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ORIGINAL RESEARCH

Therapeutic Effects of Topical Traditional Chinese Medicine on Upper Extremity Fractures

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Background and Objectives: Effective pain and soft tissue management in conservatively treated upper extremity fractures remains challenging. Despite widespread use of traditional Chinese medicine (TCM) topicals for musculoskeletal injuries, robust evidence remains limited. This pilot study evaluated the safety and efficacy of two established TCM formulations during the acute phase of injury.

Patients and Methods: In this single-center, four-arm randomized controlled trial (NCT04593849), 24 adults with conservatively managed upper extremity fractures and Tscherne C0 or C1 tissue injuries were allocated to one of four groups: Wan-Yin-Gao-Jia-Jean-Wey (WYGJJW), Ru-Yih-Jin-Huang-Saan (RYJHS), TCM placebo, or control. Treatments were applied daily for 7 days. Feasibility (adherence, compliance) and primary outcomes (limb swelling, adverse skin reactions) were assessed by a blinded evaluator. Pain (VAS) and function (QuickDASH) were secondary outcomes. Non-parametric tests were used for analysis.

Results: A total of 24 participants were equally randomized into four study groups, achieving 100% adherence, with no missed doses or clinic visits [retention rate: 100%; drug compliance rate: 100%]. Both WYGJJW and RYJHS groups showed statistical significance in swelling reduction [WYGJJW: 0.95 cm (IQR: 0.9–1.9); RYJHS: 1.05 cm (0.5–5.35)], pain relief [WYGJJW: 2 points (0.88–4.5); RYJHS: 2 (1–2.25)], and functional improvement [WYGJJW: 7.96 points (2.95–16.48); RYJHS: 4.39 (2.27–14.72)]. The WYGJJW group reported fewer skin rashes (16.7%) compared to RYJHS (50.0%), suggesting a more favorable safety profile. When compared to the TCM placebo and control groups, WYGJJW demonstrated significantly greater swelling reduction, and marginally greater functional improvement compared to the TCM placebo group.

Conclusion: This study supports the safety, feasibility, and therapeutic potential of integrative TCM medicine for patients with upper extremity fractures and acute musculoskeletal injuries when surgical intervention is not recommended. A larger clinical trial is warranted to confirm these preliminary findings and to further assess long-term clinical effectiveness and safety.

Clinicaltrials.gov.id: NCT04593849 was registered on October 9, 2020.

Keywords: Ru-Yih-Jin-Huang-Saan (RYJHS), topical traditional Chinese medicine, upper extremity fractures, Wan-Yin-Gao-Jia-Jean-Wey (WYGJJW)

Introduction

Bone fractures represent a significant public health issue, with approximately 178 million new cases occurring globally in 2019,[1] which resulted in 25.8 million years lived with disability and marking a 65.3% increase since 1990.[2] Specifically, upper extremity fractures account for nearly half of the cases and tend to increase with age, often due to underlying frailty and higher fall risk,[3,4] leading to substantial medical costs and a profound impact on patients' socioeconomic well-being.[5]

In clinical practice, the management of fractures is determined by several factors, including the location of the injury and the types of the fracture. Treatment strategies range from conservative approaches, such as casting and splinting, to surgical interventions involving internal fixation. Fortunately, most upper extremity fractures, namely those in mid-clavicle, radius,

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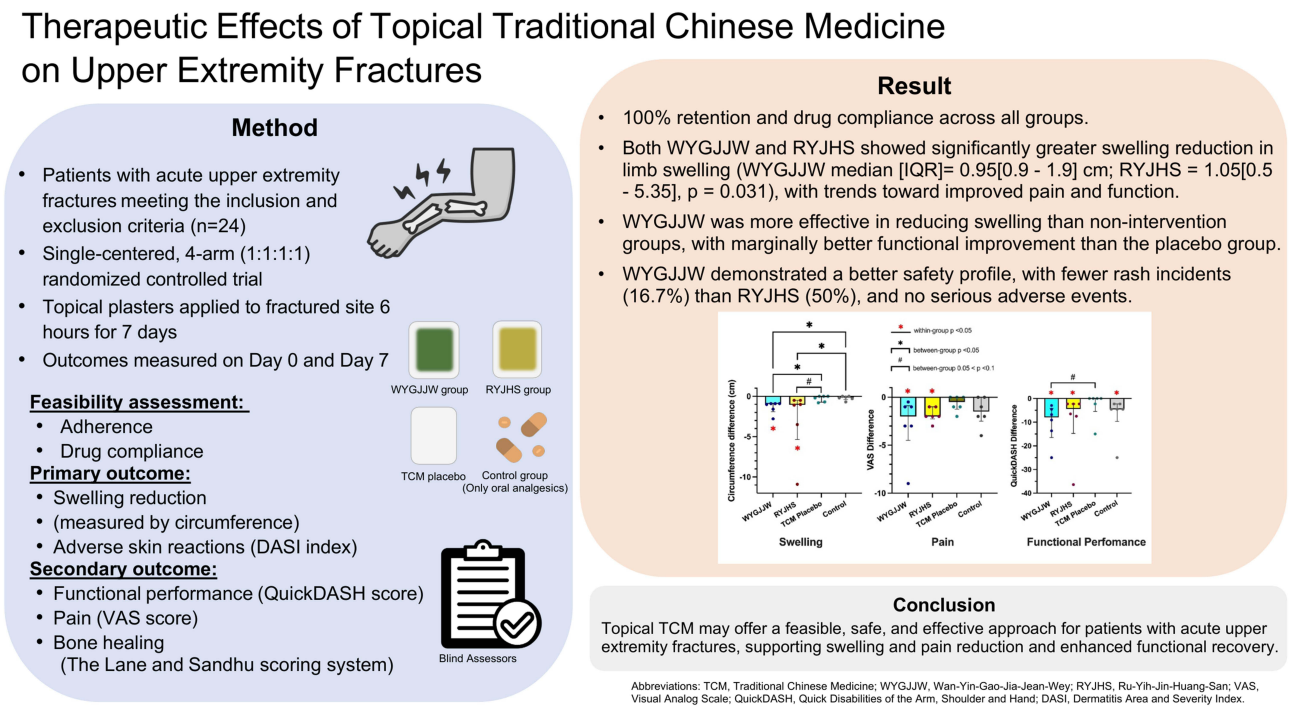
Graphical Abstract



Abbreviations: TCM, Traditional Chinese Medicine; WYGJJW, Wan-Yin-Gao-Jia-Jean-Wey; RYJHS, Ru-Yih-Jin-Huang-San; VAS, Visual Analog Scale; QuickDASH, Quick Disabilities of the Arm, Shoulder and Hand; DASI, Dermatitis Area and Severity Index.

mid-shaft humerus, and stable metacarpal, often heal with conservative treatment compared to lower extremity fractures, due to their non-weight-bearing nature, generally leading to fewer complications and a faster recovery.[6]

Although non-opioid analgesics, such as acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs), remain the general principle of pain management for fracture patients in orthopedic clinics, the efficacy of non-opioid analgesics is often suboptimal for patients with localized injuries due to potentially undesirable side-effects, such as gastrointestinal ulcers and bleeding, or concerns of impaired bone repair.[7] Given these limitations, there is growing interest in exploring complementary therapies that may enhance or support conventional treatments in managing musculoskeletal pain.

In traditional Chinese medicine (TCM), bone setting and injury therapy have lasted a long-standing history for over 3,000 years. TCM practitioners traditionally rely on topical herbal patches, through the essence of herbs believed to penetrate directly into the underlying tissues and initiate metabolic enhancements for tissue repair.[8] Compared to conventional oral administration, topical herbal patches offer several advantages: bypassing initial hepatic metabolism, providing continuous absorption of the active ingredients, reducing potential systemic side effects, and eliminating the need for invasive procedures.[9] For instance, a study showed that topical capsaicin, derived from chili peppers, had better pain-relieving effects in degenerative knee osteoarthritis than orally administered NSAIDs.[10] Furthermore, TCM offers promising topical applications of herbal formulations, having been used historically to reduce pain and limb swelling and promote fracture healing, and may be considered a potentially better, cost-effective alternative.[11]

Previous preclinical and clinical studies have indicated the efficacy of topical TCM for musculoskeletal injuries.[12–17] In clinical practice, Ru-Yih-Jin-Huang-Saan (RYJHS) is the most commonly used topical TCM but may cause skin allergies or contact dermatitis with frequent use.[18] RYJHS (licensed by the Taiwan Department of Health, DOH-OM-000913) is prepared as a paste (herbal powder mixed with water) that is spread on cloth and secured to the affected area with gauze.

In 2005, Chang Gung Memorial Hospital in Linkou, Taiwan, used Wan-Yin-Gao (WYG), a commonly prescribed topical herbal formulation, to treat tendonitis of the upper extremities and demonstrated a significant reduction in pain.[19]

Nevertheless, a notable gap emerged in scientific evidence regarding the efficacy of the topical TCM in the context of bone fracture healing. To address this gap and enhance analgesic effects, a modified WYG called Wan-Yin-Gao-Jia-Jean-Wey (WYGJJW, licensed by the Taiwan Department of Health, DOH-OM-015078) was developed as an herbal plaster. WYGJJW shares WYG's circulation-promoting, pain-relieving mechanism but omits *Sophorae Flavescentis Radix* and adds *Myrrha* and *Olibanum* to strengthen its anti-inflammatory properties. Furthermore, to explore the potential molecular mechanisms underlying the observed clinical effects, this study incorporated bioinformatics analyses using SymMap and g:Profiler to identify relevant signaling pathways and molecular functions associated with the herbal components of WYGJJW and RYJHS.

This study aimed to evaluate the clinical effects of topical TCM on upper extremity fractures using WYGJJW and RYJHS, the two most commonly prescribed medicated plasters in Taiwan. Both are officially approved and widely used for treating bruises, sprains, and rheumatic pain. We hypothesized that adjunctive use of these herbal medicines, alongside oral analgesics, would enhance treatment effectiveness during the early inflammatory phase of musculoskeletal injuries and accelerate recovery.

Materials and Methods

Study Design

This randomized, controlled clinical trial aimed to assess the efficacy and safety of topical TCM in treating upper extremity fractures, compared with TCM placebo and standard oral analgesic treatment. This clinical trial was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB No. 202001174A3) and registered on ClinicalTrials.gov (Identifier: NCT04593849) and conducted following the Declaration of Helsinki. Written informed consent was obtained from all study participants before the study commenced.

Participants

Patients were enrolled in outpatient clinics at Keelung Chang Gung Memorial Hospital between October 2020 and May 2023. Informed consent was obtained from each patient for study participation. The following inclusion and exclusion criteria were used for selection:

Inclusion Criteria

1. Patients aged 18 and above experiencing upper extremity fractures, including clavicle fractures, upper arm fractures, forearm fractures, wrist fractures, finger and hand fractures, etc.
2. Fracture types include simple fractures with non-displacement or mild displacement, such as transverse fractures, oblique fractures, linear fractures, impacted fractures, etc.
3. Patients assessed by orthopedic physicians as not requiring surgery for initial medical treatment.
4. Willingness to sign a written informed consent form and compliance with the medical advice from specialists.
5. Patients assessed by orthopedic physicians using Tscherne classification (for open/closed fractures) with tissue injury severity of C0, C1, and no high risk of tissue infection.[20] (Table A1, Supplementary Material)

Exclusion Criteria

1. Compound fractures.
2. Simple fractures with moderate or severe displacement.
3. Simple fractures with instability, such as comminuted fractures, segmental fractures, etc.
4. Patients assessed by orthopedic physicians as requiring surgery.
5. Severe open fractures with a high risk of tissue infection.
6. Tissue injury severity assessed by orthopedic physicians using Tscherne classification as C2 or higher with a high risk of tissue infection.
7. Inability to complete the trial questionnaire or compliance with the trial instructions.
8. Patients with skin allergies or hypersensitivity to ointments, plasters, or patches.
9. Pregnant patients.

10. Patients with severe smoking addiction.
11. Patients with severe anemia, poorly controlled blood sugar, or thyroid-related diseases.
12. Patients undergoing ongoing electrical stimulation or acupuncture on the upper extremities.
13. Patients currently using other herbal medicines or alternative therapy to treat closed fractures of the upper extremities.

Randomization and Blinding

After enrollment in the study, participants were randomly assigned via computer-generated sequence to one of four groups: Group A (WYGJJW treatment), Group B (RYJHS treatment), TCM placebo Group, or Control Group (oral analgesics only), with an allocation ratio of 1:1:1:1. Due to the distinct administrative pattern and the nature of the treatments, double blinding was not feasible. As a result, we used a blinded assessor during data collection as an alternative method. In addition, participants were instructed not to share any information regarding group assignment or health condition until the end of study.

Intervention

Participants began their assigned treatments immediately after enrollment, with all groups receiving standard fracture care (eg splint or cast immobilization as appropriate and routine advice on limb elevation and movement). The interventions for each group were as follows:

- WYGJJW (Group A): Patients received the WYGJJW. This is a topical paste prepared from a mixture of Chinese medicinal herbs intended to reduce inflammation and swelling. The paste was spread on a cotton cloth (approximately covering the injured area) and applied directly over the fracture site. It was then secured with a layer of gauze. Each application was kept in place for 6 hours per day, after which the plaster was removed. A fresh plaster was applied daily for a total of 7 consecutive days. Patients were instructed on how to apply and remove the plaster at home and advised to monitor for any skin irritation. They were also allowed to take oral acetaminophen as rescue analgesia if needed.
- RYJHS (Group B): The primary components of RYJHS include *Trichosanthis radix, Rhei radix et Rhizoma, Phellodendri cortex, Curcumae longae rhizoma, Angelicae dahuricae radix, Magnoliae cortex, Glycyrrhizae radix et Rhizoma, Citri reticulatae pericarpium vetum, Atractylodis rhizoma*, and *Arisaematis rhizome*. RYJHS was prepared by mixing 9 grams of powder with 21 mL of water, which is then evenly spread onto a cotton cloth and covered with gauze for later use. Similar to the WYGJJW group, the RYJHS remaining on the skin for 6 hours daily for 7 days. This formulation is a TCM herbal patch known for its anti-inflammatory and analgesic effects. Patients were likewise allowed rescue oral analgesics if necessary.
- TCM Placebo group: Patients in this group received a placebo patch with no active herbal ingredients. To mimic the experience of the herbal plaster without providing specific therapeutic herbs, which was then applied to the injury area and secured with gauze. This patch had no known therapeutic effect but provided the same coverage as the real plasters. It was worn for 6 hours daily for 7 days, identical to the active treatment groups. Like the other groups, these patients could use oral analgesics as per standard care if needed.
- Control group: Patients in the control arm did not receive any form of topical patch. Instead, they were managed with standard oral analgesic therapy only. In our clinic protocol for conservatively managed fractures, this typically involves non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for pain relief, as appropriate for the patient's age and medical condition. The dosing and choice of analgesic were left to the treating physician's discretion, following usual practice, and could be adjusted according to pain levels.

Throughout the 7-day treatment period, all participants were monitored for adverse events. Any adverse reactions were documented and tracked with imaging evidence, followed by an adjustment of the topical treatment course, including avoidance of allergic skin region, shortened treatment duration, or temporary suspension of the treatment, depending on the severity of adverse skin reactions.

Outcome Measures

To evaluate the feasibility of the study protocol, we monitored key implementation metrics, including adherence rate, drug compliance rate, and participant retention. Adherence was assessed by tracking each participant's attendance at scheduled clinic visits, engagement in symptom monitoring, and their ability to integrate the treatment regimen into daily life. Drug compliance specifically referred to the correct and consistent application of the topical treatment, as prescribed —6 hours per day over the fractured site, avoiding any open wounds. Compliance was monitored through family member supervision and occasional photo submissions for verification of application accuracy. Retention was evaluated based on study completion without withdrawal or loss to follow-up.

Primary outcomes included swelling reduction, measured by circumference at the affected site compared to the healthy side using a caliper. Markings were made during each measurement to ensure consistency and the absence of adverse skin reactions (DASI index) was documented.[21] (Table A2, Supplementary Material) Secondary outcomes encompassed functional performance (QuickDASH score),[22,23] pain reduction (Visual Analogue Scale, VAS),[24] and recovery of bone alignment and union (radiographic images using The Lane and Sandhu scoring system).[25,26] (Table A3, Supplementary Material)

Sample Size and Data Collection

A priori sample size estimation was conducted using G*Power 3.1 for a two-tailed paired *t*-test, with an alpha of 0.05, power of 80%, and a minimal detectable change of 0.6 cm in limb circumference (the primary outcome). A total sample size of 24 was estimated as required to achieve prespecified power, with six subjects in the respective study group. The study endpoints were set at the date of follow-up after one week of treatment starting from the baseline visit. All the outcome measures, including limb circumference for swelling, functionality, pain, x-ray for bone fracture union assessment and skin reaction assessment, were collected by medical staff.

Statistical Analysis

Descriptive analyses were conducted to assess baseline comparability across four study groups regarding demographic and clinical characteristics. ANOVA was used for continuous variables summarized in means and standard deviations (SDs), including participants' age, BMI, pain score (VAS), radiographic bone union score (The Lane and Sandhu) and functionality (QuickDASH). Categorical variables, including gender, affected limb and fracture site, education level, and diabetes mellitus status, were summarized as frequencies and percentages. Group comparisons were conducted using the chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was applied in cases of small sample sizes or when expected cell counts were less than five, to ensure the accuracy of statistical inference.

For within-group comparisons of continuous outcomes (eg, swelling circumference, pain, and functional scores) from baseline to endpoint, paired t-tests were initially planned. However, when normality assumptions were violated, the non-parametric Wilcoxon signed-rank test was used instead. For between-group comparisons of outcome changes, a one-way ANOVA was initially considered; however, when normality or homogeneity of variance assumptions were not met, the Kruskal–Wallis test was applied. When significant differences were observed in Kruskal–Wallis tests, post hoc Dunn's pairwise comparisons with Bonferroni adjustment were performed to control for multiple testing.

All statistical tests were two-tailed, with a significance threshold set at $p < 0.05$. Analyses were conducted using STATA (version 17.0), and visualizations were generated using GraphPad PRISM (version 10.1.1).

Results

Study Population and Patient Characteristics

A total of 24 patients met the inclusion criteria and were randomized equally into four study groups (WYGJJW, RYJHS, TCM Placebo, and Control; n = 6 per group). All participants initiated treatment and completed the 7-day intervention period, resulting in a drop-out rate of 0% and a 100% retention rate. Adherence to the study protocol—including scheduled clinic visits and symptom monitoring—was maintained by every participant. Drug compliance was verified primarily through family or caregiver supervision. Although a few participants reported mild skin irritation or rashes during treatment, these events were tolerable and did not lead to missed doses or disruption of the prescribed regimen (Figure 1).

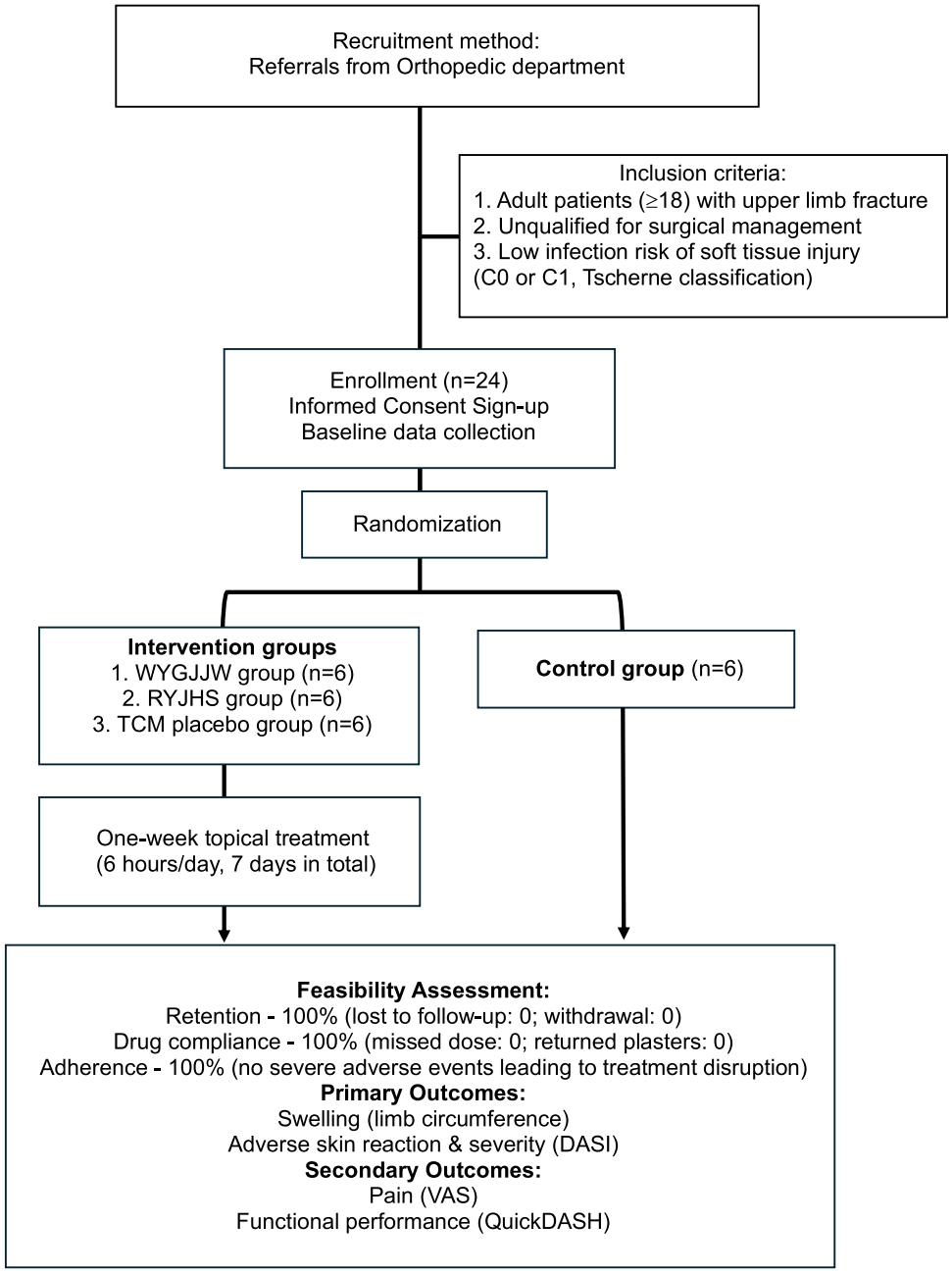


Figure 1 Consort Diagram. Flowchart illustrating the study process, including participant recruitment, intervention allocation and timeline, and follow-up through to final analysis (n = 24).

Baseline characteristics of the 24 patients included in the final analysis are summarized across the four study groups [mean age (SD) = 68.96 (15.95)]. Among these participants, 21 (87.5%) had wrist fractures and 3 (12.5%) had humerus fractures, with no significant difference in fracture distribution across groups. While the control group had a statistically lower proportion of female participants (p = 0.045), the other three groups were predominantly female. Participants in the WYGJJW and RYJHS groups were significantly older compared to other groups (p = 0.011), and had a higher proportion of individuals with lower educational attainment (junior high school or below), though this difference was not statistically significant (p = 0.208). Other baseline variables—including height, weight, body mass index, affected limb dominance, and diabetes mellitus status—were generally comparable across groups. Notably, the WYGJJW group had the highest proportion of participants with diabetes (67%), although this difference did not reach statistical significance (Table 1).

Table 1 Baseline Characteristics of Participants

Characteristics	WYGJJW Group (n=6)	RYJHS Group (n=6)	TCM Placebo Group (n=6)	Control Group (n=6)	P value
Female, n (%)	4(67)	6(100)	4(67)	1(17)	0.045
Age, mean (SD)	76.33(7.31)	72(12.6)	60.66(22.25)	66.83(17.29)	0.011
Height (cm), mean (SD)	157.6(8.83)	154.9(7.80)	158.36(13.67)	153.93(3.78)	0.813
Weight (kg), mean (SD)	60.96(10.97)	62.93(14.36)	69.78(19.83)	50.81(3.88)	0.145
Body mass index, mean (SD)	24.49(3.96)	25.94(3.96)	27.37(5.09)	21.43(1.26)	0.079
Affected limb, dominant, n (%)	3(50)	3(50)	2(33)	4(67)	0.944
Fracture site, n (%)					
Wrist fracture	5(83)	5(83)	5(83)	6(100)	1.0
Humerus fracture	1(17)	1(17)	1(17)	0(0)	1.0
Diabetes mellitus, n (%)	4(67)	1(17)	2(33)	1(17)	0.373
Education, n (%)					0.208
Junior high school or below	6(100)	5(83)	3(50)	3(50)	
Senior high school or above	0(0)	1(17)	3(50)	3(50)	
Baseline score					
Tscherne classification (C0 %)	100%	100%	100%	100%	
The Lane and Sandhu scoring, mean (SD)	3(1.89)	2.83(2.4)	4.5(1.76)	2.83(2.04)	0.436
Affect limb circumference (cm), mean (SD)	21.52(1.86)	24.3(5.01)	19.87(0.99)	18.97(0.52)	0.543
VAS, mean (SD)	4.75(2.75)	4.83(2.63)	3.66(2.8)	5(2.6)	0.824
QuickDASH, mean (SD)	66.24(12.7)	71.61(9.88)	57.3(15.1)	78.4(13.2)	0.062

Primary Outcome: Swelling and Skin Adverse Reaction

Given the non-normal distribution of collected data, a one-sample Wilcoxon signed-rank test was used to assess pre- and post-intervention changes within each group. We observed a significant improvement in swelling condition for both RYJHS and WYGJJW group, with a median reduction in affected limb circumference of 0.95 centimeters (IQR = 0.9–1.9, p = 0.031) and 1.05 centimeters (IQR = 0.5–5.35, p = 0.031), respectively. In contrast, the swelling improvement was barely observable in either the TCM placebo group (median: - 0.1, IQR = - 0.73–0) or control group (median: - 0.15, IQR = - 0.4–0). (Table 2)

Table 2 Outcome Summary for Each Study Group

Group/Outcome	WYGJJW (n=6)	RYJHS (n=6)	TCM Placebo (n=6)	Control (n=6)
Swelling, circumference of the fractured limb (cm)				
Pre	20.95 (18.2–24.5)	18.15 (16.13–35.5)	20.75 (18.9–21.13)	19.25 (17.75–19.98)
Post	20 (16.78–23.13)	16.2 (12.85–33.88)	20.4 (18.25–21.13)	19.2 (17.6–19.58)
Difference, median (IQR)	0.95 (0.9–1.9) *	1.05 (0.5–5.35) *	0.1 (0–0.73)	0.15 (0–0.4)
Difference, mean (SD)	1.35 (0.76)	2.92 (4.07)	0.28 (0.37)	0.22 (0.26)
Pain, Visual Analogue Score (VAS)				
Pre	4.75 (2–6.75)	4 (2.75–8)	3 (1.75–5.25)	5 (2.75–7.25)
Post	2 (0.75–3)	2.5 (1–5.25)	2.5 (1–4.25)	3.5 (2–5)
Difference, median (IQR)	2 (0.88–4.5) *	2 (1–2.25) *	0.5 (0–1.25)	1.5 (0–2.5)
Difference, mean (SD)	2.92 (3.16)	1.83 (0.75)	0.67 (0.82)	1.5 (1.52)
Functional Performance, QuickDASH				
Pre	65.91 (57.9–74.43)	68.25 (64.77–80.11)	56.81 (44.53–63.29)	78.41 (67.61–91.47)
Post	56.82 (44.83–70.51)	61.25 (54.54–69.31)	56.81 (40.78–71.59)	69.32 (63.06–82.95)
Difference, median (IQR)	7.96 (2.95–16.48) *	4.39 (2.27–14.72) *	0 (0–5.45)	4.55 (2.27–9.66) *
Difference, mean (SD)	10.34 (8.1)	9.53 (13.35)	2.88 (6.01)	7.2 (8.79)

(*Continued*)

Table 2 (Continued).

Group/Outcome	WYGJJW (n=6)	RYJHS (n=6)	TCM Placebo (n=6)	Control (n=6)
Adverse Reaction Incident and Severity (DASI score)				
No. event (%)	1 (16.67%)	3 (50%)	0 (0)	0 (0)
DASI score, Median (IQR)	0 (0–1.5)	0.5 (0–1)	0 (0–0)	0 (0–0)

Notes: *Within-group comparison (Wilcoxon test) p value < 0.05. Differences were reported as absolute changes in measurement units from pre- to post-intervention status.
Abbreviations: IQR, Interquartile range; Pre, measurements before study intervention; Post, measurements after study intervention; SD, standard deviation.

Additionally, significant improvement in swelling was found between two or more groups based on the non-parametric Kruskal–Wallis test (p = 0.002), prompting a post-hoc analysis for multiple pairwise comparisons. The improvement was found significantly differentiable between WYGJJW and TCM placebo (p = 0.004), WYGJJW and control (p = 0.029), and RYJHS and control (p = 0.043). A marginally significance was observed between RYJHS and TCM placebo group (p = 0.055) (Figure 2A).

During the study period, four participants reported adverse skin reactions—one from the WYGJJW group (16.7%) and three from the RYJHS group (50%). Regarding severity, the WYGJJW case was classified as a second-degree skin reaction, characterized by redness, mild crusting, and itching, with a corresponding DASI score of median = 0 (IQR: 0–1.5). The three reactions in the RYJHS group were classified as first-degree allergic responses, with a median DASI score of 0.5 (IQR: 0–1) (Table 2). Importantly, these adverse events did not interfere with the study timeline or treatment adherence, and 100% drug compliance was maintained across all groups.

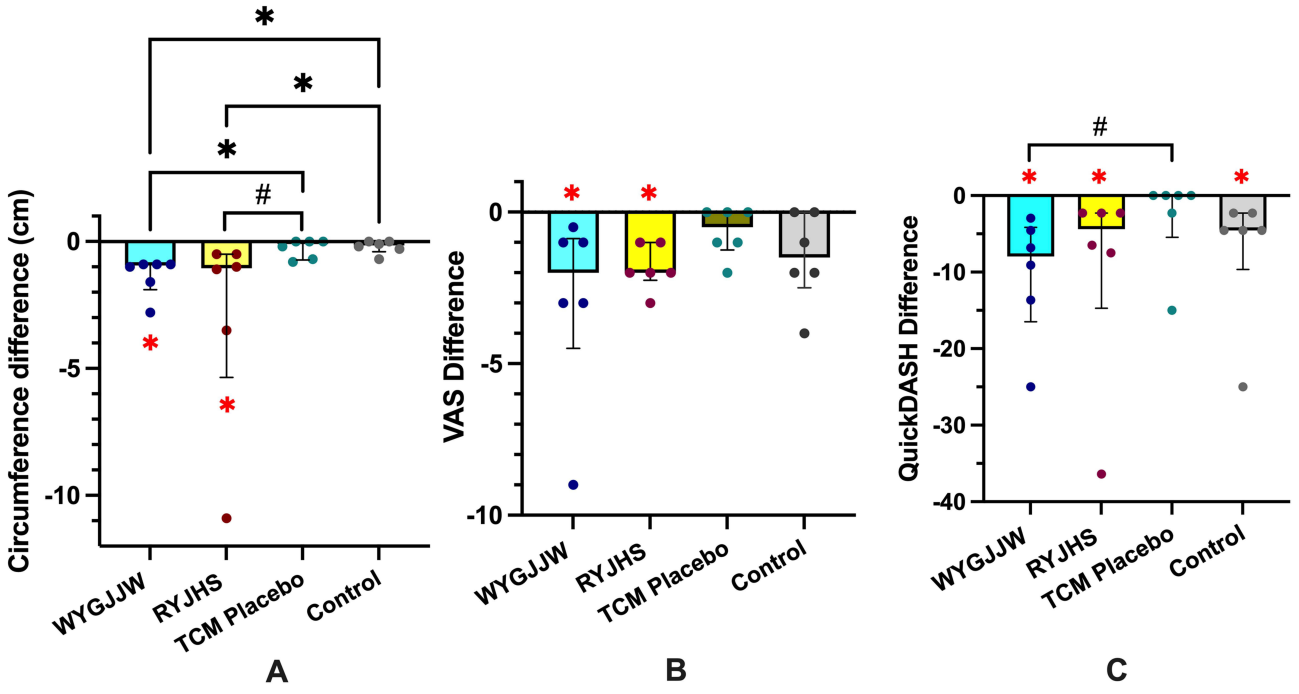


Figure 2 Changes in swelling (**A**), pain (**B**), and functional performance (**C**) before and after the intervention period across study groups. Each bar represents the median, and error bars represent the interquartile range (IQR) of measurement differences from pre- to post-intervention for each study group. Red asterisks (*) indicate statistically significant (p < 0.05) within-group changes based on Wilcoxon signed-rank tests. Black asterisks (*) above brackets indicate statistically significant (p < 0.05) between-group differences based on pairwise comparisons following the Kruskal–Wallis test. Number signs (#) above brackets indicate marginally significant between-group differences (0.05 < p < 0.10) based on pairwise comparisons following the Kruskal–Wallis test.

Secondary Outcome: Pain (VAS Score) and Functionality (Quick DASH)

For the pain outcome, both the WYGJJW and RYJHS group showed statistically significant reductions in VAS scores from baseline to study endpoint. The WYGJJW group showed a median decrease of 2 points (IQR: 0.88–4.5; p = 0.031), while the RYJHS group showed a median decrease of 2 points with smaller variation (IQR: 1.0–2.25; p = 0.031). However, the Kruskal–Wallis test did not detect statistically significant differences between groups. A post hoc power analysis indicated insufficient power (56.7%) for detecting inter-group differences, likely due to the small sample sizes and the narrow scale of the VAS measure, which may have inflated variability. Despite these limitations, the WYGJJW group exhibited the greatest mean decrease in VAS scores (mean = 2.9, SD = 3.16), followed by the RYJHS group (mean = 1.8, SD = 0.75), with minimal changes observed in the TCM placebo (mean = 0.7, SD = 0.82) and control groups (mean = 1.5, SD = 1.52). This trend may suggest a clinically meaningful improvement in pain among patients receiving the WYGJJW topical treatment (Table 2 and Figure 2B).

For functional outcomes measured by QuickDASH, significant improvements from baseline were observed in all groups except the TCM placebo group. Median improvements were as follows: WYGJJW group, 8.0 points (IQR: 2.95–16.48; p = 0.031); RYJHS group, 4.4 points (IQR: 2.27–14.72; p = 0.031); control group, 4.6 points (IQR: 2.27–9.66; p = 0.031). The Kruskal–Wallis test indicated a borderline global significance across the four groups (p = 0.064), and post hoc pairwise comparisons revealed a borderline difference between the WYGJJW and TCM placebo groups (p = 0.051) (Table 2 and Figure 2C). Given our a priori interest in comparing the intervention to the placebo/control groups, we conducted an exploratory Wilcoxon rank-sum test comparing the WYGJJW and TCM placebo groups, which showed a statistically significant difference (p = 0.034). This suggests that the WYGJJW intervention may offer a more efficient improvement in functional recovery compared to placebo.

Discussion

In this randomized controlled, four-armed pilot study, both the WYGJJW and RYJHS demonstrated therapeutic potential in reducing limb swelling, alleviating pain, and improving functional outcomes in the acute phase of upper limb fracture. These effects were reflected in changes in circumference measurements, VAS scores, and QuickDASH assessments. Notably, WYGJJW showed a statistically significant reduction in swelling compared to both the TCM placebo and control groups. Although the differences in pain relief and functional improvement did not meet conventional thresholds for statistical significance, the trends suggest a clinically meaningful benefit of WYGJJW over non-intervention groups. This may be explained by limited statistical power due to the small sample size and narrow measurement scales, rather than a true absence of effect. Importantly, the trial demonstrated strong feasibility, with 100% retention, adherence, and drug compliance rates, and no treatment interruptions despite minor, self-limited adverse skin reactions. Moreover, we observed three cases (50%) from the RYJHS group reporting skin rashes and vesicles over the standard treatment course, as opposed to one case (16.7%) of skin rashes from intervention treatment, which suggested a better safety profile of this new treatment, WYGJJW.

In our study, the application of WYG and its modified version, WYGJJW is supported by the therapeutic properties of these TCM formulations. While specific studies on WYG and WYGJJW are limited, the broader context of TCM provides insights into the potential benefits of WYG and WYGJJW. TCM formulations, similar to WYG and WYGJJW, have shown a range of therapeutic effects. For instance, a research team developed a novel topical plaster, named "fracture healing" based on TCM theory, containing extracts from six CHM ingredients: *Dipsacus asper, Sambucus williamsii, Panax notoginseng, Carthamus tinctorius, Rheum palmatum, and Gardenia jasminoides*. The in vitro and in vivo results demonstrated that the plaster exhibits anti-inflammatory effects, promotes blood vessel repair, and enhances osteoblast activity when applied to rabbit tibial fractures.[27] Another study focused on traumatic thoracolumbar vertebral fractures, involving TCM fumigation with a formula made from *Carthami Flos, Angelicae Sinensis Radix, Panacis Quinquefolii Radix, and Culleniae Fructus*, significantly reducing postoperative pain, swelling, and increasing bone density.[28] The potential of these formulations in modulating tissue repair and inflammation is relevant to the healing process in fractures.

The use of RYJHS in our study aligns with the growing body of evidence supporting its therapeutic potential in TCM. RYJHS has shown rapid and thorough healing of fractures in animal models, enhancing collagen formation and bone cell metabolism,[16] which aligns with our findings that the RYJHS application resulted in improved fracture healing and reduced recovery time in patients with upper extremity fractures. Furthermore, RYJHS has demonstrated a range of therapeutic effects, including reducing swelling, anti-inflammation, promoting blood flow, and aiding in joint rehabilitation.[29] These properties are particularly relevant in the context of upper extremity fractures, where swelling and inflammation can significantly impact recovery and functional outcomes. In our study, reduced swelling and pain in the RYJHS group have corroborated these effects. Interestingly, RYJHS has also been noted for its broader applications in oncology, showing efficacy in improving post-operative symptoms and enhancing the effectiveness of chemotherapy.[30] Even though our study did not explore these aspects, the efficacy of RYJHS highlights its multifaceted nature and potential utility in various therapeutic contexts.

The RYJHS users commonly reported adverse skin reactions due to potentially irritating components, such as raw *Arisaematis Rhizoma*,[31,32] causing irritation, redness, and, in severe cases, contact dermatitis on patients' hands. Fortunately, only three cases (50%) in RYJHS reported rashes and blisters without requiring treatment suspension. In line with a previous study on phlebitis treatment, a high efficacy of RYJHS with minimal adverse effects,[33] endorsing the safety feasibility for RYJHS in the clinical settings when applying traditional medicines at acute phase of soft tissue injuries. In addition, only one case (16.7%) in the WYGJJW group experienced mild rash, suggesting that WYGJJW may have even better safety. Regardless, further clinical studies with larger sample sizes are needed to validate the evidence for clinical improvement and adversity.

Of importance, RYJHS shown in previous animal studies[16] increased the content of hydroxyproline and molecular synthesis in bone tissue from fractured rat bones, hence suggesting its effects in promoting the formation of collagen and the metabolism and growth of bone cells.[16,34] However, in the current study, no healing change of fractured bones was observed in radiographic images or the Lane and Sandhu scores after the intervention period. We attributed these underserving results to the narrow observation window. Similarly, a vivo study revealed a significant increased bone volume after 42-day application of herbal pastes with shared compounds on fractured tibia bones in experimental rats.[35] Indeed, the fracture healing process is a multi-stage journey, beginning with the soft callus formation to provide initial stability within one to three weeks post-injury, ossification to six weeks as a firmer stabilizer, then the remodeling stage, potentially extending for several months to years, and finally the maturity of bone's original structure for healing and nonunion.[36] In the present study, expectedly, one week of follow-up period still sustains an early inflammatory stage, prior to any observable form of bone healing process.

The efficacy of TCM formulations has been a novel subject of interest in modern biomedical studies. Bioinformatics, for example, integrates biological data with computational techniques that helps elucidate the mechanistic actions of complex herbal formulations, in an attempt to improve understanding of the multi-component herbal medicine network.[37–39] As such, we performed a biological pathways analysis encompassing KEGG, Reactome, and WikiPathways that indicate influences by the core targets of WYGJJW and RYJHS. SymMap and g:Profiler were also utilized to explore the molecular interactions and functions of bioactive compounds in WYGJJW and RYJHS, via biological interpretations of functional enrichment analysis and genomic data,[40] mapping to a comprehensive Gene ontology analysis (GO). The bioinformatics analysis of WYGJJW and RYJHS revealed distinct and overlapping molecular mechanisms related to anti-inflammatory and bone metabolic pathways. WYGJJW was associated with Arachidonic acid metabolism, PI3K-Akt signaling, and NF-kappa B signaling, while RYJHS showed significant involvement in pathways, such as Estrogen signaling and TNF signaling (Table 3A and B). In the GO analysis, similarly, the GO Molecular Function (GOMF) results for RYJHS display a wide range of mechanisms, including those related to immunomodulation, vitamin D, and estrogen pathways (Figure 3). On the other hand, the GOMF results for WYGJJW indicate that the mechanism of this medicine is clearly associated with prostaglandin-endoperoxide synthase activity, suggesting a shared pharmacological property of anti-inflammatory action with NSAIDs (Figure 4).

Table 3 Inferred Molecular Pathways of (A) WYGJJW and (B) RYJHS

Pathway Name	Adjusted p Value	Source
(A) WYGJJW		
Arachidonic acid (AA, ARA) oxylipin metabolism	5.691×10^{-4}	Wikipathway
Estrogen signaling pathway	4.044×10^{-3}	KEGG
Aspirin and miRNAs	7.140×10^{-3}	Wikipathway
Eicosanoid synthesis	8.095×10^{-3}	Wikipathway
Estrogen signaling pathway	8.095×10^{-3}	Wikipathway
Relationship between inflammation, COX-2 and EGFR	9.257×10^{-3}	Wikipathway
PI3K-Akt signaling pathway	9.432×10^{-3}	KEGG
NF-kappa B signaling pathway	1.073×10^{-2}	KEGG
Eicosanoid metabolism via cyclooxygenases (COX)	1.231×10^{-2}	Wikipathway
Prostaglandin and leukotriene metabolism in senescence	1.231×10^{-2}	Wikipathway
Prostaglandin and leukotriene metabolism in senescence	1.353×10^{-2}	Wikipathway
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	1.665×10^{-2}	REACTOME
Prostaglandin synthesis and regulation	1.762×10^{-2}	Wikipathway
PI3K-Akt signaling pathway	1.765×10^{-2}	Wikipathway
Vitamin D receptor pathway	2.265×10^{-2}	Wikipathway
Vitamins A and D - action mechanisms	2.558×10^{-2}	Wikipathway
Estrogen-dependent gene expression	3.176×10^{-2}	REACTOME
COX reactions	3.176×10^{-2}	REACTOME
Arachidonic acid metabolism	3.715×10^{-2}	REACTOME
(B) RYJHS		
Estrogen signaling pathway	6.335×10^{-4}	KEGG
ESR-mediated signaling	9.036×10^{-4}	REACTOME
Arachidonic acid (AA, ARA) oxylipin metabolism	1.058×10^{-3}	Wikipathway
TNF signaling pathway	2.247×10^{-3}	KEGG
Synthesis of Prostaglandins (PG) and Thromboxanes (TX)	3.662×10^{-3}	REACTOME
Estrogen receptor pathway	3.703×10^{-3}	Wikipathway
Quercetin and Nf-kB / AP-1 induced apoptosis	4.566×10^{-3}	Wikipathway
PI3K/AKT/mTOR - vitamin D3 signaling	7.004×10^{-3}	Wikipathway
Estrogen signaling pathway	7.234×10^{-3}	Wikipathway
Eicosanoid synthesis	7.234×10^{-3}	Wikipathway
Relationship between inflammation, COX-2 and EGFR	8.397×10^{-3}	Wikipathway
Eicosanoid metabolism via cyclooxygenases (COX)	1.203×10^{-2}	Wikipathway

(*Continued*)

Table 3 (Continued).

Prostaglandin and leukotriene metabolism in senescence	1.203×10^{-2}	Wikipathway
NF-kappa B signaling pathway	1.270×10^{-2}	KEGG
COX reactions	1.301×10^{-2}	REACTOME
Osteoclast differentiation	1.867×10^{-2}	KEGG
Prostaglandin synthesis and regulation	1.922×10^{-2}	Wikipathway
RANKL/RANK signaling pathway	2.458×10^{-2}	Wikipathway
Arachidonic acid metabolism	3.133×10^{-2}	REACTOME

Notes: RYJHS demonstrated notable activity in pathways, such as Estrogen signaling and TNF signaling. In contrast, WYGJJW was linked to pathways involving Arachidonic acid metabolism, PI3K-Akt signaling, and NF-kappa B signaling, highlighting the diverse therapeutic potentials of these formulations.

Abbreviations: AA, Arachidonic Acid; AKT, Protein Kinase B; AP-1, Activator Protein 1; ARA, Arachidonic Acid; BMI, Body Mass Index; CI, Confidence Interval; COX, Cyclooxygenase; EGFR; Epidermal Growth Factor Receptor; ESR, Estrogen Receptor; GO, Gene Ontology; GOMF, Gene Ontology Molecular Function; KEGG, Kyoto Encyclopedia of Genes and Genomes; miRNA, microRNA; mTOR, Mammalian Target of Rapamycin; NF-κB, Nuclear Factor kappa B; PG, Prostaglandins; PI3K, Phosphatidylinositol 3-kinase; TNF, Tumor Necrosis Factor; TX, Thromboxanes.

Strengths and Limitations

To our knowledge, this is the first randomized controlled trial to evaluate the feasibility and clinical effectiveness of topical herbal medicine in patients with acute upper extremity fractures. Our study incorporated multiple indicators to assess the practicality and acceptability of the intervention in a real-world setting, demonstrating high feasibility, full compliance, and a strong safety profile. We attribute these outcomes to the favorable study design—characterized by a condensed treatment timeline, a simple topical application regimen, and a lack of alternative therapies beyond oral analgesics for non-surgical, low-grade fracture cases. A notable strength of this study is the incorporation of both objective (limb circumference, DASI) and subjective (VAS, QuickDASH) outcome measures, allowing for a more comprehensive assessment of safety and effectiveness. These findings may inform future clinical applications and support the design of larger trials in similar patient populations. Moreover, the incorporative bioinformatic analysis, leveraging the capabilities of SymMap and g:Profiler, provides subsequent biological validations, strengthening the scientific evidence for the understanding of potential therapeutic mechanisms in TCM formulations at the molecular level.

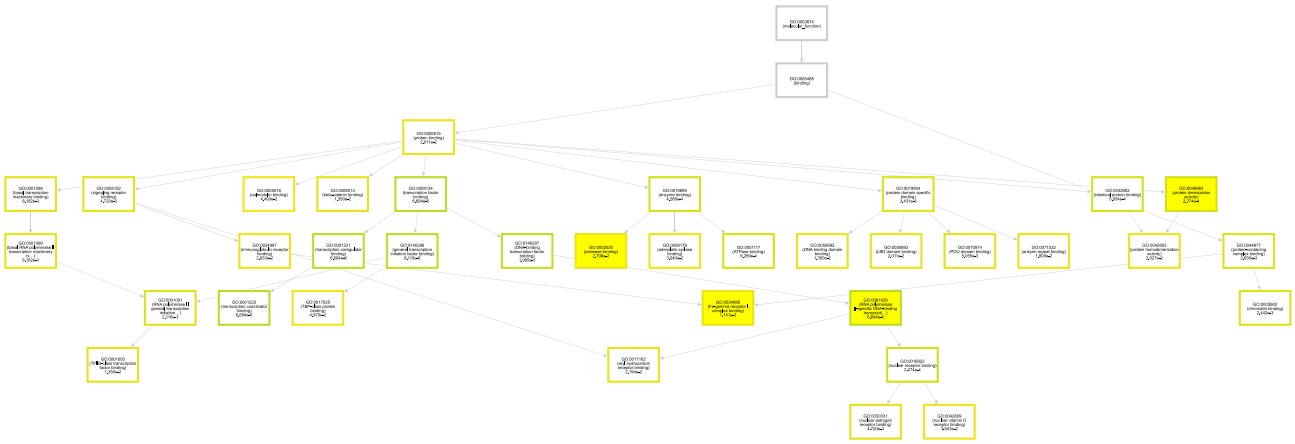


Figure 3 Gene Ontology (GO) Molecular Function (GOMF) analysis for RYJHS. The result demonstrates a significant diversity. The GOMF reveals a spectrum of mechanisms of RYJHS encompassing immunomodulation, vitamin D, and estrogen-related pathways, with a notable concentration of these molecular activities occurring within the nucleus.

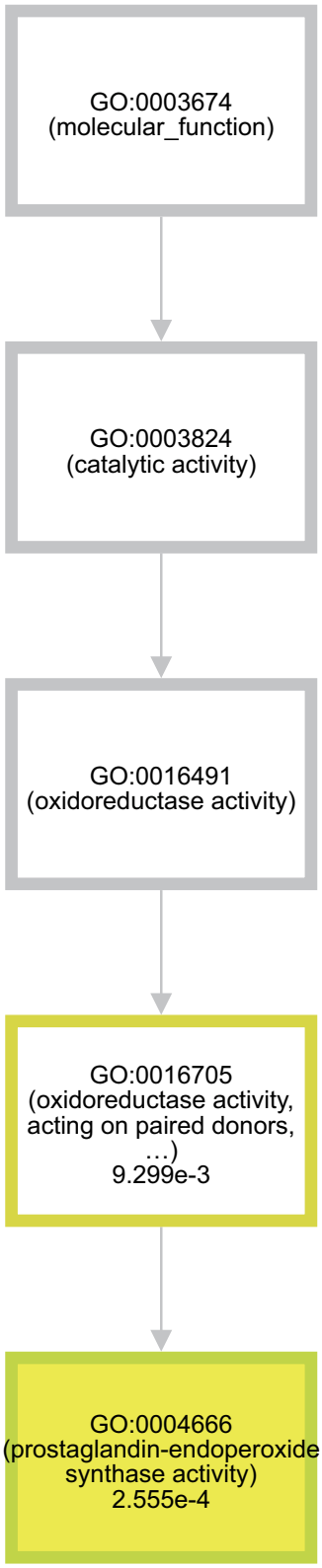


Figure 4 GOMF analysis for WYGJJW. The GOMF analysis shows a distinct association of this TCM with prostaglandin-endoperoxide synthase activity, highlighting its potential mechanism of action.

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Several limitations are acknowledged in the current study. First, the lack of statistically significant differences between the WYGJJW and RYJHS groups limits our ability to determine comparative efficacy, likely due to the small sample size, short follow-up period, or unremarkable baseline clinical severity for discernable change between different TCM formulations. Secondly, the 7-day observation window was too short to assess long-term healing outcomes, particularly fracture consolidation or bone remodeling. In addition, bioinformatics may offer not only numerous advantages but also challenges, since the accuracy of predictions depends on the quality of the data and the complexity of herbal formulations, adding layer of complexity to the analysis. Lastly, recruitment was limited by the single-center design, the impact of the COVID-19 pandemic, and narrow eligibility criteria, which together posed challenges for broader enrollment and limited both statistical stability and the generalizability of the findings. For example, the baseline imbalance in mean age may have introduced residual confounding, particularly for outcomes such as pain perception and functional recovery, which are known to vary by age. Nevertheless, the study enriches the broad evidence of conventional TCM research and offers valuable preliminary insights into its potential role in the conservative management of upper extremity fractures.

Conclusion

This randomized controlled pilot study investigated acute upper extremity fractured patients who only recommended conservative treatment. Both WYGJJW and RYJHS have demonstrated adequate safety and clinically meaningful efficacy in relieving acute symptoms, such as localized swelling and pain severity, and thus facilitate functional recovery. In addition, the application of bioinformatics in predicting molecular functions can validate traditional medicines using modern scientific techniques, and thus help pave the way for their informed use in contemporary healthcare settings. Future clinical studies with a larger sample size and a longer follow-up period are warranted for statistical verification of the therapeutic role of topical TCM among patients with acute bone fractures.

Abbreviations

AA, Arachidonic Acid; AKT, Protein Kinase B; AP-1 Activator Protein 1; BMI, Body Mass Index; CI, Confidence Interval; COX, Cyclooxygenase; DASI, Dyshidrotic Eczema Area and Severity Index; EGFR, Epidermal Growth Factor Receptor; ESR, Estrogen Receptor; GO, Gene Ontology; GOMF, Gene Ontology Molecular Function; KEGG, Kyoto Encyclopedia of Genes and Genomes; miRNA, microRNA; mTOR, Mammalian Target of Rapamycin; NF-κB, Nuclear Factor kappa B; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; PG, Prostaglandins; PI3K, Phosphatidylinositol 3-kinase; QuickDASH, Quick Disabilities of the Arm, Shoulder and Hand; RYJHS, Ru-Yih-Jin-Huang-Saan; SD, Standard Deviation; SymMap, Symptom Mapping database; TCM, Traditional Chinese Medicine; TNF, Tumor Necrosis Factor; TX, Thromboxanes; VAS, Visual Analogue Scale; WYG, Wan-Yin-Gao; WYGJJW, Wan-Yin-Gao-Jia-Jean-Wey.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted according to the principles of the Declaration of Helsinki and good clinical practice guidelines. Prior to the commencement of the study, ethical approval was obtained from the Institutional Review Board of the Chang Gung Medical Foundation (IRB No. 202001174A3). All methods were performed in accordance with the relevant guidelines and regulations. All the participants provided written informed consent.

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2. **2024 Chang Gung Medical Week**, Kaohsiung County, Taiwan (R.O.C.), October 18–20, 2024.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

References

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392 (10159):1789–1858.
2. McMeniman PJ. Management of common fractures of the upper limb. *Aust Fam Physician*. 1987;16(6):783–791.
3. Solaiman RH, Irfanullah E, Navarro SM, et al. Rising incidence of stair-related upper extremity fractures among older adults in the United States: a 10-year nationwide analysis. *Osteoporos Int*. 2023;34(7):1241–1248. doi:10.1007/s00198-023-06769-9
4. Hoveidaei AH, Nakhostin-Ansari A, Namdari S, et al. Increasing burden of upper-extremity fractures in the middle East and North Africa (MENA): a 30-year analysis of the epidemiology and causes of injuries. *J Bone Joint Surg Am*. 2024;106(4):323–336. doi:10.2106/JBJS.23.00262
5. O'Hara NN, Isaac M, Slobogean GP, Klazinga NS. The socioeconomic impact of orthopaedic trauma: a systematic review and meta-analysis. *PLoS One*. 2020;15(1):e0227907.
6. Court-Brown CM, Aitken S, Hamilton TW, Rennie L, Caesar B. Nonoperative fracture treatment in the modern era. *J Trauma*. 2010;69 (3):699–707. doi:10.1097/TA.0b013e3181b57ace
7. Kurmis AP, Kurmis TP, O'Brien JX, Dalén T. The effect of nonsteroidal anti-inflammatory drug administration on acute phase fracture-healing: a review. *J Bone Joint Surg Am*. 2012;94(9):815–823. doi:10.2106/JBJS.J.01743
8. Ma L. Introduction of the Chinese medicine treatment on bone fracture. *Mod J Integr Chin Tradit West Med*. 1998;(7):74–75.
9. Ghosh TK, Pfister W, Yum SI. *Transdermal and Topical Drug Delivery Systems*. Boca Raton: Taylor & Francis; 1997.
10. McKay L, Gemmell H, Jacobson B, Hayes B. Effect of a topical herbal cream on the pain and stiffness of osteoarthritis: a randomized double-blind, placebo-controlled clinical trial. *J Clin Rheumatol*. 2003;9(3):164–169. doi:10.1097/01.RHU.0000073450.85179.55
11. Jiang WR, Luo MJ, Zhou ZB, He YJ, Zhuang JY, Yang ZY. Review of external plasters in traditional Chinese orthopedics. *J Tradit Chin Orthop Med*. 2004;3:27–33.
12. Chai X. Clinical observation of topical compound Jinhuang powder ointment in the treatment of ankle sprain. *Chin J Hosp Pharm*. 2011;31 (11):955–956.
13. Li Q. Topical application of modified Ruyi Jinhuang powder for the treatment of 120 cases of fractures. *Liaoning J Tradit Chin Med*. 2005; (12):1286–1287.
14. Wang D. Treatment of acute ankle sprain with "Niushang San". *Chin Prim Health Care*. 1988;(9):38–39.
15. Wang Y, Fu D, Liu Y. Clinical observation on the efficacy of external application of traditional Chinese medicine in treating acute ankle sprain. *Mod J Integr Tradit Chin West Med*. 2006;(2):167–168.
16. Huang HF, You JS. The use of Chinese herbal medicine on experimental fracture healing. *Am J Chin Med*. 1997;25(3–4):351–356. doi:10.1142/S0192415X97000391
17. Peng Y, Li C, Zhang G. Efficacy observation on herbal fumigation and topical application for treatment of early closed fracture. *Chin J Exp Tradit Med Formulae*. 2013;19(13):333–335.
18. Yeh YH, Chen WY, Shih HC, Chen WC, Chu DC. Skin allergic reactions to the traditional Chinese medicine Ru Yi Jin Huang San in three different medium bases. *Taipei City Med J*. 2005;2(9):820–828.
19. Chang HH, Tai YC, Cheng PP, Chen CH, Hsu KH, Lin IH. Therapeutic effects of Chinese herbal patch Wan-Yin-Gao on the upper extremity tendinitis induced by repetitive strain injury. *J Chin Med*. 2005;16(2&3):89–99.
20. Ibrahim DA, Swenson A, Sassoon A, Fernando ND. Classifications in brief: the tscherne classification of soft tissue injury. *Clin Orthop Relat Res*. 2017;475(2):560–564. doi:10.1007/s11999-016-4980-3
21. Vocks E, Plötz SG, Ring J. The dyshidrotic eczema area and severity index - A score developed for the assessment of dyshidrotic eczema. *Dermatology*. 1999;198(3):265–269. doi:10.1159/000018127
22. R KYC, Leung YC, F KLL, et al. Reliability and validity of the Chinese (Queen Mary Hospital, Hong Kong version) of the disabilities of the arm, shoulder and hand on patients with upper extremity musculoskeletal disorders in Hong Kong. *Hong Kong J Occup Ther*. 2019;32(1):62–68. doi:10.1177/1569186119849502
23. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The upper extremity collaborative group (UECG). *Am J Ind Med*. 1996;29(6):602–608. doi:10.1002/(SICI)1097-0274(199606)29:6<602::AID-AJIM4>3.0.CO;2-L

24. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med*. 2001;8(12):1153–1157. doi:10.1111/j.1553-2712.2001.tb01132.x
25. Lane JM, Sandhu HS. Current approaches to experimental bone grafting. *Orthop Clin North Am*. 1987;18(2):213–225. doi:10.1016/S0030-5898(20)30385-0
26. Tawonsawatruk T, Hamilton DF, Simpson AH. Validation of the use of radiographic fracture-healing scores in a small animal model. *J Orthop Res*. 2014;32(9):1117–1119. doi:10.1002/jor.22665
27. Peng LH, Ko CH, Siu SW, et al. In vitro & in vivo assessment of a herbal formula used topically for bone fracture treatment. *J Ethnopharmacol*. 2010;131(2):282–289. doi:10.1016/j.jep.2010.06.039
28. Wang XL, Zhu XP, Ji DX, et al. Beneficial effect of traditional Chinese medicine fumigation "bone-healing powder" in postoperative pain and recovery of neurological function of traumatic thoracolumbar spine fractures: a case-control study. *Medicine* 2018;97(35):e11983. doi:10.1097/MD.0000000000011983
29. Huang HF. Exploration esoterica of "book of shaolin martial arts cupreous body" and DA-CHILY-SANN(DCS). *J Tradit Chin Orthop Med*. 2010;9:7–12.
30. Qi F, Zhao L, Zhou A, et al. The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer. *Biosci Trends*. 2015;9(1):16–34. doi:10.5582/bst.2015.01019
31. Qi CY, Wang J, Wu X, et al. Botanical, traditional use, phytochemical, and toxicological of arisaematis rhizoma. *Evid Based Complement Alternat Med*. 2021;2021:9055574. doi:10.1155/2021/9055574
32. Zhong LY, Wu H. Current researching situation of mucosal irritant compontents in Araceae family plants. *Zhongguo Zhong Yao Za Zhi*. 2006;31(18):1561–1563.
33. Hong J. Effect of Ru Yi Jin Huang powder on phlebitis during the intermittent period of PICC treatment. *Journal of Hainan Medical University*. 2011;17(3):312–314.
34. Huang HF, You JS. Effects of Ru-Yih-Jin-Huang-Saan (RYJHS) and Jie-Guu-Saan (JGS) on the healing of experimental fracture in an animal model. *Am J Chin Med*. 2007;(6):32–38.
35. Siu WS, Ko CH, Lam KW, et al. Evaluation of a topical herbal agent for the promotion of bone healing. *Evid Based Complement Alternat Med*. 2015;2015:905270. doi:10.1155/2015/905270
36. Elliott DS, Newman KJ, Forward DP, et al. A unified theory of bone healing and nonunion: BHN theory. *Bone Joint J*. 2016;98-b(7):884–891. doi:10.1302/0301-620X.98B7.36061
37. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682–690. doi:10.1038/nchembio.118
38. Lee YR, Chang CM, Yeh YC, et al. Honeysuckle aqueous extracts induced let-7a suppress EV71 replication and pathogenesis in vitro and in vivo and is predicted to inhibit SARS-CoV-2. *Viruses*. 2021;13(2).
39. Yeh YC, Doan LH, Huang ZY, et al. Honeysuckle (Lonicera japonica) and Huangqi (Astragalus membranaceus) suppress SARS-CoV-2 entry and COVID-19 related cytokine storm in vitro. *Front Pharmacol*. 2021;12:765553. doi:10.3389/fphar.2021.765553
40. Raudvere U, Kolberg L, Kuzmin I, et al. g:Profiler: a web server for functional enrichment analysis and conversions of gene lists (2019 update). *Nucleic Acids Res*. 2019;47(W1):W191–w198. doi:10.1093/nar/gkz369