

Management of rheumatoid arthritis disease activity criteria with the natural compound

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Executive Summary

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and systemic complications, driven by immune dysregulation and pro-inflammatory cytokines. This study evaluated the immunomodulatory effects of Peminine, a natural compound derived from *Fritillaria imperialis*, in a mouse model of collagen-induced arthritis. Results showed that Peminine significantly reduced paw swelling, inflammatory markers (RF, CRP), nitric oxide, and myeloperoxidase levels. It also suppressed pro-inflammatory cytokines IL-1 and TNF- α while increasing the anti-inflammatory cytokine IL-10. These effects were comparable to those of Prednisolone in several aspects. Peminine demonstrated strong anti-inflammatory and immunomodulatory properties, suggesting its potential as a complementary therapy for RA. Further clinical studies are needed to confirm these findings in humans.

Keywords: Rheumatoid arthritis, Peminine, Pro-inflammatory cytokines, Immunomodulatory properties

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial joint inflammation, leading to joint damage and disability if untreated.¹ It affects about 1% of the population, with higher prevalence in women, typically onset between ages 30–50. RA can also cause systemic complications, particularly cardiovascular issues, which are a major cause of mortality.^{2,3} The exact cause of RA is unknown, but it involves immune system dysregulation—both cellular and humoral—alongside genetic, hormonal, and environmental factors.⁴ Molecular mimicry between pathogens and self-antigens may trigger autoimmunity. Pro-inflammatory cytokines like IL-1, IL-6, and TNF- α drive inflammation and tissue damage, while anti-inflammatory cytokines such as IL-10 are reduced.⁵ Collagen-induced arthritis in mice is a common experimental model for RA. This study investigates Peminine, a natural compound from *Fritillaria imperialis*, known for its anti-inflammatory and anti-tumor effects.⁶

Previous studies indicate that Peminine modulates immune responses via suppression of NF- κ B and IFN- γ pathways. The aim is to evaluate its immunomodulatory potential as an adjunct therapy for RA.⁷

Materials and Methods

This study used 6–8-week-old male BALB/c mice divided into three groups: Group 1 (Negative Control) was RA-induced and treated with intra-articular PBS; Group 2 was RA-induced and treated with Peminine; and Group 3 was RA-induced and treated with Prednisolone. RA was induced by immunizing mice with type II collagen in complete Freund's adjuvant (injected at the tail base and footpad). Disease confirmation was based on joint swelling and elevated serum RF and CRP levels. Disease severity was assessed by paw weight measurement and ELISA for RF and CRP. Immune responses were evaluated using spleen cell cultures stimulated with type II collagen. After 72 hours, cytokine levels (IL-1, IL-6, TNF- α , IL-10) were measured by ELISA, and cell proliferation was assessed

via MTT assay. Serum nitric oxide was measured using a commercial kit (absorbance at 492 nm), and myeloperoxidase (MPO) activity was assessed using the Nampox™ kit by measuring TMB oxidation at 650 nm, using a molar extinction coefficient of $3.9 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$. Statistical analysis was performed using SPSS v24 (One-way ANOVA + LSD post hoc test; $p < 0.05$ considered significant). Graphs were prepared using GraphPad software.

Results

The untreated RA group showed the highest levels of foot swelling, rheumatoid factor (RF), CRP, MPO, and nitric oxide. Both Peminine and Prednisolone significantly reduced these markers ($P < 0.05$), with no significant difference between the two treatments in most cases. In cytokine analysis, untreated mice had elevated pro-inflammatory cytokines (IL-1, IL-6, TNF- α) and lower levels of the anti-inflammatory cytokine IL-10. Peminine significantly reduced IL-1 and TNF- α , and increased IL-10 ($P < 0.05$), but had no effect on IL-6. Prednisolone significantly reduced all three pro-inflammatory cytokines and increased IL-10 ($P < 0.05$). Both treatments also reduced lymphocyte proliferation ($P < 0.05$), showing a similar immunosuppressive effect. Peminine demonstrated strong anti-inflammatory activity by modulating cytokine balance, comparable to Prednisolone in several aspects. Rheumatoid arthritis is a chronic autoimmune disease primarily affecting synovial joints, leading to joint destruction and systemic complications. It is associated with immune dysregulation, production of autoantibodies, and chronic inflammation driven by cytokines like IL-1, IL-6, and TNF- α . Genetic and environmental factors contribute to disease onset and progression. Matrix metalloproteinases (MMPs) play a key role in joint damage by degrading cartilage and bone. This study highlights the potential of Peminine as a natural immunomodulatory agent for RA treatment.

Discussion and Conclusion

Autoimmune reactions in RA involve autoantibodies like rheumatoid factor (RF), immune complex formation, and pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α .⁸ These factors contribute to chronic inflammation, joint damage, and systemic complications.⁸ While current therapies—especially anti-cytokine treatments—can reduce disease activity, achieving full remission remains difficult, and many drugs cause side effects due to their non-specific action.^{8,9} The goal of RA treatment is to control inflammation, prevent joint destruction, preserve function, and improve quality of life. Treatment includes both pharmacological and non-pharmacological approaches, with increasing interest in plant-based

remedies due to their lower side effect profile.¹⁰ Studies show that up to 90% of RA patients use complementary therapies, including herbal medicines.¹¹ This study evaluated the immunomodulatory effects of Peminine, a natural compound derived from *Fritillaria imperialis*, in a mouse model of RA. Results showed that Peminine significantly reduced Paw edema, RF and CRP levels, Myeloperoxidase and nitric oxide production, Pro-inflammatory cytokines IL-1 and TNF- α , Increased the anti-inflammatory cytokine IL-10. However, no significant change was observed in IL-6 levels. These findings suggest that Peminine has strong anti-inflammatory and immunomodulatory properties, making it a promising adjunct therapy for RA. Further clinical studies are needed to confirm its efficacy and safety in humans.

Conflicts of Interest Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent For Publication

Not applicable

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