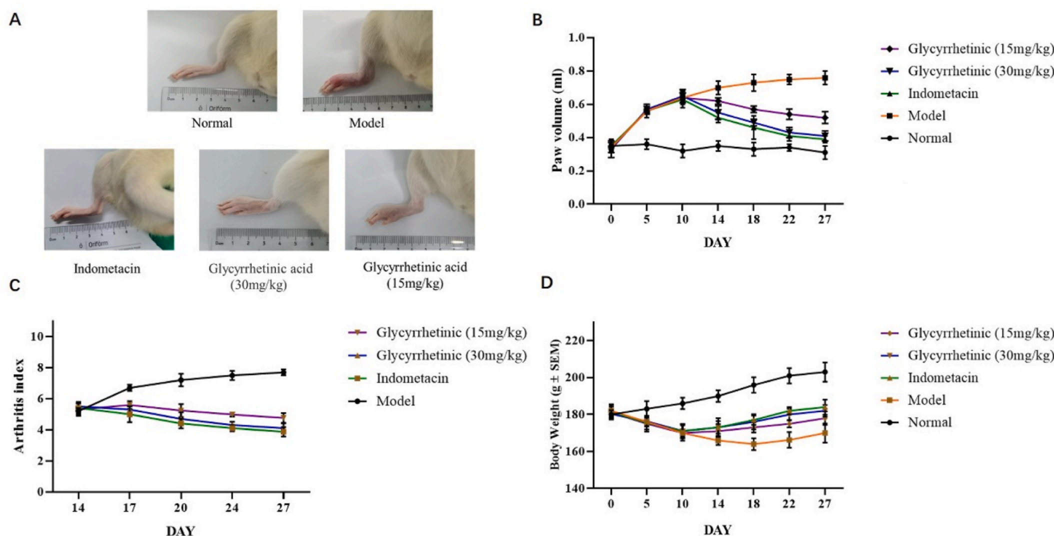

Fig. 6. Effects of Glycyrrhetinic acid on adjuvant-induced arthritic rats. (A) Pictures of treated and untreated feet of rats. Effects of Glycyrrhetinic acid on paw swelling (B), arthritis index (C) and body weight (D) in AIA model rats.

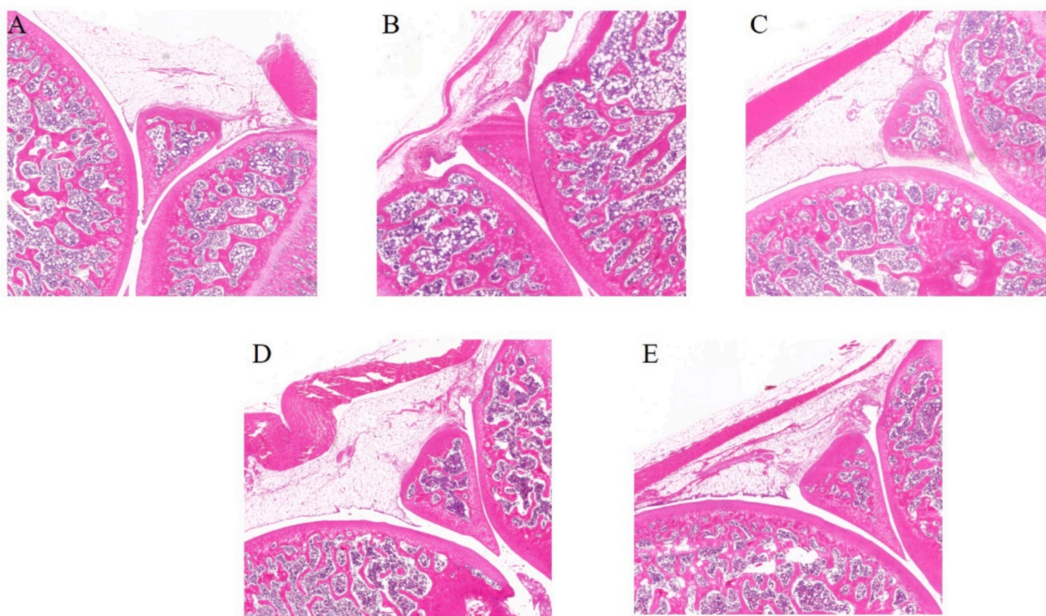

Fig. 7. The effect of Glycyrrhetinic acid on the joint pathological tissue of AIA model rats was explored by HE staining experiment (magnification × 2). (A) Normal; (B) Model; (C) Indometacin, 10 mg/kg; (D) Glycyrrhetinic acid, 30 mg/kg; (E) Glycyrrhetinic acid, 15 mg/kg.

anti-inflammatory drug on market [17]. Glycyrrhetinic acid belongs to pentacyclic triterpenoid and it has many pharmacological activities, including anti-inflammation, anti-virus, anti-osteoporosis and hepato protective effect [5,6]. With respect to anti-inflammation activities, Su et al. found that Glycyrrhetinic acid can inhibit expressions of proinflammatory factors TNF-α, IL-1β and IL-6 by inhibiting the peritoneal macrophage stimulated by lipopolysaccharides (LPS) [18]. Wang et al. proved that Glycyrrhetinic acid has obvious potential anti-inflammation activity by inhibiting LPS-induced NO and PGE2 in RAW264.7 cells [10]. Sun et al. discovered that Glycyrrhetinic acid can downregulate levels of IL-6 and TNF-α in insulin-resisting HepG2 cells [19]. Fibroblast-like synovial cells (FLS) in synovial intima play a key role in the pathological process of rheumatoid arthritis (RA) [20,21]. During RA development, pro-inflammatory factor (IL-1β, IL-6, or TNF-α) activate FLS, changing their phenotype into the one resembling cancer (RA FLS) [22]. This cell has great proliferation and migration ability. It can not only rapidly proliferate, but also release a large number of cytokines, chemokines and adhesion molecules, which can aggravate autoinflammation and directly or indirectly destroy joint

tissue [23–25]. Although the original generation of FLS has advantages, it also has some disadvantages, such as limited supply, which is difficult to collect and establish. And data and a large number of studies show that human synovial sarcoma cells (SW982) and primary FLS have similar physiological and immune characteristics due to their sarcoma characteristics under inflammatory conditions, and IL-1β-stimulated SW982 cells can mimic the inflammatory state of synovial cells common in RA patients [26–30]. Therefore, this study chose SW982 cells as the research object and detected expression variation of inflammatory factors on the proteins and mRNA level through ELISA and real-time PCR. It concludes that Glycyrrhetinic acid can inhibit expressions of IL-6, IL-8 and MMP-1, and further proves the anti-inflammation effect of Glycyrrhetinic acid in human synovial cells.

NF-κB has been viewed as a key regulating factor of inflammation and it is a polygenes-targeted transcription factor that controls several cell functions, including immune-inflammatory responses, cell adhesion, differentiation, apoptosis, stress reaction, anti-apoptosis, multiple chronic diseases, and so on [31,32]. NF-κB is often located in the cytoplasm in non-activated cells as a polymer that consists of p50, p65, and IκB proteins [33]. In response to an activation signal, NF-κB becomes phosphorylated and degraded. Furthermore, various pro-inflammatory agents, including interleukins, cytokines, chemokines, iNOS, and COX-2, are promoted in transcription [34].To understand the effect of Glycyrrhetinic acid on IL-1β-activated NF-κB signaling pathway, the expression of the relative protein of-p65, phospho p65, COX-2, and INOS were checked by Western blot assay. Results showed that when Glycyrrhetinic acid is added in, phosphorylation of p65 and the certain downstream signaling molecules, such as iNOS and COX-2, were inhibited significantly, indicating that Glycyrrhetinic acid might inhibit expressions of inflammatory factors through NF-κB signal pathways. Molecular docking reveals the binding mode between Glycyrrhetinic acid and the active site (NLS Polypeptide) of NF-κB p65 [35]. Su et al. proved that Glycyrrhetinic acid inhibits expression of inflammatory factors in LPS-induced RAW264.7 cells through the NF-κB signal pathways, thus proving the conclusion of this study [18]. In addition, according to *in vivo* studies, compared with the model group, the treatment group (Glycyrrhetinic acid) effectively reduced inflammation in the AIA rat model. Feng et al. found that in the TNF-α-induced human RA fibroblast-like synovial (FLS) cell line MH7A and the LPS-induced macrophage cell line RAW264.7, 18β-Glycyrrhetinic acid can inhibit cell viability, inhibit the MAPK/NF-κB signaling pathway and reduce IL-1β, IL-6 and COX-2 mRNA levels. In vivo experiments also demonstrated that 18β- Glycyrrhetinic acid showed good therapeutic effects in a mouse model of collagen-induced arthritis by reduce joint pathological changes and reduce serum levels of TNF-α, IL-1β and IL-6 [36]. Different from it is, we selected another cell line, human synovial sarcoma cell line (SW982 cells), as an *in vitro* inflammation model. In addition, molecular docking confirmed that Glycyrrhetinic acid can interact with key protein NF-κB p65 active pocket in IL-1β-activated SW982 cell in NF-κB signal pathway, which is also different. In another selected *in vivo* model of RA, glycyrrhetinic acid also can reduce inflammation in the rat model of AIA. This is further confirmed that Glycyrrhetinic acid has a great potential for the treatment of RA.

5. Conclusions

In summary, this research preliminarily confirmed the anti-arthritis effect of Glycyrrhetinic acid *in vitro* and *vivo*. And the anti-inflammatory effect of Glycyrrhetinic acid may be partly due to the regulation of NF-κB signaling pathway. This is of great significance for the study of Glycyrrhetinic acid as a leading compound of anti-arthritis drugs.

Author contribution statement

Yongqiang Yu: Conceived and designed the experiments.
Yang Song, Xinyu Xing, Jing Shen: Performed the experiments.
Guo Chen, Li Zhao: Analyzed and interpreted the data.
Lu Tian, Jie Ying: Contributed reagents, materials, analysis tools or data.
Yang Song wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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