doi.org/10.36721/PJPS.2026.39.2.REG.14159.1

Influence of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* with traditional Chinese medicine directed drug delivery on $CD3^+$, $CD4^+$, $CD8^+$ and joint function in rheumatoid arthritis patients

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Abstract: **Background**: Rheumatoid arthritis (RA) is characterised by persistent synovitis and progressive joint destruction, frequently accompanied by abnormal T-cell subsets. *Tripterygium wilfordii* Hook F (TwHF) and *Caulis Sinomenii* (CS) are widely used in China for "dispelling wind-dampness", but their systemic toxicity limits dosage. Targeted drug delivery of traditional Chinese medicine (TCM) concentrates herbal actives in affected joints while reducing systemic exposure. **Objectives**: To evaluate whether TwHF plus CS combined with TCM improves peripheral $CD3^+$, $CD4^+$, and $CD8^+$ T-cell counts, disease activity and joint function more effectively than oral TwHF plus CS alone. **Methods**: This randomized controlled trial (conducted from January 2020 to November 2023) enrolled 82 RA patients who were randomly assigned to either a medication group (receiving *Tripterygium wilfordii* and *Caulis Sinomenii* alone) or a combination group (herbal medicine plus TCM targeted drug delivery). **Results**: Clinical and immunological parameters were assessed before treatment, at 30 days, and at 60 days. The combination group demonstrated significantly greater reductions in inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as Disease Activity Score-28 (DAS28) scores, compared to the medication-only group ($P < 0.05$). Immune profiling showed notably higher levels of $CD3^+$, $CD4^+$, and $CD8^+$ T-cell subsets in the combination therapy group. Furthermore, patients receiving combined treatment exhibited more substantial improvements in joint pain, morning stiffness, swelling, and cold intolerance, reflected by lower TCM syndrome scores ($P< 0.05$). Adverse events, including nausea, vomiting, diarrhea, elevated liver enzymes, and oral ulcers, were also significantly less frequent in the combination group. **Conclusion**: These findings suggest that integrating herbal treatment with TCM targeted drug delivery synergistically enhances immunomodulation, improves joint function, alleviates clinical symptoms and reduces side effects in RA patients.

Keywords: Adverse reaction; *Caulis Sinomenii*; Directed drug delivery; Immune function; Joint function; Rheumatoid arthritis; *Tripterygium wilfordii* Hook F; Traditional Chinese Medicine; TCM syndrome

Submitted on 20-02-2025 – Revised on 14-06-2025– Accepted on 18-06-2025

INTRODUCTION

Rheumatoid arthritis (RA), as outlined by Cush *et al*. (2022), is a persistent autoimmune condition. Its primary manifestations include sustained synovial growth and joint tissue degradation, typically affecting the proximal facet joints such as the hands, feet, wrists and ankles in a symmetric bilateral pattern, resulting in swelling and pain. According to Díaz-González *et al*. (2023), patients may also suffer from symptoms beyond the joints. Without appropriate management, RA may progressively deteriorate, leading to joint deformation and functional impairment, which severely affects patients' physical, mental and social well-being (Jang *et al*., 2022). In China, there are roughly 5 million individuals living with RA, with the prevalence growing by approximately 0.42% annually (Lin *et al*., 2020). Consequently, prompt and effective diagnosis and management of RA are crucial to halt disease progression, mitigate joint damage, enhance life quality and facilitate better societal integration for patients. Given the critical condition of RA, research into its medical treatment in China has intensified. Currently, RA management primarily involves pharmacotherapy, physiotherapy, surgical interventions and lifestyle modifications. Focusing on pharmacotherapy, researchers have formulated various medications targeting distinct symptoms based on RA's etiology, such as non-steroidal anti-inflammatory drugs, glucocorticoids and immunosuppressants. These treatments effectively reduce joint swelling and pain, curb synovial growth and decelerate disease progression (Venetsanopoulou *et al*., 2022). However, due to the chronic nature of RA, patients need long-term medication, so side effects and tolerance of drugs also require close monitoring (Figus *et al*., 2021). Physiotherapy is another important link in the treatment of RA. Acupuncture, massage, thermotherapy and other means can effectively relieve joint stiffness and pain and improve the mobility of joints (Wu *et al*., 2022). At the same time, physical therapy can also help patients improve blood circulation and promote the absorption of inflammation, which has a positive effect on improving the overall condition of patients.

In recent years, TCM has increasingly demonstrated its distinct benefits in addressing Rheumatoid Arthritis (RA). In particular, the medicinal substances *Tripterygium*

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wilfordii Hook F and *Caulis Sinomenii* have emerged as effective treatments, charting a novel course for RA management. This approach leverages TCM principles and the specialized application of Chinese medicine in drug delivery (Kadura*et al*., 2021). Known for its therapeutic heritage, *Tripterygium wilfordii* Hook F offers several pharmacological properties, including anti-inflammatory, immunosuppressive and anti-tumor benefits (Song *et al*., 2020).In the treatment of RA, *Tripterygium wilfordii* Hook F can improve symptoms such as joint swelling and pain in patients and delay disease progression by inhibiting inflammatory response, regulating immune system function, reducing the production of autoantibodies and other mechanisms (Zhao *et al*., 2022).*Caulis Sinomenii*, recognized for its historical usage in rheumatic conditions, effectively dispels wind, alleviates dampness, clears meridians and eases pain (Zhang *et al*., 2023). The method known as TCM directed drug delivery therapy marries ancient Chinese medical principles with contemporary scientific practices. This technique ensures that medications target the affected areas precisely through specialized formulations and delivery mechanisms, enhancing efficacy and minimizing broader side effects.Such directed therapy is particularly advantageous for rheumatoid arthritis treatments, given that the primary affected sites in rheumatoid arthritis are the joints.Directed drug delivery can make the drug act directly on the joints and play a more effective therapeutic role.

CD3+, CD4+ and CD8+ are critical T lymphocyte subsets in the immune system, which bear the important responsibility of maintaining the body's immune balance and resisting pathogen infection (Chraa*et al*., 2019). CD3+ represents mature T lymphocytes and plays a key role in the pathogenesis of rheumatoid arthritis (Menon *et al*., 2023). RA is a joint inflammation caused by abnormal autoimmune regulation and T lymphocytes are one of the main inflammatory cells. In the synovial tissue of RA, a large number of moderate to large lymphocyte infiltrates can be observed, most of which are T-lymphocytes that express CD3+. When CD3+ T cells are abnormal, it may indicate the presence of an immune system disease. CD4+ is a marker of T-helper lymphocytes (also known as T4 cells), which playa role in helping and inducing immune responses (Yang *et al*., 2020). In RA, CD4+ T cells may be involved in the development of disease by promoting an inflammatory response and joint destruction. CD8+ is a marker of cytotoxic T lymphocytes, which can kill infected cells or cancer cells through cytotoxic effects. In the case of RA, CD8+ T cells are implicated in the disease's pathogenesis. Research indicates that these cells can be activated by citrulline antigens through the MHCI class I pathway, which contributes to the deterioration of synovial and joint tissues and, subsequently, to the onset of RA (Dolina *et al*., 2021). Increased activation and elevated toxicity marker expression in CD8+ T cells have been observed in the blood of RA patients. These cells are likely to facilitate joint damage through the secretion of effector molecules such as granzyme. Consequently, managing the equilibrium of T lymphocyte subsets may help ameliorate the symptoms of rheumatoid arthritis.

This research aims to refine the treatment protocols for RA, particularly focusing on the combined efficacy of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* with TCM directed drug delivery therapy. The primary goal is to investigate the impact of this integrated treatment approach on T-lymphocyte subsets, including CD3+, CD4+ and CD8+ in patients and to assess its specific benefits in enhancing joint function.The actual efficacy and safety of this treatment strategy in RA will be fully evaluated by carefully comparing the data on changes in T-lymphocyte subsets and improvement in joint function before and after treatment. In addition, this study will deeply analyze the synergistic effect and its mechanism of *Tripterygium wilfordii* Hook Fand *Caulis Sinomenii* in TCM directed drug delivery therapy, to provide a more solid theoretical basis and scientific basis for clinical application.

MATERIALS AND METHODS

General data

Clinical data from 82 patients diagnosed with RA, treated between January 2020 and November 2023, were analyzed and categorized into two groups: a medication-only group and a combined medication and orientation therapy group, with each group comprising 41 patients. Informed consent was obtained from all patients or their representatives. The study included Adults over 18 years old who met the RA diagnostic criteria. It excluded individuals with: 1) Limb amputations or pathological fractures; 2) Co-existing immune disorders like psoriasis and vitiligo; 3) Rheumatic myocarditis; 4) A history of allergy to glucocorticoids or immunotherapeutic drugs. Data comparison between the groups showed no significant differences (P>0.05), as presented in table 1.

Methods

Medication group

Treated with *Tripterygium wilfordii* Hook F and *Caulis Sinomenii*. Tripterygium Glycosides (Suzhou Yifan Pharmaceutical Co., Ltd., GYZZ Z34021048, strength: 10 mg/tablet), 20 mg/time, three times a day + Zhengqing Fengtong Ning Tablets for treatment on palindromic rheumatism (Hunan Zhengqing Pharmaceutical Group Co., Ltd., GYZZ Z20010174, each tablet contains 60 mg of sinomenine hydrochloride), 2 tablets/time, twice daily.

Medication + orientation group

Based on drug therapy with *Tripterygium wilfordii* Hook F and *Caulis sinomenii*, combined with TCM directed drug delivery therapy was given. The observation time was 30 days after treatment and 60 days after treatment. (1) Preparation stage: Determine the acupoints to be treated according to the patient's condition and meridian conditions, such as inner and outer knees eye. Then, the

corresponding electrode patches and drugs were prepared. (2) Directed drug delivery prescription: The basic tolerant prescription is selected traditional Chinese medicinal materials, including Wood Cranesbill (15 g), Chuanlong Yam (15 g), Glandularstalk St. Paulswort Herb (15 g), Glabrous Greenbrier Rhizome (15 g), Giant Knotweed Root (15 g), Raw Radix Sanguisorbae (15 g), Paniculate Swallowwort Root or Herb (10 g) and Chinese Ephedrs Herb (6 g). These herbs are carefully combined to act synergistically and enhance therapeutic effect. (3) Operation stage: Attach the electrode patch to the selected acupoint and ensure that the patch is closely attached to the skin. Then, connect the treatment output probe, select directed drug delivery mode, set the treatment duration to 30 minutes and the temperature to medium temperature. (4) Treatment process*: During the treatment, the Device will penetrate the active ingredients of the drug into the body through the electrode patch and directly act on the lesion. Patients may feel slight electrical stimulation and drug delivery, which is normal and not necessary to worry. (5) End stage: After the treatment, turn off the therapy device and remove the electrode patch. At this point, patients may feel relief or improvement in the lesion site. (6) Precautions: During treatment, patients should keep relaxed and avoid excessive tension or movement to ensure full penetration of the drug. In case of any discomfort or abnormality, stop treatment immediately and inform the doctor.After treatment, patients should pay attention to rest and keep warm to avoid catching cold or fatigue.

Observation items and evaluation criteria

Immune function: At three different times, before treatment and 30 and 60 days post-treatment, between 5- 10 mL of peripheral venous blood was collected from patients for the evaluation of immune cytokines like CD3+, CD4+, and CD8+ levels using flow cytometry in both study groups.

Joint function: Before treatment, 30 daysafter treatment, and60daysafter treatment, the Ritchie joint index was used, mainly including 6 aspects such as the shoulder joint, metacarpophalangeal joint, knee joint, wrist joint, toe joint and ankle joint. Each category is scored out of 3 points, making a total possible score ranging from 0 to 18. A lower score indicates a reduced severity of joint pain (Pawlotsky *et al*., 1983). TCM symptoms: Patients in both groups were evaluated using the Criteria for Diagnosis and Efficacy of Diseases and Syndromes in Internal Medicine from Traditional Chinese Medicine. This included an assessment of four key TCM symptoms: morning stiffness, joint swelling, sensitivity to cold and pain, each rated on a scale from 0 to 5. A lower score signifies greater relief from symptoms. Adverse reactions, including nausea, vomiting, raised transaminase levels, diarrhea, and oral ulcers, were monitored and compared across the two groups.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software. Normally distributed measurement data were presented as mean ± standard deviation ($\bar{x}\pm s$) and the t-test was applied for comparisons between groups. Categorical data were reported as frequency and percentage (%) and the chi-square test was utilized for inter-group comparisons. A P-value of less than 0.05 was deemed to indicate statistical significance.

RESULTS

ESR, CRP and DAS28 score

Comparison of ERS, CRP, and DAS 28 scores before treatment ($P> 0.05$); after 30 days, ERS, CRP, and DAS 28 scores at 30 days and 60 days ($P <0.05$) are shown in table 2.

Immune function

Before treatment, there was no significant difference in serum immune indicators between the two groups ($P > 0.05$). However, 30 and 60 days post-treatment, the levels of serum immune markers like CD4+, CD3+ and CD8+ in the medication plus orientation group exceeded those in the medication-only group ($P < 0.05$). Refer to Table 3 for further information. These findings are also illustrated in fig. 1.

Joint function

Initially, the arthralgia scores of both patient groups showed no significant differences ($P > 0.05$). However, at 30and 60 days post-treatment, the scores in the medication plus orientation group were significantly lower than in the medication-only group ($P < 0.05$). For more detailed information, refer to table 4.

TCM symptom score

The medication plus orientation group displayed lower scores for morning stiffness, joint swelling, cold intolerance, pain and other Traditional Chinese Medicine symptoms compared to the medication-only group ($P < 0.05$). Further details are provided in table 5 and illustrated in fig. 2.

Adverse reactions

The occurrence of adverse effects, including nausea, vomiting, increased transaminases, diarrhea and oral ulcers, was reduced in the medication plus orientation group relative to the medication group ($P<0.05$). Detailed data can be found in table 5 and illustrated in fig. 3.

DISCUSSION

Analysis revealed that the combination of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii*, when used with TCM directed drug delivery therapy, significantly enhanced the immune function of patients with rheumatoid arthritis (RA) ($P < 0.05$). *Tripterygium wilfordii* Hook F has dual effects of immunosuppression and immunomodulation. It can affect the function of T lymphocytes, including their ability to proliferate, differentiate and secrete cytokines, thus regulating the body's immune response.

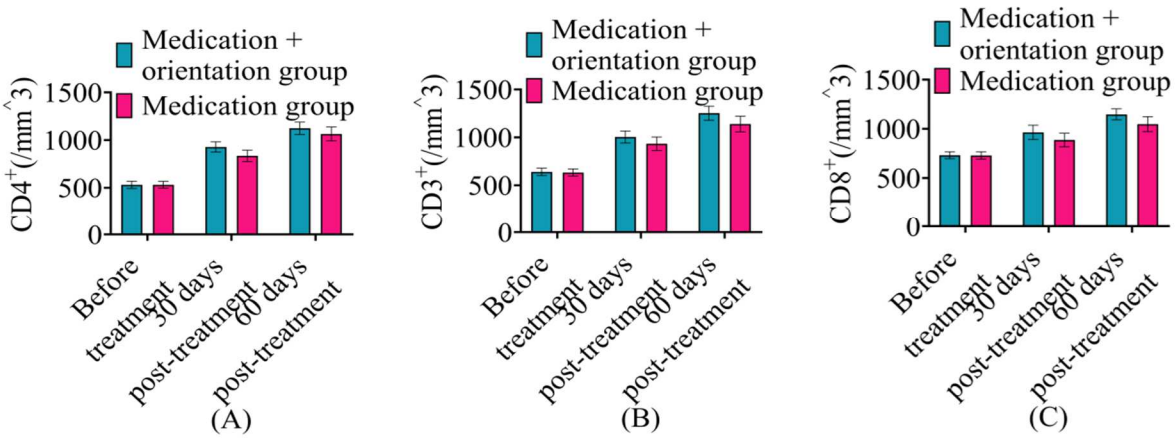

Fig. 1: Comparative study of color histograms for immune function indicators across two patient groups at various treatment intervals

Note: Figure 1(A) is CD4+; Figure 1(B) is CD3+; Figure 1(C) is CD8+; Y axis: immune function; X axis: treatment time, before treatment, 30daysaftertreatmentand60daysafter treatment; medication + orientation group (n = 41), medication group (n = 41); "*" means P < 0.001; there are differences in immune function between the two groups at different treatment times. The immune function of patients in the medication plus orientation group was markedly superior compared to those in the medication-only group, suggesting an enhancement in the former group's immune capabilities.

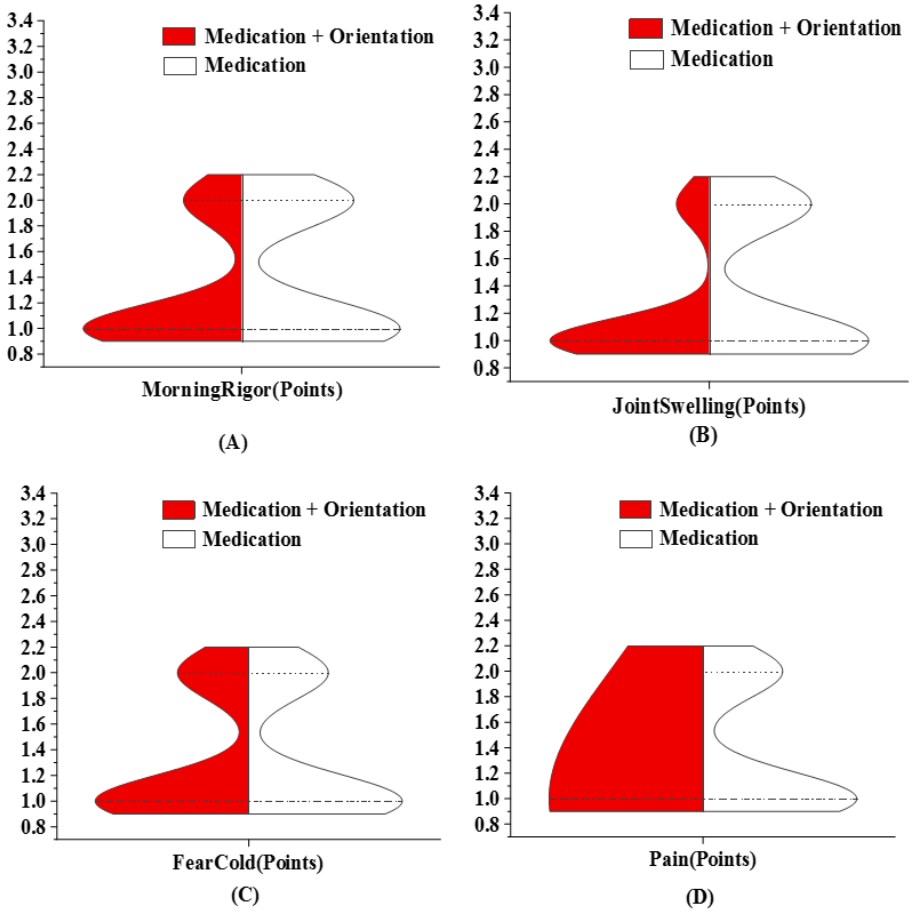

Fig. 2: Comparison of side-by-side violin charts for integrating TCM symptom data across two patient groups

Notes: Figure 2(A) shows morning stiffness; Figure 2(B) shows joint swelling; Figure2(C) is cold intolerance; Figure2(D) is pain; X axis: Symptoms of TCM; Y axis: is the score; medication + orientation (n=41), medication group (n=41); Violin shape: shows the distribution of scores for each group, with width representing density and height representing quantity; Black wire inside: is the median of the kernel density estimate; External black wire: is the range of quartiles; Time comparison: Across the graph, from left to right, the TCM symptom scores were consistently lower in the medication plus orientation group compared to the medication group.

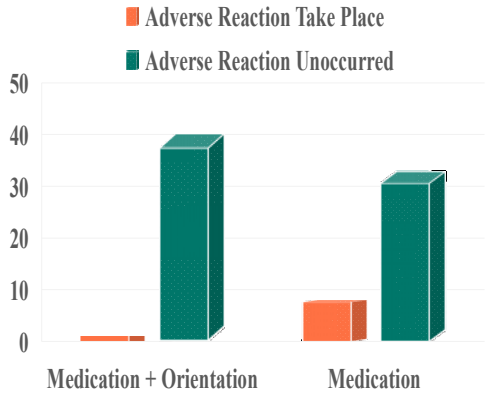

Fig. 3: Comparison of 3D histograms depicting adverse reactions across two patient groups
Note: X-axis represents the groups, with the medication + orientation group (n = 41) and the medication group (n = 41); Y-axis shows adverse reactions. There are observed differences in the incidence of adverse reactions between the two groups. Notably, the medication + orientation group exhibited a significantly lower frequency of adverse reactions compared to the medication group, suggesting improved tolerance in the combined therapy group.

Table 1: Comparison of general data across two patient cohorts [$\bar{x}\pm s$, %]

Groups	Gender (Male/Female)	Age (years)	Course of disease (years)	Education level (high school or technical secondary school and below/associate degree or bachelor's degree and above)	BMI(kg/m^2)
Medication + orientation group (n=41)	24/17	69.06±7.36	5.58±1.38	25/16	19.53±1.44
Medication group (n=41)	22/19	67.25±8.54	5.24±1.42	27/14	19.59±1.37
X^2/t	0.198	1.028	1.099	0.210	0.193
P	0.656	0.307	0.275	0.647	0.847

Table 2: Comparison analysis of ESR, CRP and DAS28 score before and after treatment in the two groups of patients

Groups	ESR(mm/h)			CRP(mg/L)			DAS28 score (points)		
	Before treatment	30 days post-treatment	60 days post-treatment	Before treatment	30 days post-treatment	60 days post-treatment	Before treatment	30 days post-treatment	60 days post-treatment
Medication + orientation group (n=41)	60.41±13.26	55.34±10.23	42.85±8.76	55.55±11.52	47.23±5.42	43.28±4.98	7.26±0.23	4.02±0.02	2.12±0.06
Medication group (n=41)	60.59±12.98	59.16±9.84	49.34±9.48	55.62±11.55	49.15±4.13	46.99±5.11	7.29±0.25	4.05±0.09	2.25±0.08
$t$value	0.073	2.035	3.719	0.032	2.230	3.884	0.653	2.107	9.277
P value	0.942	0.044	0.000	0.974	0.027	0.000	0.515	0.037	0.000

Table 3: Comparative analysis of serum immune factor levels in two patient groups before and after treatment [($\bar{x}$±s), 个/mm^3]

Groups	CD4+			CD3+			CD8+		
	Before treatment	30 days post-treatment	60 days post-treatment	Before treatment	30 days post-treatment	60 days post-treatment	Before treatment	30 days post-treatment	60 days post-treatment
Medication + orientation group (n=41)	531.43 ±38.43	928.46 ±53.47	1124.47 ±65.42	640.83 ±38.44	1004.33 ±62.53	1252.66 ±73.40	731.84 ±34.53	963.94 ±72.40	1147.42 ±55.44
Medication group (n=41)	532.01 ±36.45	835.07 ±60.55	1064.99 ±72.65	633.28 ±37.61	933.89 ±70.50	1139.48 ±81.47	729.95 ±36.59	886.42 ±69.32	1048.31 ±76.34
*t*value	0.070	7.403	3.896	0.899	4.786	6.609	0.241	4.952	6.726
P value	0.944	< 0.001	< 0.001	0.371	< 0.001	< 0.001	0.811	< 0.001	< 0.001

Table 4: Comparison of joint pain scores among two patient groups at various intervention stages [$\bar{x}$±s, points]

Groups	Joint pain		
	Before treatment	30 days post-treatment	60 days post-treatment
Medication + orientation group (n=41)	12.66±1.96	6.69±1.97	3.95±1.53
Medication group (n=41)	12.65±1.79	7.64±1.27	4.80±1.33
*t*value	0.024	2.595	2.685
p value	0.981	0.011	0.009

Table 5: Comparative evaluation of traditional chinese medicine symptom scores across two patient groups[$\bar{x}$±s, points]

Group	Morning stiffness	Joint swelling	Cold intolerance	Pain
Medication + orientation group (n=41)	1.34±0.22	1.13±0.19	1.19±0.25	1.20±0.15
Medication group (n=41)	1.48±0.33	1.42±0.23	1.48±0.29	1.44±0.19
T value	2.260	6.224	4.850	6.348
P value	0.027	< 0.001	< 0.001	< 0.001

Table 5: Comparison of adverse effects across two patient groups (%)

Group	Nausea and vomiting	Transaminases increased	Diarrhoea	Oral ulcer	Occurrence of adverse reactions
Medication + orientation group (n=41)	1(2.43)	0(0.00)	0(0.00)	0(0.00)	1(2.43)
Medication group (n=41)	3(7.32)	2(4.88)	2(4.88)	1(2.43)	8(19.51)
χ^2	/	/	/	/	6.116
P	/	/	/	/	0.013

The compound *Tripterygium wilfordii* Hook F exhibits an inhibitory action on the overly active autoimmune reactions in RA, aiding in controlling disease progression (Xie *et al*., 2024). This herb possesses anti-inflammatory properties, reducing the levels of pro-inflammatory cytokines like interleukin-1β and tumor necrosis factor-α, thus diminishing inflammation. It mitigates RA symptoms, such as swelling and pain, by curtailing the release of inflammatory mediators and lessening cellular infiltration (Li *et al*., 2019). Additionally, the alkaloids in *Tripterygium wilfordii* Hook F provide analgesic effects, decreasing joint pain associated with inflammation. They also contribute to slowing joint damage progression through antioxidative and anti-fibrotic actions. TCM directed drug delivery therapy is a technique that facilitates direct drug delivery to affected areas via the skin. This method can improve the absorption rate of drugs and make them directly act on pathological tissues, thus enhancing the therapeutic effect. CD3+, CD4+ and CD8+ serve as crucial markers on the surface of T lymphocytes, each indicating distinct subsets of T cells (Rosati *et al*., 2022). CD4+ T cells primarily regulate immune responses, whereas CD8+ T cells focus on eliminating cells infected by pathogens or cancerous cells. CD3+ is a component of the T cell receptor complex and plays a role in activating T cells and facilitating their signaling processes (Singh *et al*., 2021).Through directed drug delivery, the immunomodulatory and anti-inflammatory properties of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* enhance the immune capabilities of RA patients and mitigate inflammation. This improvement is reflected in the restoration of both the quantity and functionality of T cell subsets such as CD3+, CD4+ and CD8+. TCM directed drug delivery therapy enhances the absorption rate of these medications, allowing the active compounds in *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* to target the affected areas and immune system more directly and efficiently, thereby boosting their effect on immune regulation.

The findings indicate significant relief in arthralgia and enhanced joint function in RA patients treated with *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* through TCM directed drug delivery therapy ($P<0.05$). The biochemical composition of *Tripterygium wilfordii* Hook F is diverse, encompassing a range of active substances including sesquiterpenes, diterpenoids, triterpenoids and alkaloids. These compounds contribute to various pharmacological effects such as anti-inflammatory actions, immune modulation, anti-tumor properties and analgesia (Kun-Ming *et al*., 2020). (5R)-5-hydroxytriptolide, a potent component of *Tripterygium wilfordii* Hook F, possesses immunosuppressive properties that help mitigate inflammation (Cui *et al*., 2019). Furthermore, *Tripterygium wilfordii* Hook F has proven clinically effective in treating rheumatic conditions like RA and ankylosing spondylitis, notably reducing pain and morning stiffness in patients. Caulis Sinomenii also has the effect of dispelling wind-dampness and dredging meridians, which can effectively relieve the uncomfortable symptoms of RA patients and promote their recovery. Traditional Chinese Medicine directed drug delivery technology combines the meridian theory of TCM with modern transdermal delivery technology, so that drugs can directly act on the lesion site and improve the utilization rate and efficacy of drugs. Directed drug delivery therapy enables the active components of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* to more effectively reach joint tissues, where they exert anti-inflammatory and pain-relieving effects (Daikh *et al*., 2022). The synergistic use of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* boosts their collective efficacy, enhancing the treatment outcomes for RA. *Tripterygium wilfordii* Hook F mainly suppresses immune reactions and reduces inflammation, while *Caulis Sinomenii* is mainly used to relieve joint pain and improve joint function.

The research demonstrated significant enhancement in the TCM syndrome scores of patients ($P < 0.05$). *Tripterygium wilfordii* Hook F, characterized by its bitter and pungent qualities and cold nature, promotes blood flow to clear blocked collaterals and relieves swelling and pain while effectively treating rheumatism. Its bitter, cold attributes particularly contribute to its strong capability to alleviate symptoms such as joint redness, swelling, heat pain and morning stiffness (Lehmann *et al*., 2023). *Caulis Sinomenii*, with its bitter, pungent taste and mild nature, excels in expelling wind-dampness and freeing meridians. This makes it highly effective in alleviating discomfort in rheumatoid arthritis patients and aiding in disease recovery. When used in combination, *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* synergize to address the pathological stages of RA, thus enhancing therapeutic outcomes. The combination of *Tripterygium wilfordii* Hook F's immunosuppressive properties with *Caulis Sinomenii*'s ability to navigate through meridians allows for more effective symptom relief, including joint swelling, pain and morning stiffness. Employing Traditional Chinese Medicine directed drug delivery, this treatment strategy directly targets lesions, significantly boosting drug absorption and allowing active ingredients to act directly on affected areas, thus elevating therapeutic effectiveness (Wang *et al*., 2020). This method ensures that substances like *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* quickly reach joint tissues, effectively reducing inflammation, easing pain and dispelling rheumatism, thereby markedly improving RA's TCM symptoms.

Furthermore, there was a noted reduction in the incidence of adverse reactions among patients ($P < 0.05$). *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* are recognized in traditional Chinese medicine for their anti-inflammatory and analgesic properties, contributing positively to the treatment of rheumatoid arthritis (RA). However, the use of *Tripterygium wilfordii* Hook F alone may lead to several side effects, including nausea, vomiting

and increased transaminase levels. TCM directed drug delivery therapy employs a directed approach to administer medication directly to the affected site. This method enhances the precise and effective delivery of therapeutic agents to the targeted tissues, thereby increasing treatment effectiveness and minimizing broader side effects (Desai *et al*., 2022). The implementation of this delivery technology ensures that the medication specifically targets the diseased tissue, reducing its systemic distribution and, consequently, the occurrence of side effects such as nausea, vomiting and elevated transaminase levels. Since Traditional Chinese Medicine directs drug delivery technology, it can increase the local concentration of drugs and doctors can appropriately reduce the dosage of drugs in combination to achieve the same therapeutic effect. Decreasing the drug dose can directly reduce the occurrence of side effects (Gupta *et al*., 2024). Traditional Chinese Medicine directed drug delivery technology may reduce the metabolic burden of drugs in the liver by improving the absorption and metabolism process of drugs in diseased tissues, thus reducing the risk of liver injury, such as transaminase elevation. The anti-inflammatory and immunosuppressive properties of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* help to diminish systemic inflammation and over activation of the immune system in RA patients, thereby lowering the incidence of diarrhea and oral ulcers. Additionally, the antibacterial actions of both *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* contribute to reducing diarrhea and oral ulcers that arise from infections. Through directed drug delivery technology, drugs can act more directly on the lesion site and reduce irritation and damage to the gastrointestinal tract and oral mucosa, thus reducing the occurrence of diarrhea and oral ulcers.

CONCLUSION

In conclusion, when treating RA, combining *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* with TCM directed drug delivery therapy, aligned with TCM principles and contemporary medical practices, has yielded significant therapeutic outcomes. This approach not only enhances immune function and bolsters disease resistance but also notably improves joint mobility and alleviates patient discomfort and pain. Crucially, this treatment strategy profoundly ameliorates TCM symptoms and holistically conditions the patient's body, addressing both symptoms and underlying causes. Moreover, this regimen stands out by significantly reducing adverse reactions and minimizing discomfort and risks associated with the treatment process. Conclusion: The integration of *Tripterygium wilfordii* Hook F and *Caulis Sinomenii* with TCM directed drug delivery therapy offers a safe and effective treatment modality for RA.

Acknowledgement
Not applicable

Authors' contributions
Guangxun Yang and Min Chen wrote the main manuscript text, Xiaofeng Zou collected the data and prepared tables. Xiaofeng Zou and Wenting Zhang did the data analysis. Wenting Zhang designed and conducted the research. All authors reviewed the manuscript.

Funding
There was no funding.

Data availability statement
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by the Ethics Committee of the Taihe Hospital of Wannan Medical College (Approval NO: 2024-44).

Conflict of interest
The authors declare no competing interests

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