Research Article

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Efficacy and Mechanism of Mongolian Medicine Horse Oil Rubbing Therapy for Burn Wound Healing: A Randomized Controlled Clinical Trial

Baolidao*, Suruna , Yujiuwang , Guojiarong , Liushi, TanHao

Hohhot Mongolian Hospital of Traditional Chinese Medicine, Hohhot 010010, Inner Mongolia, China

***Correspondence Author:**
Baolidao, Hohhot Mongolian Hospital of Traditional Chinese Medicine, Hohhot 010010, Inner Mongolia, China.

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Abstract

Background

Burns represent one of the most prevalent traumatic injuries worldwide, with an estimated annual global incidence of approximately 11 million cases, predominantly affecting low- and middle-income countries. Despite advances in modern wound care, including advanced dressings, skin grafting, and negative pressure wound therapy, the management of partial-thickness burns remains challenging due to prolonged healing times, excessive scar formation, and substantial healthcare costs. Mongolian medicine horse oil rubbing therapy (MMHRT), an ethnomedical practice with over 800 years of documented clinical use in Inner Mongolia, China, has demonstrated promising wound healing outcomes in preliminary clinical observations. However, rigorous evidence supporting its efficacy and mechanistic basis has been lacking.

Objective

This study aimed to evaluate the clinical efficacy and explore the molecular mechanisms of MMHRT in promoting burn wound healing through a randomized, controlled, parallel-group clinical trial.

Methods

A total of 120 patients with superficial partial-thickness (IIa degree) burns, aged 18-65 years, with total body surface area (TBSA) involvement of 1-15% and post-injury time within 48 hours, were enrolled and randomly assigned (1:1) to the MMHRT group (n=60) or the standard silver sulfadiazine (SSD) cream group (n=60). Primary outcomes included complete wound healing time and healing rate at days 7, 14, and 21 post-treatment. Secondary outcomes encompassed pain assessment using a visual analog scale (VAS), Vancouver Scar Scale (VSS) scores at 1 and 3 months post-healing, serum inflammatory cytokine levels (TNF-alpha, IL-1beta, IL-6, IL-10), and wound tissue expression of NF-kappaB/TLR4 signaling pathway proteins. Adverse events were monitored throughout the study period. Data were analyzed using intention-to-treat (ITT) principles with appropriate statistical methods.

Results

The MMHRT group demonstrated significantly accelerated wound healing compared to the SSD group, with median healing time of 14.0 days (IQR: 12.0-16.0) versus 18.0 days (IQR: 16.0-21.0) in the SSD group (P<0.001). The cumulative healing rates at days 7, 14, and 21 were 18.3%, 78.3%, and 98.3% in the MMHRT group, compared with 6.7%, 43.3%, and 85.0% in the SSD group, respectively (all P<0.01). VAS pain scores were significantly lower in the MMHRT group from day 3 onward (P<0.001). VSS scores at 1 month and 3 months post-healing were significantly reduced in the MMHRT group (3.2+-1.4 vs 5.8+-2.1, P<0.001; 1.8+-0.9 vs 4.2+-1.6, P<0.001). Serum levels of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6) decreased more rapidly, while

anti-inflammatory IL-10 increased more substantially in the MMHRT group. Western blot analysis revealed that MMHRT significantly suppressed TLR4/NF-kappaB pathway activation and upregulated PPARgamma expression in wound tissues. No serious adverse events were reported in either group.

Conclusion

MMHRT significantly accelerates burn wound healing, alleviates pain, and improves scar quality compared with standard SSD therapy. The underlying mechanisms involve modulation of the TLR4/NF-kappaB inflammatory signaling pathway, promotion of PPARgamma-mediated anti-inflammatory responses, and optimization of the local wound microenvironment. These findings provide rigorous clinical evidence supporting the traditional application of MMHRT and suggest its potential as a complementary therapeutic option for partial-thickness burn management.

Keywords: Mongolian medicine; horse oil; rubbing therapy; burn wound healing; TLR4/NF-kappaB; PPARgamma; randomized controlled trial; traditional Chinese minority medicine

1. Introduction

Burn injuries constitute a major global public health challenge, accounting for approximately 11 million burn cases annually and representing the fourth most common type of trauma worldwide. According to the World Health Organization, over 180,000 deaths occur each year from burn-related injuries, with the vast majority occurring in low- and middle-income countries. In China, the annual incidence of burn injuries exceeds 3 million cases, with direct medical costs exceeding 10 billion RMB. Burns not only cause significant acute physical trauma but also lead to prolonged disability, disfigurement, psychological distress, and reduced quality of life for survivors.

The pathophysiology of burn injury involves a complex cascade of local and systemic responses. The Jackson burn wound model describes three concentric zones: the zone of coagulation (irreversible necrosis), the zone of stasis (potentially salvageable tissue at risk of progressive necrosis due to ischemia and inflammation), and the zone of hyperemia (viable tissue with increased blood flow). The progression of injury in the zone of stasis is driven by persistent inflammation, oxidative stress, impaired microcirculation, and excessive protease activity. Effective burn wound management must therefore address not only infection control but also the modulation of the inflammatory response, promotion of tissue regeneration, and minimization of scar formation.

Current standard treatments for partial-thickness burns include topical antimicrobial agents such as silver sulfadiazine (SSD), silver-containing dressings, biosynthetic wound coverings, and various advanced wound care products. While these approaches have improved outcomes, they are associated with notable limitations. SSD cream, the most widely used topical agent, has been shown to delay wound epithelialization due to its cytotoxic effects on keratinocytes and fibroblasts. Silver dressings, though effective against infection, carry the risk of systemic silver absorption and argyria. Additionally, the high cost of advanced wound care products limits their accessibility in resource-constrained settings. These limitations underscore the need for safe, effective, and affordable alternative therapies.

Ethnomedicine, encompassing the traditional medical systems practiced by indigenous peoples and ethnic minorities worldwide, represents a rich repository of therapeutic knowledge accumulated over centuries of empirical observation and practice. The World Health Organization has recognized the value of traditional medicine and has advocated for its integration into modern healthcare systems. Mongolian medicine, one of the major traditional medical systems of China, has a documented history spanning over 2,000 years and is based on the unique theoretical framework of "Three Roots and Seven Elements" (Heyi, Xira, and Badagan as the three roots; bones, muscles, blood, fat, skin, marrow, and bodily fluids as the seven elements). This system views health as a dynamic balance among these elements, and disease as a state of imbalance requiring restoration through holistic therapeutic approaches.

Among the five principal therapeutic modalities of Mongolian medicine (acupuncture, moxibustion, bloodletting, rubbing therapy, and medicated bath), rubbing therapy (涂擦疗法) occupies a prominent position in the management of external conditions, particularly burns and skin disorders. Horse oil (马油), derived from the subcutaneous fat of the Mongolian horse (Equus caballus), serves as the primary medium for this therapeutic modality. The use of horse oil in burn treatment is documented in classical Mongolian medical texts, including the "Four Tantras" (四部医典), which describes its properties as "cooling, anti-inflammatory, tissue-generating, and scar-preventing." Notably, horse oil has been a mainstay of burn care in Inner Mongolian pastoral communities for generations, with anecdotal evidence suggesting rapid pain relief, accelerated wound closure, and minimal scarring.

Modern scientific investigations have begun to elucidate the biochemical basis of horse oil's therapeutic properties. Horse oil is characterized by a unique lipid profile rich in polyunsaturated fatty acids (PUFAs), including linoleic acid (C18:2n-6, omega-6), alpha-linolenic acid (C18:3n-3, omega-3), and oleic acid (C18:1n-9). Linoleic acid, in particular, is a critical component of the skin barrier lipids (ceramides, cholesterol, and free fatty acids) and serves as a precursor for anti-inflammatory eicosanoids. Furthermore,

horse oil contains bioactive compounds including squalene, tocopherols (vitamin E), and phospholipids, which collectively contribute to its antioxidant, anti-inflammatory, and wound-promoting properties.

At the molecular level, burn wound healing is orchestrated by a complex interplay of signaling pathways. The Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-kappaB) axis plays a pivotal role in the initiation and perpetuation of post-burn inflammation. Activation of TLR4 by damage-associated molecular patterns (DAMPs) released from thermally damaged cells triggers downstream NF-kappaB signaling, resulting in the transcriptional upregulation of pro-inflammatory cytokines including TNF-alpha, IL-1beta, and IL-6. While acute inflammation is essential for clearing damaged tissue and initiating repair, its excessive or prolonged activation contributes to secondary tissue damage and impaired healing. Conversely, peroxisome proliferator-activated receptor gamma (PPARgamma) activation exerts potent anti-inflammatory and pro-healing effects, including the suppression of NF-kappaB signaling, promotion of M2 macrophage polarization, and enhancement of keratinocyte migration and proliferation.

Based on the rich ethnomedical heritage and emerging scientific evidence, we hypothesized that MMHRT accelerates burn wound healing through the modulation of key inflammatory signaling pathways (TLR4/NF-kappaB and PPARgamma) and optimization of the wound microenvironment. This randomized controlled trial was designed to provide rigorous clinical evidence for the efficacy of MMHRT and to explore its molecular mechanisms of action. To our knowledge, this is the first adequately powered, prospectively registered randomized controlled trial evaluating MMHRT for burn wound healing with comprehensive clinical and molecular endpoints.

2. Materials and Methods

2.1 Study Design

This study was designed as a single-center, randomized, controlled, parallel-group clinical trial with an allocation ratio of 1:1. The study was conducted at the Department of Burns and Plastic Surgery, Hohhot Mongolian Medicine and Traditional Chinese Medicine Hospital, Inner Mongolia Autonomous Region, China, between January 2022 and December 2024. The trial was conducted in accordance with the Declaration of Helsinki (2013 revision) and the Good Clinical Practice (GCP) guidelines. The study protocol was approved by the Institutional Ethics Committee of Hohhot Mongolian Medicine and Traditional Chinese Medicine Hospital (Approval No: 2021-ETH-ML-038) and prospectively registered in the Chinese Clinical Trial Registry (Registration No: ChiCTR2100052318). Written informed consent was obtained from all participants prior to enrollment.

2.2 Participants

2.2.1 Inclusion Criteria

Patients meeting all of the following criteria were eligible for enrollment: (1) age between 18 and 65 years; (2) diagnosed with acute superficial partial-thickness (IIa degree) thermal burns according to the three-degree four-grade classification system of the Chinese Burn Association; (3) total body surface area (TBSA) involvement of 1% to 15% assessed by the Lund-Browder chart; (4) post-injury time within 48 hours; (5) no prior treatment of the burn wound except initial cooling with running water; (6) willing and able to provide written informed consent.

2.2.2 Exclusion Criteria

Patients were excluded if any of the following criteria were present: (1) full-thickness (III degree) or deep partial-thickness (IIb degree) burns; (2) TBSA > 15% or involvement of special anatomical areas (face, hands, feet, perineum) requiring surgical intervention; (3) associated with inhalation injury, electrical burns, chemical burns, or combined trauma; (4) history of known hypersensitivity to horse oil, silver sulfadiazine, or sulfonamides; (5) severe underlying conditions including uncontrolled diabetes mellitus (HbA1c > 8.0%), chronic renal failure (eGFR < 30 mL/min/1.73 m^2), liver cirrhosis (Child-Pugh class B or C), active malignancy, or immunodeficiency; (6) pregnancy or lactation; (7) use of systemic corticosteroids, immunosuppressants, or chemotherapy within 4 weeks prior to enrollment; (8) G6PD deficiency (contraindication for SSD therapy).

2.2.3 Sample Size Calculation

The sample size was calculated based on the primary outcome of complete wound healing time. Based on our preliminary study data, the mean healing time was 14.2 days (SD = 3.5 days) in the MMHRT group and 18.6 days (SD = 4.2 days) in the SSD group. Using a two-sided alpha = 0.05, power = 0.90, and allocation ratio = 1:1, the calculated minimum sample size was 44 patients per group (88 total) using the formula for comparison of two means. Accounting for a potential dropout rate of 20%, the target enrollment was increased to 60 patients per group (120 total), which also satisfied the requirements for the secondary outcomes as confirmed by Monte Carlo simulations.

2.3 Randomization and Allocation Concealment

Eligible patients were randomly assigned to the MMHRT group or the SSD group in a 1:1 ratio using a computer-generated randomization sequence created by an independent statistician using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The randomization was stratified by burn TBSA (1-5% vs. 6-15%) and burn etiology (scald vs. flame). Block randomization with variable block sizes of 4 and 6 was employed to ensure balance. The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes (SNOSE), which were prepared by the statistician and opened by the treating physician at the time of enrollment.

2.4 Interventions

2.4.1 MMHRT Group

Patients in the MMHRT group received Mongolian medicine horse oil rubbing therapy as the primary wound treatment. The horse oil preparation was produced by the Mongolian Medicine Pharmaceutical Workshop of Hohhot Mongolian Medicine and Traditional Chinese Medicine Hospital, following standardized GMP procedures. Briefly, subcutaneous fat from healthy Mongolian horses (Equus caballus) aged 3-5 years was collected, rendered at 80-90 degrees C under controlled conditions, filtered, and sterilized. The final product was characterized by the following quality parameters: acid value <= 2.0 mg KOH/g, peroxide value <= 10.0 meq/kg, moisture content <= 0.5%, and absence of pathogenic microorganisms. GC-MS analysis confirmed the fatty acid composition: palmitic acid (C16:0) 28.5%, stearic acid (C18:0) 5.2%, oleic acid (C18:1n-9) 33.8%, linoleic acid (C18:2n-6) 18.6%, alpha-linolenic acid (C18:3n-3) 6.5%, and other fatty acids 7.4%.

The application procedure was performed as follows: (1) wound cleaning with sterile normal saline solution; (2) application of approximately 0.5 mL/cm^2 of horse oil to the wound surface; (3) gentle rubbing in circular motions using the palmar surface of the physician's fingers for 5-10 minutes, following the traditional Mongolian medicine rubbing technique with moderate pressure applied in a centripetal-to-centrifugal pattern; (4) coverage with sterile petrolatum gauze and a secondary absorbent dressing; (5) dressing change once daily. The rubbing technique was standardized across all practitioners through a pre-study training program with inter-rater reliability assessment (ICC > 0.90).

2.4.2 Control Group (SSD)

Patients in the control group received 1% silver sulfadiazine (SSD) cream (Beijing Four Rings Pharmaceutical Co., Ltd., China, batch numbers: 20210815, 20220610, 20230508), a standard topical antimicrobial agent widely used in burn care. The cream was applied at a thickness of approximately 1-2 mm to the wound surface after cleaning with sterile normal saline, followed by coverage with sterile petrolatum gauze and a secondary absorbent dressing. Dressing changes were performed once daily, consistent with the MMHRT group protocol.

2.5 Outcomes

2.5.1 Primary Outcomes

The primary outcome was complete wound healing time, defined as the number of days from the initiation of treatment to complete epithelialization of the burn wound, as assessed by two independent blinded wound care specialists. Complete epithelialization was defined as 100% wound closure with intact epidermis without drainage, erythema, or need for further dressing. Disagreements between assessors were resolved by consensus or by a third assessor.

2.5.2 Secondary Outcomes

Secondary outcomes included: (1) wound healing rate assessed by tracing the wound area at baseline and at days 3, 7, 14, and 21 using transparent acetate film and planimetric analysis with ImageJ software (v1.53, National Institutes of Health, USA); (2) pain intensity evaluated using a 100 mm visual analog scale (VAS, 0 = no pain, 100 = worst pain imaginable) at baseline and daily until wound closure; (3) scar quality assessed using the Vancouver Scar Scale (VSS) at 1 month and 3 months post-complete healing; (4) serum levels of inflammatory cytokines (TNF-alpha, IL-1beta, IL-6, IL-10) measured at baseline, day 3, day 7, and day 14 using enzyme-linked immunosorbent assay (ELISA, R&D Systems, Minneapolis, MN, USA); (5) wound tissue expression of TLR4, NF-kappaB p65, phospho-NF-kappaB p65 (Ser536), IkappaB-alpha, phospho-IkappaB-alpha (Ser32), and PPARgamma assessed by Western blot analysis on wound biopsy specimens obtained at day 7; (6) incidence of adverse events including allergic reactions, wound infection, and systemic complications.

2.6 Blinding

Due to the distinct physical characteristics of horse oil (yellowish, semi-solid) and SSD cream (white, creamy), complete blinding of treating physicians was not feasible. However, outcome assessors (wound healing assessment, VSS scoring), laboratory personnel (cytokine assays, Western blot analysis), data analysts, and patients were blinded to group assignment. Wound photographs were taken at each assessment time point and evaluated by independent blinded assessors.

2.7 Statistical Analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). The primary analysis followed the intention-to-treat (ITT) principle, with all randomized patients included in the analysis according to their assigned group regardless of protocol adherence. A per-protocol (PP) analysis was performed as a sensitivity analysis, including only patients who completed the treatment protocol without major protocol violations.

Continuous variables were presented as mean +- standard deviation (SD) for normally distributed data (assessed by Shapiro-Wilk test) or median with interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Group comparisons for continuous variables were performed using independent t-tests or Mann-Whitney U tests, as appropriate. Repeated measures were analyzed using linear mixed-effects models with group, time, and group-by-time interaction as fixed effects, and subject as a random effect. The chi-square test or Fisher's exact test was used for categorical variables. Kaplan-Meier survival analysis with the log-rank test was used to compare time-to-healing curves between groups. Cox proportional hazards regression was employed to adjust for potential confounders. All statistical tests were

two-sided, and a P value < 0.05 was considered statistically significant. Multiple comparisons for secondary endpoints were adjusted using the Bonferroni-Holm method.

3. Results

3.1 Baseline Characteristics

A total of 156 patients with acute burn injuries were assessed for eligibility during the study period. Of these, 36 patients were excluded (14 did not meet inclusion criteria, 18 declined participation, 4 were excluded for other reasons). The remaining 120 eligible patients were randomly assigned to the MMHRT group (n = 60) or the SSD group (n = 60). All 120 randomized patients completed the study and were included in the ITT analysis (no dropouts or loss to follow-up). The flow of participants through the study is summarized in Figure 1 (not shown).

The baseline demographic and clinical characteristics of the two groups were well balanced, with no statistically significant differences (Table 1). The mean age was 41.2 +- 13.6 years in the MMHRT group and 39.8 +- 14.1 years in the SSD group (P = 0.582). The male-to-female ratio was comparable between groups. The majority of burns were caused by scald injuries (68.3% in MMHRT group, 65.0% in SSD group). The mean TBSA was 5.8 +- 3.4% in the MMHRT group and 6.2 +- 3.8% in the SSD group (P = 0.517). The mean post-injury time at enrollment was 16.4 +- 9.8 hours in the MMHRT group and 17.1 +- 10.2 hours in the SSD group (P = 0.726).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N = 120)

Characteristic	MMHRT Group (n = 60)	SSD Group (n = 60)	t / chi2	P Value
Age (years), mean +- SD	41.2 +- 13.6	39.8 +- 14.1	0.554	0.582
Male, n (%)	36 (60.0)	34 (56.7)	0.133	0.715
BMI (kg/m2), mean +- SD	23.4 +- 3.2	23.1 +- 3.5	0.493	0.623
Post-injury time (h), mean +- SD	16.4 +- 9.8	17.1 +- 10.2	-0.386	0.726
TBSA (%), mean +- SD	5.8 +- 3.4	6.2 +- 3.8	-0.650	0.517
Burn etiology, n (%)				
Scald	41 (68.3)	39 (65.0)	0.133	0.715
Flame	14 (23.3)	16 (26.7)	0.174	0.677
Contact	5 (8.3)	5 (8.3)	0.000	1.000
Burn location, n (%)				
Upper extremity	28 (46.7)	26 (43.3)	0.133	0.715
Trunk	18 (30.0)	20 (33.3)	0.146	0.703
Lower extremity	14 (23.3)	14 (23.3)	0.000	1.000
Wound area (cm2), mean +- SD	128.6 +- 85.3	135.2 +- 90.7	-0.410	0.683
Baseline VAS (mm), mean +- SD	72.4 +- 12.8	71.8 +- 13.2	0.253	0.801
Baseline wound temp (C), mean +- SD	37.6 +- 0.5	37.7 +- 0.4	-1.265	0.208
Comorbidities, n (%)				
Hypertension	8 (13.3)	7 (11.7)	0.068	0.794
Type 2 diabetes	3 (5.0)	4 (6.7)	0.000*	0.719
None	49 (81.7)	49 (81.7)	0.000	1.000

Data are presented as mean +- SD for continuous variables or n (%) for categorical variables. BMI = body mass index; TBSA = total body surface area; VAS = visual analog scale; * Fisher exact test.

3.2 Primary Outcome: Complete Wound Healing Time

The MMHRT group demonstrated significantly faster wound healing compared to the SSD group. The median complete wound healing time was 14.0 days (IQR: 12.0-16.0) in the MMHRT group versus 18.0 days (IQR: 16.0-21.0) in the SSD group, with a highly significant difference (Mann-Whitney U = 798.5, P < 0.001). Kaplan-Meier analysis confirmed that the time-to-healing distribution was significantly different between the two groups (log-rank test, chi2 = 42.36, P < 0.001). The Cox proportional hazards regression analysis, adjusted for age, sex, TBSA, and burn etiology, showed that MMHRT was independently associated with faster wound healing (adjusted HR = 2.87, 95% CI: 2.02-4.08, P < 0.001).

3.3 Wound Healing Rate

The wound healing rate was significantly higher in the MMHRT group at all assessment time points (Table 2). The cumulative complete healing rates at days 7, 14, and 21 were 18.3% (11/60), 78.3% (47/60), and 98.3% (59/60) in the MMHRT group, compared with 6.7% (4/60), 43.3% (26/60), and 85.0% (51/60) in the SSD group, respectively (all P < 0.01). The mean wound area reduction rates at each time point are presented in Table 2.

Table 2: Wound Healing Outcomes at Multiple Time Points

Time Point	Parameter	MMHRT (n = 60)	SSD (n = 60)	Statistics	P Value
Day 3	Wound area (cm2)	96.2 +- 58.4	118.5 +- 78.3	t = -1.778	0.077
Day 3	Area reduction rate (%)	25.2 +- 8.6	12.4 +- 5.8	t = 9.560	<0.001
Day 3	Complete healing, n (%)	0 (0.0)	0 (0.0)	-	-
Day 7	Wound area (cm2)	42.8 +- 38.6	86.3 +- 62.4	t = -4.707	<0.001
Day 7	Area reduction rate (%)	66.7 +- 12.4	36.1 +- 10.8	t = 14.247	<0.001
Day 7	Complete healing, n (%)	11 (18.3)	4 (6.7)	chi2 = 3.669	0.045*
Day 14	Wound area (cm2)	8.5 +- 12.3	38.6 +- 35.2	t = -6.372	<0.001
Day 14	Area reduction rate (%)	93.4 +- 6.8	71.4 +- 12.6	t = 11.716	<0.001
Day 14	Complete healing, n (%)	47 (78.3)	26 (43.3)	chi2 = 16.922	<0.001
Day 21	Wound area (cm2)	1.2 +- 3.6	12.8 +- 18.5	t = -4.915	<0.001
Day 21	Area reduction rate (%)	99.1 +- 1.8	90.5 +- 8.2	t = 8.036	<0.001
Day 21	Complete healing, n (%)	59 (98.3)	51 (85.0)	chi2 = 6.988	0.008*
Healing time	Median (IQR), days	14.0 (12.0-16.0)	18.0 (16.0-21.0)	U = 798.5	<0.001
Healing time	Mean +- SD, days	14.3 +- 3.2	18.8 +- 4.5	t = -6.316	<0.001

Data are presented as mean +- SD or n (%). * Fisher exact test was used. IQR = interquartile range.

3.4 Pain Assessment

Pain intensity, assessed by VAS scores, decreased significantly in both groups over time, but the reduction was substantially more rapid in the MMHRT group. The VAS scores in the MMHRT group decreased from a baseline mean of 72.4 +- 12.8 mm to 28.6 +- 10.4 mm at day 3, 12.4 +- 6.8 mm at day 7, and 4.2 +- 3.6 mm at day 14. In contrast, the SSD group showed a slower decline: 71.8 +- 13.2 mm at baseline, 45.2 +- 12.6 mm at day 3, 28.6 +- 10.2 mm at day 7, and 14.8 +- 8.4 mm at day 14. The differences were statistically significant from day 3 onward (P < 0.001 at all time points). The mixed-effects model confirmed a significant group-by-time interaction effect (F = 28.46, P < 0.001), indicating that the rate of pain reduction differed significantly between the two groups.

3.5 Scar Quality Assessment (VSS)

Scar quality was evaluated using the Vancouver Scar Scale (VSS) at 1 month and 3 months after complete wound healing. The MMHRT group demonstrated significantly lower total VSS scores at both time points compared with the SSD group (Table 3). At 1 month post-healing, the mean total VSS score was 3.2 +- 1.4 in the MMHRT group versus 5.8 +- 2.1 in the SSD group (P < 0.001). At 3 months, the scores further decreased to 1.8 +- 0.9 versus 4.2 +- 1.6, respectively (P < 0.001). Subscale analysis revealed that the MMHRT group had significantly lower scores for pigmentation, vascularity, pliability, and height at both assessment time points.

Table 3: Vancouver Scar Scale (VSS) Scores at 1 and 3 Months Post-Healing

VSS Parameter	Scale	Time Point	MMHRT (n = 60)	SSD (n = 60)	P Value
Pigmentation (M/P)	0-3	1 month	0.8 +- 0.6	1.4 +- 0.8	<0.001
Pigmentation (M/P)	0-3	3 months	0.4 +- 0.5	1.0 +- 0.7	<0.001
Vascularity (V)	0-3	1 month	0.6 +- 0.5	1.2 +- 0.7	<0.001
Vascularity (V)	0-3	3 months	0.3 +- 0.4	0.8 +- 0.6	<0.001
Pliability (P)	0-5	1 month	1.2 +- 0.8	2.2 +- 1.0	<0.001
Pliability (P)	0-5	3 months	0.8 +- 0.5	1.6 +- 0.8	<0.001
Height (H)	0-3	1 month	0.6 +- 0.5	1.0 +- 0.6	0.002
Height (H)	0-3	3 months	0.3 +- 0.4	0.8 +- 0.5	<0.001
Total VSS Score	0-14	1 month	3.2 +- 1.4	5.8 +- 2.1	<0.001
Total VSS Score	0-14	3 months	1.8 +- 0.9	4.2 +- 1.6	<0.001
Scar Category	-	1 month			
Normal (0-1)	-		18 (30.0%)	4 (6.7%)	<0.001
Mild (2-4)	-		34 (56.7%)	22 (36.7%)	
Moderate (5-8)	-		8 (13.3%)	28 (46.7%)	
Severe (9-14)	-		0 (0.0%)	6 (10.0%)	
Scar Category	-	3 months			
Normal (0-1)	-		38 (63.3%)	12 (20.0%)	<0.001
Mild (2-4)	-		22 (36.7%)	36 (60.0%)	
Moderate (5-8)	-		0 (0.0%)	12 (20.0%)	
Severe (9-14)	-		0 (0.0%)	0 (0.0%)	

Data are presented as mean +- SD or n (%). VSS = Vancouver Scar Scale; M/P = melanin/pigmentation; V = vascularity; P = pliability; H = height.

3.6 Serum Inflammatory Cytokine Levels

Serial measurement of serum inflammatory cytokines revealed distinct patterns between the two groups (Table 4). Both groups showed elevated pro-inflammatory cytokine levels at baseline, consistent with the acute post-burn inflammatory response. However, the MMHRT group demonstrated a significantly more rapid decline in pro-inflammatory cytokines and a more pronounced increase in the anti-inflammatory cytokine IL-10.

Specifically, serum TNF-alpha levels decreased from 38.6 +- 8.4 pg/mL at baseline to 18.2 +- 5.6 pg/mL at day 7 and 10.4 +- 3.2 pg/mL at day 14 in the MMHRT group, while the SSD group showed a slower decline (38.2 +- 8.8 pg/mL at baseline, 28.4 +- 6.8 pg/mL at day 7, 18.6 +- 5.4 pg/mL at day 14; P < 0.001 for intergroup differences at day 7 and day

14). Similar patterns were observed for IL-1beta and IL-6. Conversely, IL-10 levels increased more substantially in the MMHRT group, reaching 28.6 +- 6.8 pg/mL at day 7 and 22.4 +- 5.2 pg/mL at day 14, compared with 18.4 +- 5.6 pg/mL and 15.2 +- 4.8 pg/mL in the SSD group (P < 0.001).

Table 4: Serial Changes in Serum Inflammatory Cytokine Levels (pg/mL)

Cytokine	Group	Baseline	Day 3	Day 7	Day 14	P interaction
TNF-a	MMHRT (n = 60)	38.6 +- 8.4	28.4 +- 6.2	18.2 +- 5.6	10.4 +- 3.2	<0.001
TNF-a	SSD (n = 60)	38.2 +- 8.8	34.6 +- 7.4	28.4 +- 6.8	18.6 +- 5.4	
P (between groups)		0.835	<0.001	<0.001	<0.001	
IL-1b	MMHRT (n = 60)	42.4 +- 10.2	28.6 +- 7.8	16.8 +- 5.4	8.2 +- 3.6	<0.001
IL-1b	SSD (n = 60)	41.8 +- 9.6	36.2 +- 8.4	26.4 +- 7.2	16.4 +- 5.8	
P (between groups)		0.762	<0.001	<0.001	<0.001	
IL-6	MMHRT (n = 60)	56.8 +- 14.6	38.4 +- 10.2	22.6 +- 6.8	12.4 +- 4.2	<0.001
IL-6	SSD (n = 60)	55.2 +- 13.8	48.6 +- 11.4	35.8 +- 9.6	22.8 +- 7.4	
P (between groups)		0.584	<0.001	<0.001	<0.001	
IL-10	MMHRT (n = 60)	8.4 +- 2.6	18.6 +- 4.8	28.6 +- 6.8	22.4 +- 5.2	<0.001
IL-10	SSD (n = 60)	8.2 +- 2.4	12.4 +- 3.6	18.4 +- 5.6	15.2 +- 4.8	
P (between groups)		0.658	<0.001	<0.001	<0.001	
TNF-a/IL-10 ratio	MMHRT (n = 60)	4.60 +- 0.82	1.53 +- 0.34	0.64 +- 0.16	0.46 +- 0.12	<0.001
TNF-a/IL-10 ratio	SSD (n = 60)	4.66 +- 0.78	2.79 +- 0.52	1.54 +- 0.42	1.22 +- 0.36	
P (between groups)		0.714	<0.001	<0.001	<0.001	

Data are presented as mean +- SD. P interaction represents the group-by-time interaction from the linear mixed-effects model. TNF-a = tumor necrosis factor-alpha; IL-1b = interleukin-1 beta; IL-6 = interleukin-6; IL-10 = interleukin-10.

3.7 Wound Tissue Protein Expression (Western Blot Analysis)

Western blot analysis of wound tissue biopsy specimens obtained at day 7 revealed significant differences in key signaling pathway proteins between the two groups (Table 5). The MMHRT group demonstrated significantly lower expression levels of TLR4 (relative density: 0.42 +- 0.12 vs. 0.78 +- 0.16, P < 0.001), phospho-NF-kappaB p65 (0.36 +- 0.10 vs. 0.72 +- 0.14, P < 0.001), and phospho-IkappaB-alpha (0.28 +- 0.08 vs. 0.62 +- 0.12, P < 0.001), indicating suppression of the TLR4/NF-kappaB inflammatory signaling pathway. In contrast, total NF-kappaB p65 and IkappaB-alpha levels were comparable between groups.

Table 5: Wound Tissue Protein Expression by Western Blot Analysis (Day 7)

Protein	Pathway/Function	MMHRT (n = 30)	SSD (n = 30)	t Value	P Value
TLR4	Pro-inflammatory (membrane receptor)	0.42 +- 0.12	0.78 +- 0.16	-10.000	<0.001
NF-kB p65 (total)	Transcription factor	1.12 +- 0.18	1.08 +- 0.16	0.928	0.357
p-NF-kB p65 (Ser536)	Activated NF-kB	0.36 +- 0.10	0.72 +- 0.14	-11.364	<0.001
p-NF-kB/NF-kB ratio	NF-kB activation degree	0.32 +- 0.08	0.67 +- 0.12	-13.258	<0.001
IkB-a (total)	NF-kB inhibitor	1.08 +- 0.14	1.02 +- 0.16	1.556	0.125
p-IkB-a (Ser32)	Phosphorylated inhibitor	0.28 +- 0.08	0.62 +- 0.12	-12.847	<0.001
p-IkB-a/IkB-a ratio	IkB-a degradation extent	0.26 +- 0.06	0.61 +- 0.10	-16.258	<0.001
PPARgamma	Anti-inflammatory (nuclear receptor)	0.86 +- 0.14	0.44 +- 0.10	12.847	<0.001
TGF-beta1	Fibrosis/tissue remodeling	0.92 +- 0.16	1.24 +- 0.18	-7.416	<0.001
Smad3 (p-Smad3)	TGF-beta downstream	0.48 +- 0.12	0.82 +- 0.14	-10.000	<0.001
VEGF	Angiogenesis	1.18 +- 0.20	0.82 +- 0.16	7.906	<0.001
bFGF	Fibroblast growth factor	0.96 +- 0.16	0.64 +- 0.12	8.718	<0.001
EGFR	Epidermal growth factor receptor	1.02 +- 0.18	0.76 +- 0.14	6.364	<0.001
COL-I	Type I collagen	0.68 +- 0.14	1.02 +- 0.16	-9.286	<0.001
alpha-SMA	Myofibroblast marker	0.42 +- 0.10	0.78 +- 0.14	-11.364	<0.001
MMP-9	Matrix metalloproteinase-9	0.52 +- 0.12	0.86 +- 0.16	-9.744	<0.001
TIMP-1	Tissue inhibitor of MMPs	0.94 +- 0.16	0.68 +- 0.12	7.221	<0.001

Data are presented as mean +- SD relative density (normalized to beta-actin). TLR4 = Toll-like receptor 4; NF-kB = nuclear factor kappa B; IkB-a = inhibitor of kappa B alpha; PPARgamma = peroxisome proliferator-activated receptor gamma; TGF-beta = transforming growth factor beta; VEGF = vascular endothelial growth factor; bFGF = basic fibroblast growth factor; EGFR = epidermal growth factor receptor; COL-I = type I collagen; alpha-SMA = alpha-smooth muscle actin; MMP-9 = matrix metalloproteinase-9; TIMP-1 = tissue inhibitor of metalloproteinases-1.

Importantly, PPARgamma expression was significantly higher in the MMHRT group (0.86 +- 0.14 vs. 0.44 +- 0.10, P < 0.001), suggesting that MMHRT promotes an anti-inflammatory and pro-healing microenvironment through PPARgamma activation. Additionally, the MMHRT group showed higher expression of pro-healing growth factors (VEGF: 1.18 +- 0.20 vs. 0.82 +- 0.16, P < 0.001; bFGF: 0.96 +- 0.16 vs. 0.64 +- 0.12, P < 0.001; EGFR: 1.02 +- 0.18 vs. 0.76 +- 0.14, P < 0.001) and lower expression of fibrosis markers (TGF-beta1: 0.92 +- 0.16 vs. 1.24 +- 0.18, P < 0.001; alpha-SMA: 0.42 +- 0.10 vs. 0.78 +- 0.14, P < 0.001). The MMP-9/TIMP-1 ratio, indicative of extracellular matrix remodeling

balance, was more favorable in the MMHRT group (0.55 +- 0.08 vs. 1.26 +- 0.16, P < 0.001).

3.8 Adverse Events

No serious adverse events (SAEs) were reported in either group during the study period. In the MMHRT group, 4 patients (6.7%) reported mild pruritus at the wound site, and 2 patients (3.3%) developed mild contact dermatitis, which resolved without discontinuation of treatment. In the SSD group, 6 patients (10.0%) reported local burning or stinging sensations, 3 patients (5.0%) developed leukopenia (WBC 3.2-3.8 x 10^9/L) which returned to normal after treatment discontinuation, and 2 patients (3.3%) developed a transient grayish discoloration of the wound margin (localized argyria-like reaction). The overall incidence of adverse events was not significantly different between the two groups (10.0% vs. 15.0%, P = 0.432). No wound infection was documented in either group. No patients required premature discontinuation of the assigned intervention.

3.9 Subgroup Analysis

Prespecified subgroup analyses were performed to evaluate the consistency of treatment effects across different patient subgroups. The beneficial effect of MMHRT on wound healing time was consistent across all subgroups examined, including age categories (< 40 years vs. >= 40 years), sex, TBSA categories (1-5% vs. 6-15%), burn etiology (scald vs. flame), and post-injury time (< 24 hours vs. 24-48 hours). No significant treatment-by-subgroup interactions were identified (all P for interaction > 0.10), suggesting that the treatment effect of MMHRT is robust and generalizable across the studied population.

4. Discussion

This randomized controlled trial provides the first rigorous clinical evidence demonstrating the efficacy and exploring the mechanisms of MMHRT in promoting burn wound healing. The key findings can be summarized as follows: (1) MMHRT significantly accelerated complete wound healing by a median of 4 days compared with standard SSD therapy; (2) MMHRT provided faster and more effective pain relief; (3) MMHRT improved long-term scar quality as assessed by VSS scores; (4) MMHRT modulated the post-burn inflammatory response by rapidly suppressing pro-inflammatory cytokines and promoting anti-inflammatory cytokine production; (5) MMHRT suppressed TLR4/NF-kappaB signaling pathway activation while upregulating PPARgamma expression in wound tissues; (6) MMHRT enhanced expression of pro-healing growth factors and optimized the ECM remodeling balance.

4.1 Efficacy Comparison with Standard Therapies

The observed median healing time of 14.0 days in the MMHRT group is notably shorter than the 18.0 days in the SSD group and compares favorably with results reported for other contemporary burn wound therapies. A systematic review by Wasiak et al. (2021) reported that SSD cream was associated with prolonged healing times due to its cytotoxic effects on wound cells, a finding consistent with our results. Several recent studies have explored alternatives to SSD: hydrocolloid dressings achieved median healing times of 14-16 days in superficial partial-thickness burns, biosynthetic dressings (e.g., Biobrane) demonstrated healing in 10-14 days, and topical honey preparations showed healing in 12-16 days. The performance of MMHRT in our study is comparable to these advanced therapies, while offering advantages in terms of cost-effectiveness and accessibility.

The accelerated healing observed with MMHRT may be attributed to multiple factors operating synergistically. First, the lipid-rich composition of horse oil provides an optimal occlusive wound environment that maintains moisture balance, prevents desiccation of exposed tissue in the zone of stasis, and facilitates keratinocyte migration. Second, the high concentration of PUFAs, particularly linoleic acid, directly supports the synthesis of ceramides and other skin barrier lipids essential for epidermal reconstruction. Third, the rubbing technique itself may provide mechanical stimulation that enhances local microcirculation, promotes lymphatic drainage, and stimulates mechanotransduction pathways involved in tissue repair.

4.2 Mechanistic Insights: TLR4/NF-kappaB and PPARgamma Signaling

The molecular mechanisms underlying the therapeutic effects of MMHRT appear to involve a coordinated modulation of key inflammatory and reparative signaling pathways. Our Western blot analysis demonstrated that MMHRT significantly suppressed the TLR4/NF-kappaB signaling axis, as evidenced by reduced expression of TLR4, decreased phosphorylation of NF-kappaB p65 and IkappaB-alpha, and preservation of total IkappaB-alpha levels. This finding is of particular significance because the TLR4/NF-kappaB pathway is a central mediator of post-burn inflammation and secondary tissue damage.

Following thermal injury, damaged cells release DAMPs, including heat shock proteins, HMGB1, and mitochondrial DNA fragments, which activate TLR4 on resident immune cells and keratinocytes. TLR4 activation triggers downstream signaling through MyD88-dependent and TRIF-dependent pathways, culminating in NF-kappaB nuclear translocation and the transcriptional induction of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6), chemokines, and adhesion molecules. While this initial inflammatory response is necessary for host defense and tissue debridement, its excessive or prolonged activation leads to sustained inflammation, oxidative stress, and collateral damage to viable tissues in the zone of stasis.

The ability of MMHRT to suppress TLR4/NF-kappaB signaling may be mediated through several mechanisms. Linoleic acid and its metabolites have been shown to modulate TLR4 membrane microdomain organization and inhibit receptor dimerization. Oleic acid, another major component of horse oil, activates PPARgamma, which physically interacts with NF-kappaB p65 and prevents its binding to target gene promoters. Squalene, a minor but bioactive component

of horse oil, has demonstrated antioxidant and anti-inflammatory properties that may reduce DAMP generation and TLR4 ligand availability.

Concomitant with the suppression of pro-inflammatory signaling, MMHRT significantly upregulated PPARgamma expression in wound tissues. PPARgamma is a nuclear receptor that plays a central role in the resolution of inflammation and the promotion of tissue repair. Activation of PPARgamma exerts anti-inflammatory effects through multiple mechanisms: (1) transrepression of NF-kappaB target genes through competition for coactivator molecules; (2) induction of IkappaB-alpha expression, which sequesters NF-kappaB in the cytoplasm; (3) promotion of M2 macrophage polarization, which shifts the wound environment from a pro-inflammatory (M1) to a pro-healing (M2) phenotype; and (4) direct enhancement of keratinocyte proliferation, migration, and differentiation through the PPARgamma/PI3K/Akt signaling axis.

4.3 Pain Relief Mechanism

The rapid and sustained pain relief observed with MMHRT represents a clinically significant advantage, as pain management is a major concern in burn care. The faster pain reduction in the MMHRT group (VAS 28.6 mm vs. 45.2 mm at day 3) may be attributed to several factors. The occlusive lipid layer formed by horse oil protects exposed nerve endings from environmental stimuli, including air movement, temperature changes, and mechanical irritation. The anti-inflammatory effects mediated through NF-kappaB suppression reduce the local production of algogenic mediators (prostaglandins, bradykinin, substance P). Additionally, the rubbing technique may activate cutaneous mechanoreceptors and gate pain signal transmission through the gate control theory of pain modulation. The presence of oleic acid in horse oil may also contribute to analgesia through activation of TRPV1 channels and modulation of nociceptive signaling.

4.4 Scar Quality Improvement

The superior scar outcomes in the MMHRT group, as demonstrated by significantly lower VSS scores at 1 and 3 months post-healing, suggest that MMHRT not only accelerates wound closure but also modulates the quality of tissue repair. This finding is particularly important given the substantial psychosocial and functional impact of burn scars. The improved scar quality may be related to several mechanisms identified in our molecular analysis.

First, the balanced regulation of TGF-beta1/Smad3 signaling (reduced TGF-beta1 and p-Smad3 expression in MMHRT group) may prevent excessive fibroblast activation and collagen deposition, which are hallmarks of hypertrophic scar formation. Second, the lower expression of alpha-SMA, a marker of myofibroblast differentiation, suggests that MMHRT promotes a more regenerative (rather than fibrotic) healing phenotype. Third, the optimized MMP-9/TIMP-1 ratio in the MMHRT group indicates a favorable balance between matrix degradation and synthesis, allowing for proper ECM remodeling. Finally, the higher VEGF expression in the MMHRT group may contribute to more organized neovascularization, which is associated with reduced scar formation.

4.5 Horse Oil Composition and Therapeutic Implications

The therapeutic efficacy of MMHRT is intimately linked to the unique biochemical composition of horse oil. Compared with other animal fats commonly used in traditional medicine, horse oil is distinguished by its high content of unsaturated fatty acids (approximately 60% of total fatty acids), with a favorable ratio of omega-6 to omega-3 fatty acids (approximately 2.9:1, close to the recommended dietary ratio). Linoleic acid (18.6%), the most abundant PUFA in horse oil, is an essential component of the epidermal lipid barrier and serves as a precursor for anti-inflammatory arachidonic acid metabolites (PGE1, 15-HETE) through the 15-lipoxygenase pathway. Alpha-linolenic acid (6.5%) is a precursor for anti-inflammatory resolvins and protectins through the omega-3 pathway.

Notably, the fatty acid composition of horse oil closely resembles that of human sebum and epidermal lipids, which may explain its excellent skin compatibility and biocompatibility. This compositional similarity allows horse oil to integrate seamlessly with the damaged skin barrier, supporting ceramide synthesis and accelerating barrier restoration. In contrast, SSD cream lacks these lipid components and may actually impair barrier function through its desiccant properties.

4.6 Implications for Mongolian Medicine Theory

The findings of this study provide a modern scientific interpretation for the traditional Mongolian medicine understanding of burn pathology and the mechanism of rubbing therapy. In the framework of the "Three Roots and Seven Elements" theory, burns are considered a "Xira" (bile-type) disorder characterized by excessive heat, inflammation, and tissue damage. The "yellow water" (Seruang Shui) pathological concept, unique to Mongolian medicine, describes an inflammatory exudate that impairs wound healing and promotes scar formation. The therapeutic action of horse oil rubbing therapy, as understood in traditional terms, involves "cooling the Xira heat, eliminating the yellow water, promoting tissue generation, and restoring elemental balance."

Our molecular findings provide empirical support for this traditional framework. The suppression of TLR4/NF-kappaB-mediated inflammation corresponds to the concept of "cooling Xira heat," the promotion of PPARgamma-mediated anti-inflammatory responses corresponds to "eliminating yellow water," and the enhancement of growth factor expression corresponds to "promoting tissue generation." This alignment between traditional ethnomedical concepts and modern molecular mechanisms strengthens the case for integrating MMHRT into evidence-based burn care protocols.

4.7 Strengths and Limitations

This study has several notable strengths, including its randomized controlled design, adequate sample size, comprehensive clinical and molecular endpoints, standardized intervention protocols, and intention-to-treat analysis. The multi-dimensional assessment of treatment effects, encompassing wound healing, pain, scar quality, inflammatory biomarkers, and signaling pathway proteins, provides a thorough characterization of the therapeutic profile of MMHRT.

However, several limitations should be acknowledged. First, the single-center design may limit the generalizability of findings to other clinical settings and populations. Second, the inability to blind treating physicians due to the distinct physical characteristics of the interventions introduces potential performance bias, although this was mitigated by the blinding of outcome assessors and laboratory personnel. Third, the molecular analyses were performed on a subset of patients (n = 30 per group for Western blot), and the biopsies were obtained at a single time point (day 7), which may not capture the full temporal dynamics of signaling pathway modulation. Fourth, the study did not include an economic analysis to assess the cost-effectiveness of MMHRT. Fifth, the follow-up period for scar assessment was limited to 3 months, and longer-term outcomes (6-12 months) warrant further investigation. Finally, the rubbing technique component was not isolated from the horse oil component in the study design, precluding conclusions about the specific contribution of each element to the therapeutic effect.

4.8 Future Research Directions

Based on the findings of this study, several future research directions are warranted. First, multi-center, large-scale randomized controlled trials with diverse populations should be conducted to confirm the generalizability of our results. Second, studies directly comparing MMHRT with newer topical agents such as nanocrystalline silver dressings, Mepilex Ag, or Suprathel would provide valuable comparative effectiveness data. Third, component-isolation studies comparing horse oil alone versus horse oil with rubbing versus rubbing alone would help elucidate the relative contributions of the pharmacological and mechanical components. Fourth, in vitro and in vivo mechanistic studies are needed to further characterize the molecular pathways through which horse oil modulates wound healing, including transcriptomic and proteomic analyses. Fifth, formulation optimization studies, including the incorporation of MMHRT into standardized topical preparations or dressings, could enhance its practical applicability in clinical settings.

5. Conclusion

This randomized controlled trial demonstrates that Mongolian medicine horse oil rubbing therapy significantly accelerates burn wound healing, provides superior pain relief, and improves long-term scar quality compared with standard silver sulfadiazine therapy in patients with superficial partial-thickness burns. The molecular mechanisms underlying these therapeutic effects involve the coordinated modulation of the TLR4/NF-kappaB pro-inflammatory signaling axis, the activation of PPARgamma anti-inflammatory pathways, the enhancement of pro-healing growth factor expression, and the optimization of extracellular matrix remodeling. These findings provide rigorous clinical evidence supporting the traditional application of MMHRT for burn wound management and suggest its potential as a safe, effective, and affordable complementary therapy in evidence-based burn care protocols. The integration of ethnomedical wisdom with modern scientific validation exemplifies a productive approach to discovering and developing novel therapeutic strategies from traditional medical heritage.

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