



Research paper

The efficacy of honey and a Thai Herbal Oil preparation in the treatment of pressure ulcers based on Thai traditional medicine wound diagnosis versus standard practice: An open-label randomized controlled trial

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ABSTRACT

Background: Scientific support for Thai traditional medicine (TTM) practice is warranted for reintroduction into modern healthcare systems. A promising TTM practice for treatment of pressure ulcers was selected to conduct a clinical trial. This study aimed to evaluate the efficacy of the TTM practice for the treatment of pressure ulcers using honey or a Thai Herbal Oil preparation (THO) based on the TTM wound diagnosis comparing with the standard practice.

Methods: The study design was an open-label randomized controlled trial. Sixty-six participants, with pressure ulcers at least stage II-IV or unstageable, were allocated to two groups via minimization. A TTM practice group received honey or THO depending on the TTM diagnosis via the Thai Traditional Medicine Pressure Ulcer Assessment Tool (TTM-PUAT). A standard practice group received advanced dressings, including hydrogel, alginate, silver-impregnated, or hydrocolloid dressings. The primary outcome was the Pressure Ulcer Scale for Healing (PUSH).

Results: Both TTM practice and standard practice showed a significant reduction in PUSH scores after treatments. However, there was no significant difference in PUSH score reduction between the groups. The mean PUSH score reduction over the 6-week period was 2.58 ± 3.38 (95% CI 1.34–3.82) in the TTM practice group and 3.24 ± 3.49 (95% CI 1.91–4.57) in the standard practice group ($p = 0.284$). The TTM practice and standard practice accelerated pressure ulcer healing without statistically significant difference between the practices, during 6 weeks in a home-based care setting. This finding supported the TTM practice as an alternative treatment for pressure ulcer.

1. Introduction

Pressure ulcer (PU) decreases quality of life and increases morbidity, mortality, costs, and hospitalization [1]. The high-risk population of pressure ulcers include patients with lengthy operations, neurologic conditions, spinal cord injuries and advanced age, especially those who are immobilized. There is no evidence of high-quality research on a single dressing that is consistently superior to others [2]. From a

practical point of view, the selection of a dressing depended on wound assessment, care conditions, plans for dressing change and cost.

The role of traditional medicine treatments has received more attention through robust research, for an effective PU treatment [1]. There is a routine Thai Traditional Medicine (TTM) practice at Kab-chong Hospital, Thailand. Honey or a Thai Herbal Oil preparation (THO) was selected for a specific PU that was diagnosed based on a TTM concept, Tri-Dosha. PU was diagnosed as a Wata wound recommended

Abbreviations: BWAT, Bates-Jensen Wound Assessment Tool; ITT, intention-to-treat; NPUAP / EPUAP, National Pressure Ulcer Advisory Panel and the European Pressure Ulcer Advisory Panel; PP, per-protocol; PU, pressure ulcer; PUSH, Pressure Ulcer Scale for Healing; RCT, randomized controlled trials; THO, Thai Herbal Oil preparation; TTM, Thai traditional medicine; TTM-PUAT, Thai Traditional Medicine Pressure Ulcer Assessment Tool; TLC, thin layer chromatography; TAMC, total aerobic microbial count; TYMC, total combined yeasts and molds count.

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for treatment with honey or as a Pitta wound recommended for treatment with THO, made from *Clinacanthus nutans* (Burm. f.) Lindau (leaf), and *Zingiber montanum* Link ex A. Dietr. (rhizome) [3]. In our previous study, a diagnostic tool based on TTM was established, namely the Thai Traditional Medicine Pressure Ulcer Assessment Tool (TTM-PUAT) [4]. The reliability of TTM-PUAT was 78.8% agreement with the expert assessment and 73.09% interrater reliability with 0.46 Kappa statistic. A link between TTM wound diagnosis, Tri-Dosha, and the international PU classification was also revealed.

Honey and THO possess pharmacological activities related to wound healing, antimicrobial activity, anti-inflammatory activity, antioxidant activity, and stimulation of wound regeneration [5–9]. In clinical studies, after being treated with honey, the pressure ulcers were voided from bacteria [10], necrotic tissue [11], and malodor [12]. There were 3 randomized controlled trials (RCT) on honey, but no trials on THO, *C. nutans*, or *Z. montanum* in the treatment of pressure ulcers. Three RCTs on honey showed that the results favored the honey treatments over the control treatments [13–15]. However, the quality of evidences was limited [16]. According to recent findings, honey is recommended for PU stage II and mild infection or for heavily contaminated or infected pressure ulcers [1,17].

Reintroducing a TTM practice to a modern healthcare system needs supporting scientific evidence, especially clinical trials. However, conducting an RCT designed for treating disease based on the modern medicine concept could yield limited model validity and cause mismatching between the traditional medicine diagnosis and the appropriate treatment [18]. Incorporating traditional medicine diagnosis into an RCT design has improved model validity and increased the possibility of new findings for specific indications, with higher effective rates. However, there was no fundamental pattern for designing the trials.

In this study, we aimed to determine the efficacy of the TTM practice for PU treatment, using honey or THO following the TTM diagnosis via TTM-PUAT, compared to that of standard treatment. Moreover, a novel hybrid methodology was proposed as a pattern for designing the RCT based on the traditional medicine concept.

2. Design and methods

2.1. Study design

We undertook an open-label randomized controlled trial in 7 hospitals in Thailand: Ramathibodi Hospital (Bangkok), Lumsonthi Hospital (Lopburi Province), Wangnamyen Hospital (Sakaeo Province), Wattanakorn Hospital (Sakaeo Province), Tawatburi Hospital (Roi et Province), Ponthong Hospital (Roi et Province), and Khawsinarin Hospital (Surin Province). The study setting was home-based care. A protocol of this study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (MURA2015/27). This study was registered in Thai Clinical Trials Registry (TCTR) (TCTR20160915004).

2.2. Participants

The included participants were older than 18 years with at least one PU that was stage II-IV or unstageable as classified by the National Pressure Ulcer Advisory Panel and the European Pressure Ulcer Advisory Panel (NPUAP/EPUAP) [1]. The participants were excluded if they had severe allergies to any topical agents in this study; if they had severe conditions that disabled them from continuing to be monitored for 6 weeks; or if they needed surgical procedures or any therapies that were incompatible with any treatments in this study. Written consent was obtained from each participant before inclusion. The participants were recruited by research team members at 7 study sites through doctors, nurses, or TTM practitioners.

2.3. Randomization

The participants were allocated into the TTM practice group or standard practice group via minimization [19]. Four minimization factors were selected: severity of PU (stage II, stage II-IV or unstageable), age (<65, 65 or above), diabetes (present, absent) and study site. First, the severity of PU was categorized using the PU classification system [1]. The cut-off point of PU severity was set at stage II according to the estimated healing time at which PU stage II could heal within 6 weeks, while more severe ulcers could not [20]. Second, increasing age caused delayed wound healing. The cut-off point of age in this study was set at 65 years because it was comparable to that in international studies of elderly subjects. Third, diabetes was associated with PU development. Last, this study consisted of 7 study sites. The participants were recruited by research team members at 7 study sites while being allocated, case by case, by SC.

2.4. Procedures

All participants were assessed with the Braden scale and provided advice on recommended care following the Braden score interventions: 2-hour repositioning, pressure-reducing support surface, nutrition, and hygiene [21]. Participants who had repositioning problems were offered an alternating pressure mattress. PUs were cleaned with normal saline and dressed with the assigned treatments for 6 weeks. The participants and their care givers were advised on PU care and usage of the assigned treatments at the beginning of the study and at every home visit. We could not blind the participants, care givers, or research team members to the assigned treatments because of the characteristics and usages of the topical agents and dressings. The research team conducted home visits every 2 weeks for 6 weeks to monitor wound healing and to offer medical supplies and advice on PU care. During the trial, participants and their care givers were responsible for managing the PUs. Surgical debridement was applied depending on the study site where it was available.

In the standard practice group, participants were offered hydrogel (Intrasite gel - Smith & Nephew), fiber (Algisite - Smith & Nephew, Aquacel Ag - Convatec, Durafiber - Smith & Nephew), hydrocolloid (Duoderm CGF - DuoDERM) or foam (Allevyn - Smith & Nephew) dressings, following the guidelines [1,21]. PUs were cleaned with normal saline and dressed with the assigned products. The hydrogel was used with gauze. The other dressings were used according to their indications. The dressings were fixed by an adhesive (Fixomull - BSN medical), tape (Micropore - Nexcare 3 M, Transpore - Nexcare 3 M), or film (Opsite flexifix - Smith & Nephew, Tegaderm Film - 3 M). The dressing was changed every 1–2 days (hydrogel) or up to 7 days according to the indication of each product (fiber dressing, foam dressing, or hydrocolloid) or changed more often if leakage of exudate was apparent, the absorbance was saturated, or the dressing became dirty, for example, with feces or urine.

In the TTM practice group, participants were offered honey or THO according to the TTM wound diagnosis. The PUs were diagnosed through TTM via the Thai Traditional Medicine Pressure Ulcer Assessment Tool (TTM-PUAT) [4]. Honey was assigned to the Wata wound, and THO was assigned to the Pitta wound. The PUs were cleaned by normal saline, dressed by a gauze moistened with honey or THO, packed with dry gauze and fixed by the adhesive (Fixomull - BSN medical), tape (Micropore - Nexcare 3 M, Transpore - Nexcare 3 M), or film (Opsite flexifix - Smith & Nephew, Tegaderm Film - 3 M). The dressing was changed every 1–2 days or changed more often if leakage of exudate was apparent or the dressing became dirty, for example, with feces or urine.

A batch of genuine honey was purchased from Supha Bee Farm, Chiangmai Province. The honey was collected from a wildflower source in Tha Wang Pha District, Nan Province, Thailand. The honey was irradiated at 15 kGy by the Thailand Institute of Nuclear Technology (Public Organization), Pathumthani Province, Thailand. A batch of THO

was prepared traditionally at Kabchoeng Hospital, Surin Province, as the routinely used product. The preparation consists of *Clinanacnathus nutans* (Burm. F.) Lindau (leaves) and *Zingiber montanum* Link ex A. Dietr. (rhizome), fried in palm oils. The finished products of honey and THO passed the criteria for microbiological quality of nonsterile pharmaceutical preparations for broken skin, in the Thai Pharmacopoeia II 2011 [22]; Total Aerobic Microbial Count (TAMC) and Total Combined Yeasts and Molds Count (TYMC) had to be less than 2×10^1 cfu per g or per ml and void of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

The thin layer chromatography (TLC) technique was used for quality control of the tested THO for a chemical fingerprint to ensure that the consistency of the preparations was acceptable for testing in the trial.

2.5. Outcomes

The primary outcome was the score on the Pressure Ulcer Scale for Healing (PUSH) [23]. The range of the score is 0–17, that is, from completely healed to the greatest severity. The scale consists of 3 domains: length times width (10-scale), exudate amount (none, light, moderate, and heavy), and tissue type (necrotic tissue, slough, granulation tissue, epithelial tissue and closed wound). The secondary outcome was the score on the Bates-Jensen Wound Assessment Tool (BWAT) [24]. The range of the score is 13–65, that is, from completely healed to the greatest severity. The scale consists of 13 domains on a Likert 5-scale (1 = best, 5 = worst): size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding the wound, peripheral tissue edema, peripheral tissue induration, granulation tissue, and epithelialization. All ulcers were assessed by SC.

PU healing was assessed every 2 weeks for 6 weeks. Baseline and serial photos were used with standard photographic techniques [1]. Photos of an exudate on the dressing and a PU with a scale were taken by mobile phone camera (M8 - HTC). The photos of the exudate were taken when the dressing was changed. After cleansing, the photos of PU with a scale (adhesive 2-axis scale – printed ruler scale on sticker paper) or with a measuring device (sterile DM stick with foam tip wound measuring device - Puritan) for underlining the ulcer were taken. The width, length and depth of the PU were measured using a computer program, ImageJ, and then these data were used to generate PUSH and BWAT scores. Moreover, researcher team members asked the participants or care givers about the participant conditions and care procedures to detect adverse events before the next visit.

2.6. Statistical analysis

The sample size was designed to allow the detection of 2 score differences of PUSH between groups with a 5% Type 1 error and an 80% study power. The two-sided hypothesis testing equation, $n = 2 (Z_{\alpha/2} + Z_{1-\beta})^2 \sigma^2 / \delta^2$, was calculated [25]. The sigma (σ) was set at 2.5 in accordance with previous studies [26] and data from our preliminary study. The percentage of exclusion participants and loss to follow-up was estimated to be 30% from our preliminary study. The sample size was 66 (33 in each group).

There were 6 approaches of statistical analysis (Table 1). The primary analysis was an intention-to-treat (ITT) analysis for PUSH and BWAT scores of 1 ulcer/participant data set. In patients with more than one PU, only one ulcer was selected for comparing the efficacy between two groups. The ulcer selection criteria were as follows: 1) the ulcer with complete follow-up data, 2) the ulcer with the highest PUSH score, and 3) the ulcer with the largest size. The second analysis was a per-protocol (PP) method for PUSH scores of 1 ulcer/participant data set. The per-protocol method analyzed only the participants who completed the treatment allocated. The second analysis was conducted for comparison with the primary analysis to reduce the risk of attrition bias [27]. The third analysis was a subgroup analysis focused on the predominant treatments, namely, honey in the TTM practice group and hydrogels in

Table 1
Six approaches of statistical analysis.

No.	Data set	Method	Sub-group	Sample size (TTM practice: Standard practice)	Outcome
1 ^a	1 ulcer/participant	ITT	–	N = 66 (33: 33)	PUSH, BWAT
2	1 ulcer/participant	PP	–	N = 60 (31: 29)	PUSH
3	1 ulcer/participant	ITT	Wounds which treated with honey and hydrogel	N = 55 (30: 25)	PUSH
4	All ulcers	ITT	–	N = 124 (65: 59)	PUSH
5	All ulcers	ITT	Wata wounds	N = 93 (50: 43)	PUSH
6	All ulcers	ITT	Pitta wounds	N = 31 (15: 16)	PUSH

ITT = Intention-to-treat, PP = Per-protocol.

^a The primary analysis.

the standard practice group. The third analysis was an ITT method for PUSH scores of 1 ulcer/participant data set, which was comparable to the primary analysis. Another 3 approaches were an ITT method for PUSH scores of all wound data sets. The fourth analysis was conducted on all wounds for comparison with the primary analysis. The fifth and sixth analyses were conducted to contribute more information on TTM wound diagnosis and treatment outcomes; they were subgroup analyses of Wata wounds and Pitta wounds, respectively.

Statistical analyses were performed using SPSS software version 18 for Windows and an interactive calculation tool for chi-square tests [28]. First, for comparison of baselines between groups, the *t*-test and the Mann-Whitney test were used for continuous variable data, and the chi-square test, Fisher's exact test or Yates' chi-square test were used for categorical data. Second, comparison outcomes within the group, between before and after treatment, were performed using Friedman's test and the Wilcoxon signed rank test. Finally, comparison outcomes between groups was performed using the *t*-test and the Mann-Whitney test for continuous variable data and the chi-square test for categorical data.

3. Results

Between Sep 14, 2016, and Aug 12, 2017, we screened 77 patients and allocated 66 participants to the TTM practice group ($n = 33$) and the standard practice group ($n = 33$). After allocation, all participants, including 66 patients and 124 ulcers, were statistically analyzed (Fig. 1). The baseline characteristics of the participants and baseline wound characteristics are shown in Table 2 and Table 3, respectively.

3.1. PUSH scores

In the comparison within groups, the mean of the PUSH scores was reduced significantly at 6 weeks, from 12.27 ± 2.84 (95% CI 11.26–13.28) at the baseline to 9.58 ± 4.32 (95% CI 8.00–11.16) in the TTM practice group ($P < 0.001$), and from 12.55 ± 2.53 (95% CI 11.65–13.44) at the baseline to 9.24 ± 4.69 (95% CI 7.46–11.02) in the standard practice group ($P < 0.001$). Comparison between groups revealed no significant difference in PUSH score reduction for 6 weeks: 2.58 ± 3.38 (95% CI 1.34–3.82) in the TTM practice group and 3.24 ± 3.49 (95% CI 1.91–4.57) in the standard practice group ($p = 0.284$).

Regarding the percentage of participants with a healing outcome at 6 weeks, there was no significant difference between the 2 groups ($P = 0.772$). Three patients (9.1%) in the TTM practice group and 4 patients (12.1%) in the standard practice group were completely healed, and the PUSH score was reduced to 0 within 6 weeks. Seventeen patients (51.5%) and 20 patients (60.6%), respectively, were better, and the PUSH score was reduced by at least 1 point but did not reach 0. Thirteen

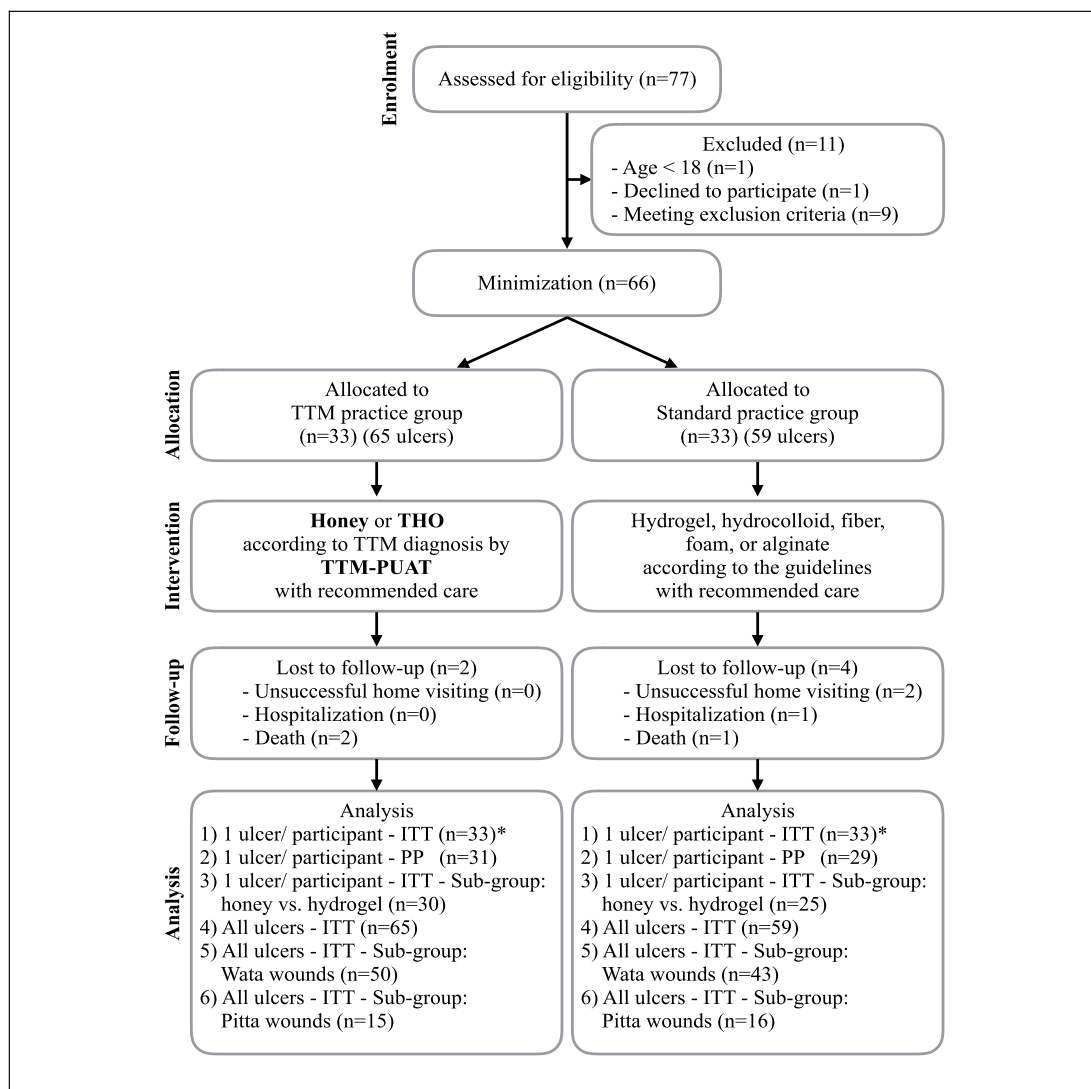


Fig. 1. Trial profile, * primary analysis.

Table 2
Baseline character of the intention-to-treat population.

	TTM practice (n = 33)	Standard practice (n = 33)
Age	63.6 ± 21.4	67.6 ± 21.1
Gender		
Female	17 (51.5%)	14 (42.4%)
Male	16 (48.5%)	19 (57.6%)
Ethnic origin – Asian	33 (100%)	33 (100%)
Braden score	15.5 ± 1.97	15.0 ± 1.95
Diabetes	10 (30.3%)	6 (18.2%)
Diagnosis		
Spinal cord injuries	11 (33.3%)	7 (21.2%)
Senility	8 (24.2%)	7 (21.2%)
Cerebrovascular accident	3 (9.1%)	6 (18.2%)
Weakness	4 (12.1%)	2 (6.1%)
Lumbar radiculopathy	1 (3.0%)	2 (6.1%)
Spinal tuberculosis	2 (6.1%)	1 (3.0%)
Others	4 (12.1%)	8 (24.2%)
Number of pressure ulcer		
1 ulcer	18 (54.5%)	17 (51.5%)
2 ulcers	9 (27.3%)	8 (24.2%)
3 ulcers	4 (12.1%)	4 (12.1%)
4–8 ulcers	2 (6.1%)	4 (12.1%)

Data are n(%) and mean ± SD.

patients (39.4%) and 9 patients (27.3%), respectively, were not healed, and the PUSH score was not reduced.

3.2. BWAT score

For the secondary outcome, the mean BWAT score was reduced significantly within the groups at 6 weeks, from 33.30 ± 5.68 (95% CI 31.29–35.32) at the baseline to 28.71 ± 7.93 (95% CI 25.80–27.68) in the TTM practice group (P < 0.001), and from 30.67 ± 5.84 (95% CI 28.60–32.74) at the baseline to 25.14 ± 6.67 (95% CI 22.60–27.68) in standard practice group (P < 0.001). Comparison of the BWAT score reduction showed no significant differences between groups at 6 weeks: 4.84 ± 4.99 (95% CI 3.01–6.67) in the TTM practice group and 5.38 ± 5.85 (95% CI 3.16–7.60) in the standard practice group (P = 0.672).

3.3. PUSH score reduction, minor analyses

The PUSH score reduction in the 6 approaches of statistical analysis is shown in Fig. 2. The primary analysis, namely, the intention to treat (ITT) method, and the second analysis, namely, the per protocol (PP) method, showed the same results at 6 weeks. The third analysis, a subgroup analysis of wounds treated with honey and hydrogel, showed the same trend of results as the primary analysis, with no significant difference between groups (P = 0.119). The fourth analysis, with all ulcer

Table 3
Baseline character of the intention-to-treat ulcers.

	TTM practice (n = 33)	Standard practice (n = 33)
PUSH score	12.27 ± 2.84	12.55 ± 2.53
BWAT score	33.30 ± 5.68	30.67 ± 5.84
Surface area (cm ²)	37.43 ± 74.72	18.42 ± 15.84
PU classification		
Stage 2	3 (9.1%)	5 (15.2%)
Stage 3	9 (27.3%)	20 (60.6%)
Stage 4	17 (51.5%)	6 (18.2%)
Unstageable	4 (12.1%)	2 (6.1%)
Body region		
Sacrum	17 (51.5%)	19 (57.6%)
Trochanter	6 (18.2%)	3 (9.1%)
Coccyx	3 (9.1%)	3 (9.1%)
Ischium	5 (15.2%)	5 (15.2%)
Others	2 (6.1%)	3 (9.1%)
Tunnel	14 (42.4%)	10 (30.3%)
Necrotic tissue	13 (39.4%)	10 (30.3%)
TTM wound diagnosis		
Pitta	3 (9.1%)	5 (15.2%)
Wata	30 (90.9%)	28 (84.8%)
Topical agent/Dressing		
Fiber	–	4 (12.1%)
Foam	–	3 (9.1%)
Hydrocolloid	–	1 (3.0%)
Hydrogel	–	25 (75.8%)
THO	3 (9.1%)	–
Honey	30 (90.9%)	–

Data are n(%) and mean ± SD.

data sets, showed more PUSH score reduction than the primary analysis. A reason for this finding was the severity of PU in the primary analysis, which required more time to heal. The fifth analysis, with all ulcer data sets and Wata wound subgrouping, showed significant differences between the two groups ($P = 0.038$). The standard practice yielded better healing than the TTM practice. A reason for this finding was the significant difference in the severity of PUs between groups. The TTM practice group was predominantly in stage IV (52.0%) compared to the standard practice group (18.6%). The standard practice group was predominantly in stage III (72.1%) compared to the TTM practice group (34.0%) ($P = 0.001$). The sixth analysis, with all ulcer data sets and Pitta wound subgrouping, showed the highest PUSH score reduction by 7.00 ± 2.78 in the TTM practice group and 6.20 ± 3.97 in the standard practice group ($P = 0.784$). The results of the Pitta wound subgroup analysis showed the same trend as the results of the primary analysis, with no significant difference between groups.

3.4. Safety issue

Three patients died during the trial. However, the causes of death were not related to any interventions from the study. Two patients in the TTM practice group died because of respiratory infection and cerebral hypoxia. A patient in the standard practice group died because of a urinary tract infection.

4. Discussion

This clinical trial showed no significant difference in the efficacy of PU treatment between the TTM practice and standard practice groups within 6 weeks. After treatment, the PUSH score of both groups was reduced significantly compared to the score at baseline. The finding supported routine TTM practices at Kabchoeng Hospital, that is, using honey and THO with TTM wound diagnosis, as an alternative treatment for PU. In the subgroup analysis, there was no significant difference in the efficacy of honey and hydrogel for the treatment of a Wata wound PU. The findings confirmed the efficacy of honey as did the previous RCTs of honey for PU treatment [13–15]. Moreover, this study is the first RCT to show the efficacy of honey for the treatment of severe pressure

ulcers, namely those that are stage III, stage IV or unstageable.

This study had a limitation on unblinding of the participants, care givers, or research team members due to the characteristics and usages of the interventions. The unblinding trial could lead to the risk of performance bias especially the trial with subjectivity outcomes [27]. To reduce the bias, the outcome in this study was designed as objective assessments via PUSH and BWAT. For example, the wound characters for assessment were length and width of PUs, type of tissue confirmed with serial PUs photos.

The effect of honey and THO on PU treatment is explained by their pharmacological activities. For honey, a mechanism for wound healing has been reported. The glucose oxidase enzyme can generate peroxide for antimicrobial and autolytic debridement, as well as various metabolites, depending on the flower source [5]. For THO, the nonpolar portion is the active part. Active compounds of *Z. montanum* have been identified as phenylbutanoids, including compound D with anti-inflammatory and analgesic activities, Cassumunarins A, B, and C with anti-inflammatory and antioxidant activities, and essential oils with antimicrobial activities [6,7]. The active compound of *C. nutans* is Purpurin-18 phetyl ester (P18PE), which has anti-inflammatory, wound healing, antioxidant, and antibiofilm activities [8,9].

A recommendation for dressing selection is proposed that combines the benefit of both TTM practice and standard practice (Table 4). Honey and THO were competitive options for PU treatment. The TTM practice with TTM wound diagnosis performed with no significant difference in the efficacy to that of the standard practice, within 6 weeks, in a home-based care setting. However, the outstanding benefit of honey and THO was the cost per unit (1–1.5 \$), which was 2–14 times cheaper than the advance dressings (3.5–18 \$).

Please be aware that the success of PU healing in the home-based care setting was mainly because of the cooperation among care givers, patients, and healthcare providers. The success was not only because of the effective dressing but also a result of advising, educating, and training the participants on the recommended care—for example, reducing pressure, 2-h repositioning, nutrition, hygiene, and social and mental support. Some ulcers did not heal within 6 weeks, including those in 13 patients (39.4%) in the TTM practice group and 9 patients (27.3%) in the standard practice group. There were 4 risk factors found in these patients: 1) limitation of reducing pressure on their ulcers, 2) limitation of moisture control, 3) malnutrition, and 4) severity of the PUs (stage III-IV and unstageable). The limitation of care and malnutrition prolonged the time healing. On one hand, the participants and their care givers were not able to manage the risk factors within 6 weeks. On the other hand, the PUs of these patients had a high stage of severity and required a longer time than 6 weeks to monitor healing based on the PUSH score [20].

This study was an attempt to design a clinical trial for demonstrating the efficacy of TTM practice with respect to TTM diagnosis. TTM diagnosis was important for selecting a proper herbal medicine, whether honey or THO. Ignorance of the TTM diagnosis could lead to a mismatch between the disease and treatment. Pitta wounds and Wata wounds were diagnosed using the TTM-PUAT. We propose a novel hybrid methodology as a pattern for designing an RCT based on the traditional medicine concept. The purpose of the hybrid methodology was to present a traditional medicine perspective that can be understandable from a modern medicine point of view.

This study was developed with a hybrid methodology in 5 steps (Fig. 3). The first step, TTM practice for PU treatment, was defined into 3 components: diagnosis, treatment, and evaluation. The second step was to propose an interconnected diagnosis between traditional medicine and modern medicine. This study was designed to stratify PU with TTM wound diagnosis for selecting the appropriate herbal medicine. For this purpose, the TTM diagnostic tool, that is, the TTM-PUAT, was established and used. The third step was to select the comparable treatments. For TTM practice, honey and THO, the studied interventions, were topical agents used to optimize the wound healing environment. For

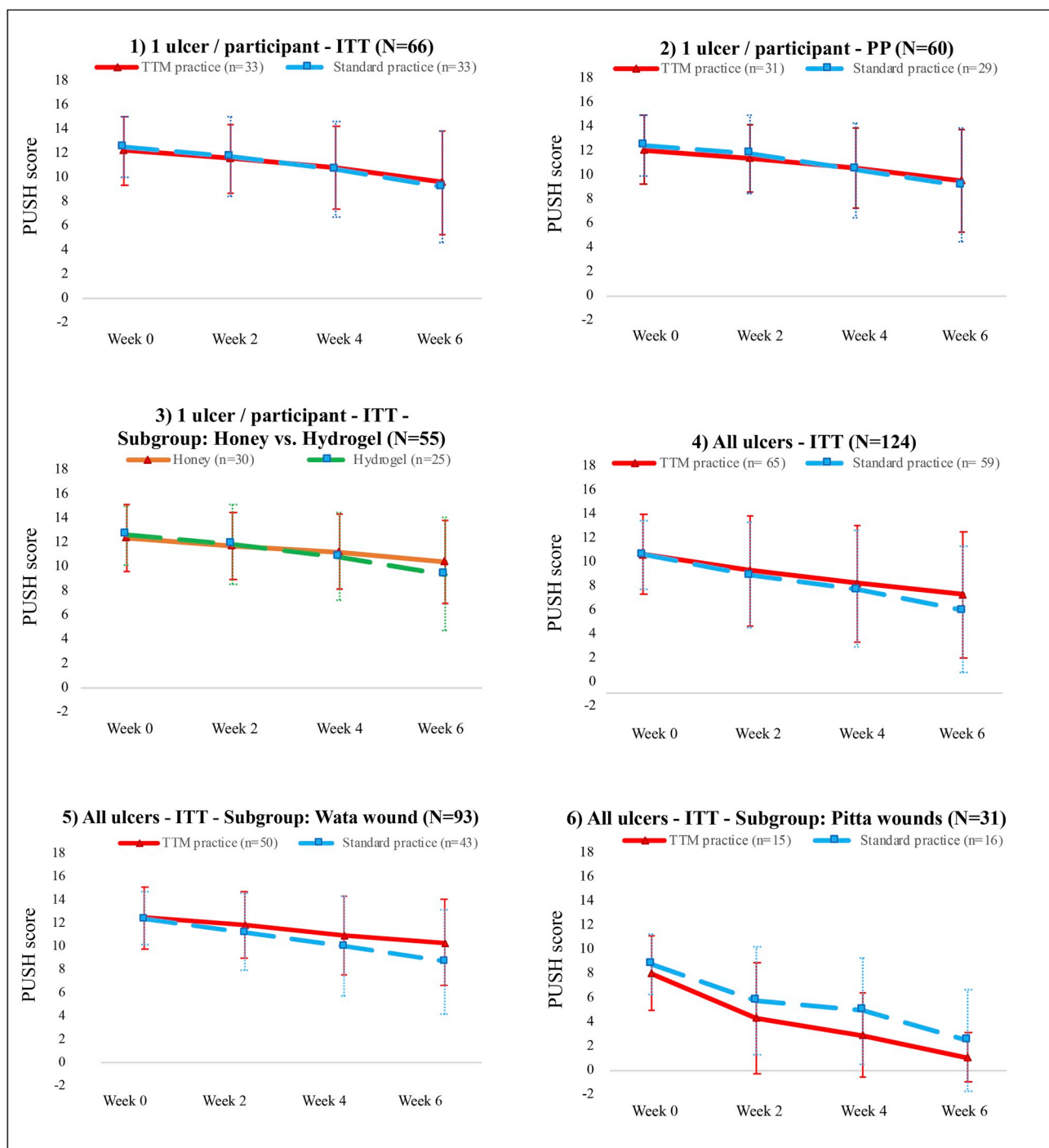


Fig. 2. PUSH scores of the 6 approaches of statistical analysis.

modern medicine practice, wound dressings used in standard treatment were selected as the intervention of the control group. The fourth step was to select an acceptable outcome. Complete wound healing was the most convincing outcome in both traditional and modern medicine; however, PU was commonly chronic, or in some cases, the PU had never healed. Therefore, PUSH and BWAT were selected as outcomes of this study, which can monitor wound healing within 6 weeks. Finally, the fifth step was incorporating the comparable diagnosis, treatment, and evaluation of traditional and modern medicine. The hybrid methodology can be applied for traditional medicine research with a variety of practices worldwide. It will enhance the scientific support of traditional medicine practices with the appropriate methodology and contribute

traditional medicine knowledge in modern contexts.

Further studies could use the TTM-PUAT with more specific types of PU, for example, focusing on PU-Wata wounds and monitoring for more than 6 weeks or focusing on PU-Pitta wounds that may undergo fast healing. The studies could investigate cost effectiveness between TTM treatments and advanced dressings. TTM treatments are 2–14 times cheaper than advanced dressings, but the advanced dressings could save time and cost of labor for dressing changes. Pharmacologically active compounds in honey and THO and their mechanisms of action could be considered.

Table 4
The recommendation of dressing selection.

Wound characters		TTM diagnosis - Wata wound		TTM diagnosis - Pitta wound	
		Necrotic tissue	Granulation tissue	Stage II	
		Stage III or Stage IV			
		Without inflammation		With inflammation	
Nondraining	Without undermining	Honey, Hydrogel, Hydrocolloid		THO, Hydrogel, Hydrocolloid	
	With undermining	Honey, Hydrogel		THO, Hydrogel	-
Draining	With or without undermining	Honey, Alginate, Fiber	Honey, Alginate, Fiber, Foam	THO, Alginate, Fiber, Foam	

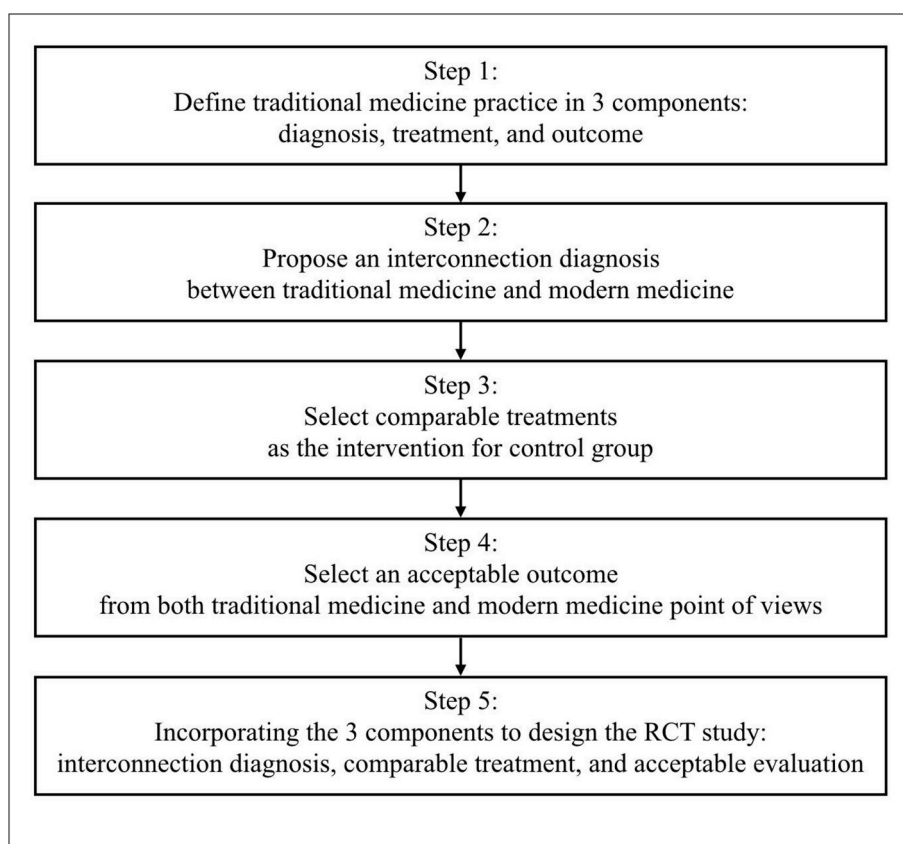


Fig. 3. Hybrid methodology for designing the RCT based on traditional medicine concept.

5. Conclusions

The TTM practice and standard practice accelerated the healing of stage II-IV and unstageable PU without statistically significant difference between the practices, in home-based care settings within 6 weeks. Honey and THO, with TTM wound diagnosis *via* the TTM-PUAT, were supported as an alternative treatment. We propose the recommendation of a dressing selection that includes honey and THO with advance dressings. Moreover, this study is the first RCT designed based on the TTM concept, and we propose a novel hybrid methodology as a pattern for designing RCTs based on traditional medicine concepts.

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Declaration of competing interest

The authors declare that they have no competing interests.

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References

- [1] National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, Pan Pacific Pressure Injury Alliance, *Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline, 2 ed.*, Cambridge Media, Perth, 2014.
- [2] Medical Advisory Secretariat, *Management of chronic pressure ulcers: an evidence-based analysis*, Ont Health Technol. Assess Ser. 9 (3) (2009).
- [3] S. Chotchoungchatchai, P. Saralamp, T. Jenjittikul, S. Pornsiripongse, S. Prathantururug, Medicinal plants used with Thai traditional medicine in modern healthcare services: a case study in Kabchoeng hospital, Surin province, Thailand, *J. Ethnopharmacol.* 141 (1) (2012) 193–205, <https://doi.org/10.1016/j.jep.2012.02.019>.
- [4] S. Chotchoungchatchai, *An Efficacy of Honey and Thai Herbal Oil Preparation on Pressure Ulcer Treatment Using Hybrid Methodology*, Faculty of graduated study, Mahidol university, 2018.
- [5] D.S. Lee, S. Sinno, A. Khachemoune, Honey and wound healing an overview, *Am. J. Clin. Dermatol.* 12 (3) (2011) 181–190, <https://doi.org/10.2165/11538930-000000000-00000>.
- [6] K.P.P. Nair, Additional economically important ginger species, in: K.P.P. Nair (Ed.), *The Agronomy and Economy of Turmeric and Ginger*, Elsevier, Oxford, 2013, pp. 511–522, <https://doi.org/10.1016/B978-0-12-394801-4.00027-2>.
- [7] R.S. Verma, N. Joshi, R.C. Padalia, V.R. Singh, P. Goswami, S.K. Verma, H. Iqbal, D. Chanda, R.K. Verma, M.P. Darokar, A. Chauhan, M.K. Kandwal, Chemical composition and antibacterial, antifungal, allelopathic and acetylcholinesterase inhibitory activities of cassumunar-ginger, *J. Sci. Food Agric.* 98 (1) (2018) 321–327, <https://doi.org/10.1002/jsfa.8474>.
- [8] L.W. Khoo, S. Audrey Kow, M.T. Lee, C.P. Tan, K. Shaari, C.L. Tham, F. Abas, A comprehensive review on phytochemistry and pharmacological activities of *Clinacanthus nutans* (Burm.f.) Lindau, *Evid. Based Compl. Alternat. Med.* 2018 (2018) 9276260, <https://doi.org/10.1155/2018/9276260>.
- [9] M.O. Roeslan, T.D.N. Ayudhya, B.-e. Yingyongnarongkul, S. Koonongkaew, Antibiofilm, nitric oxide inhibition and wound healing potential of purpurin-18 phytol ester isolated from *Clinacanthus nutans* leaves, *Biomed. Pharmacother.* 113 (2019) 108724, <https://doi.org/10.1016/j.biopha.2019.108724>.
- [10] B. Biglari, P.H.v.d. Linden, A. Simon, S. Aytac, H.J. Gerner, A. Moghaddam, Use of Medihoney as a non-surgical therapy for chronic pressure ulcers in patients with spinal cord injury, *Spinal Cord* 50 (2) (2012) 165–169, <https://doi.org/10.1038/sc.2011.87>.
- [11] J. Belcher, A review of medical-grade honey in wound care, *Br. J. Nurs.* 21 (15) (2012), <https://doi.org/10.12968/bjon.2012.21.Sup15.S4>. S4, S6, S8–9.
- [12] G. Dunwoody, C. Acton, The use of medical grade honey in clinical practice, *Br. J. Nurs.* 17 (20) (2008) S38–S44, <https://doi.org/10.12968/bjon.2008.17.Sup9.31665>.
- [13] S.M. Weheida, H.H. Naguib, H.M. El-Banna, S. Marzouk, Comparing the effects of two dressing techniques on healing of low grade pressure ulcers, *J. Med. Res. Inst.* 12 (2) (1991) 259–278.
- [14] U.Y. Günes, I. Eser, Effectiveness of a honey dressing for healing pressure ulcers, *J. Wound, Ostomy Cont. Nurs.* 34 (2) (2007) 184–190, <https://doi.org/10.1097/01.WON.0000264833.11108.35>.
- [15] A. Saha, S. Chattopadhyay, M. Azam, P.K. Sur, The role of honey in healing of bedsores in cancer patients, *S. Asian J. Canc.* 1 (2) (2012) 66–71, <https://doi.org/10.4103/2278-330X.103714>.
- [16] A.B. Jull, N. Cullum, J.C. Dumville, M.J. Westby, S. Deshpande, N. Walker, Honey as a topical treatment for wounds, *Cochrane Database Syst. Rev.* 3 (2015) Cd005083, <https://doi.org/10.1002/14651858.CD005083.pub2>.
- [17] T.V. Boyko, M.T. Longaker, G.P. Yang, Review of the current management of pressure ulcers, *Adv. Wound Care* 7 (2) (2018) 57–67, <https://doi.org/10.1089/wound.2016.0697>.
- [18] M. Jiang, C. Lu, C. Zhang, J. Yang, Y. Tan, A. Lu, K. Chan, Syndrome differentiation in modern research of traditional Chinese medicine, *J. Ethnopharmacol.* 140 (3) (2012) 634–642, <https://doi.org/10.1016/j.jep.2012.01.033>.
- [19] A. Wade, H. Pan, S. Eaton, A. Pierro, E. Ong, An investigation of minimisation criteria, *BMC Med. Res. Methodol.* 6 (2006), <https://doi.org/10.1186/1471-2288-6-11>, 11–11.
- [20] D.R. Thomas, *Prevention and treatment of pressure ulcers: what works? what doesn't?* *Cleve. Clin. J. Med.* 68 (8) (2001), 704–707, 710–14, 717–22.
- [21] S. Baranowski, E.A. Ayello, *Wound Care Essentials: Practice Principles*, Lippincott Williams & Wilkins, Philadelphia, 2012.
- [22] Department of Medical Sciences Ministry of Public Health, Part 1, Appendix 10.5 Limits for Microbial Contamination, *Thai Pharmacopoei II, vol. 1*, Office of National Buddhism Press, Bangkok, 2011, pp. 637–639.
- [23] N.A. Stotts, G.T. Rodeheaver, D.R. Thomas, R.A. Frantz, A.A. Bartolucci, C. Sussman, B.A. Ferrell, J. Cuddigan, J. Maklebust, An instrument to measure healing in pressure ulcers: development and validation of the pressure ulcer scale for healing (PUSH), *J. Gerontol. A Biol. Sci. Med. Sci.* 56 (12) (2001) M795–M799, <https://doi.org/10.1093/gerona/56.12.M795>.
- [24] M. Mullins, S.S. Thomason, M. Legro, Monitoring pressure ulcer healing in persons with disabilities, *Rehabil. Nurs.* 30 (3) (2005) 92–99, <https://doi.org/10.1002/j.2048-7940.2005.tb00369.x>.
- [25] M. Noordzij, G. Tripepi, F.W. Dekker, C. Zoccali, M.W. Tanck, K.J. Jager, Sample size calculations: basic principles and common pitfalls, *Nephrol. Dial. Transplant.* 25 (5) (2010) 1388–1393, <https://doi.org/10.1093/ndt/gfp732>.
- [26] A. Chuangsuwanich, P. Chortrakarnkij, J. Kangwanpoom, Cost-effectiveness analysis in comparing alginate silver dressing with silver zinc sulfadiazine cream in the treatment of pressure ulcers, *Arch. Plast. Surg.* 40 (5) (2013) 589–596, <https://doi.org/10.5999/aps.2013.40.5.589>.
- [27] J.P. Higgins, D.G. Altman, Assessing risk of bias in included studies, in: J. P. Higgins, S. Green (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*, Wiley Blackwell/Cochrane Collaboration, Chichester, West Sussex, 2008.
- [28] K.J. Preacher, An Interactive Calculation Tool for Chi-Square Tests of Goodness of Fit and Independence [Computer Software], 2001. <http://quantpsy.org>. (Accessed 13 July 2018).