Inhibitory effects of *Cheongsangbangpoong-tang* on both inflammatory acne lesion and facial heat in patients with acne vulgaris: A double-blinded randomized controlled trial

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ABSTRACT

Objectives: To investigate the inhibitory effects of an herbal formulation of *Cheongsangbangpoong-tang* (CBT) on inflammatory acne lesions as the control of the 'Heat' pattern.

Design: A single center study. Randomized, placebo-controlled, parallel group, double-blind trial

Setting: Fifty-six subjects, who had more than 10 acne inflammatory lesions each, were randomly allocated into the CBT or placebo groups and took 5 g CBT extract (CBT group) or 5 g placebo extract (control group), respectively, three times a day for 8 weeks. Pattern identification, change of the inflammatory and non-inflammatory acne lesions, temperature of the facial points, serum cortisol level, serum dehydroepiandrosterone-sulfate level, number rating scale, investigator global assessment (IGA), and severity score on the Korean acne grading system were measured.

Main outcome measure: mean change of the inflammatory acne lesions.

Results: After CBT/placebo administration, the percentage count of inflammatory lesions in subjects was significantly reduced in the CBT group when compared with the control group. The other outcomes showed no significant difference between the two groups. On pattern identification, subjects with the Wind-Heat pattern (風熱型, WHP) and Disharmony of the thoroughfare and conception vessels pattern (衝任不調型, DTCVP) tended show better effect than those with other patterns.

Conclusions: CBT is a potential therapeutic agent for the treatment of acne vulgaris, linked to inhibition of inflammatory lesions and facial heat.

Trial registration: CRiS (Clinical Research Information Service, Republic of Korea), KCT0001468. Registered 06 May 2015.

1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit arising from multiple physiologic changes in skin, including altered keratinocyte differentiation, increased sebum production, bacterial colonization by *Propionibacterium acnes*, and inflammation.[1] The main treatment is with oral antibiotics (e.g., tetracycline, doxycycline) and anti-acne agents (e.g., isotretinoin). However, with the concerns about the several side effects of conventional therapies,[2] complementary and alternative medicine (CAM) has been suggested as a different approach for management of acne vulgaris.

Cheongsangbangpoong-tang (CBT) is one of the various herbal therapeutic formulas approved by the Korean Food and Drug Administration for clinical use in patients with acne vulgaris; it is frequently used by Korean medicine (KM) clinicians. CBT cleans the upper energizer pathogenic heat (上焦熱), and is hence used to treat sores and furuncles of the head and face in *Wanbinhuichun* (萬病回春, *Recovery from All Ailments*).[3] Additionally, pattern identification is considered an important process in the overall analysis of clinical data, to determine the location, cause, and nature of a patient's disease in traditional Chinese medicine (TCM) and KM.[4] The therapeutic target of CBT is the control of the '*Heat*' pattern as described in *Wanbinhuichun*. Acne is considered to be closely related to the '*Heat*' pattern in TCM and KM.[5]

However, there is lack of adequate evidence to support the therapeutic use of CBT as described in *Wanbinhuichun;* no well-designed clinical trials have been conducted to verify the effectiveness of CBT in acne vulgaris of defined heat patterns.[6]

Therefore, we carried out a randomized clinical trial to investigate the inhibitory effects of an herbal formulation of CBT on inflammatory acne lesions and facial heat related to the '*Heat*' pattern measured with the Digital infrared thermal imaging (DITI) technique. We also carried out a sub-analysis of the participants with acne vulgaris based on the acne pattern identification with the Pattern diagnosis instrument.[7]

2. Materials and methods

2.1. Study design

This was a randomized, placebo-controlled, parallel group, double-blinded and single center study. The study was registered (identification number KCT0001468) at the Clinical Research Information Service, Republic of Korea. Detailed protocol has been reported in an earlier study.[8] Written informed consent was obtained from all participants.

2.2. Participants

Participants were recruited at the Korean Medicine Clinical Trial Center (KCTC), Kyung Hee University Korean Medicine Hospital. Participants were enrolled from November 2015 to March 2016. The study was approved by the ethics committee of the Kyung Hee University Korean Medicine Hospital (KOMCIRB-150213-HR-006). Male and female participants, 19 years and older were eligible for the study if they fulfilled the following criteria: (1) presence of acne vulgaris with more than 10 inflammatory lesions between the margin of the jaw and front of the hairline (2) agreed to the use of only the intervention in this study for acne vulgaris, during the trial period. The exclusion criteria were as follows: (1) aspartate transaminase (AST) level $\geq$ 60 IU/L, alanine transaminase (ALT) level $\geq$ 60 IU/L, and creatinine level > 1.2 mg/d (2) having undergone Western or traditional medical treatment, or having taken oral contraceptives/antibiotics for acne within the 2 weeks prior to recruitment (3) pregnancy, lactation, or preparation for pregnancy (4) unwillingness to comply with the study protocol. No concomitant acne therapy was permitted during the 8-week-trial period after enrollment.

Table 1
Components for *Cheongsangbangpoong-tang* (CBT) granules (5 g/dose).

Scientific name	Amount (g)
Schizonepeta tenuifolia	0.5
Coptis japonica (Thunb.) Makino	0.5
Mentha arvensis var. *piperascens*	0.5
Ponciri fructus immaturus	0.5
Glycyrrhiza uralensis Fisch	0.5
Gardenia augusta	1.0
Cnidium officinale	1.0
Scutellaria baicalensis	1.0
Forsythia koreana	1.0
Angelica dahurica	1.0
Platycodon grandiflorum	1.0
Ledebouriella seseloides	1.0
CBT dried extract (yield: 15.8%)	1.5
Corn starch	1.2
Lactose hydrate	2.3
Total	5.0

2.3. Intervention

The CBT group received CBT granules. They were manufactured by Han Kook Shin Yak Pharm. Co. Ltd. (Republic of Korea), which has obtained Korean good manufacturing practice (KGMP) authorization. CBT granules contained 12 herbs (Table 1). The yield of CBT dried extract was approximately 15.8% (w/w, dry weight 1.5 g). With the addition of starch and lactose, the final CBT granule of 5 g was obtained by drying under reduced pressure. For quality control and purity, some standards were applied according to Korean Ministry of Food and Drug Safety. Some index component was required for efficiency. (Glycyrrhizic acid ($C_{42}H_{62}O_{16}$) above 2.3 mg, baicalin ($C_{21}H_{18}O_{11}$) above 15.3 mg and berberine($C_{20}H_{18}ClNO_4$) above 2.8 mg) For purity test, total heavy metal below 30 ppm, lead below 5 ppm and arsentic below 3 ppm is regarded per pouch.

The control group received placebo granules (manufactured by the Jeonnam Biofood Technology Center, Republic of Korea, which has obtained Korean good manufacturing practice (KGMP) authorization.) following the placebo guidelines of the Korean Ministry of Food and Drug Safety for quality control. The placebo granule consisted of corn starch (2.5 g), lactose hydrate (2.5 g), hydroxypropyl methylcellulose for a bonding agent (< 0.01 g). To evaluate the similarity of the tasty, scent and shape between the placebo and CBT, we carried out the triangle test. As a result, six out of ten panels in the specialist group and nine out of ten panels in the general group, total 15 panels (75%), incorrectly identified the odd sample. Especially, most panels in the general group (90%) cannot distinguish the differences. As triangle test has a high sensitivity, it means panels cannot distinguish the difference of the tasty, scent and shape between the placebo and CBT.

All granule pouches were identically packaged and labelled in the Jeonnam Biofood Technology Center, each containing 5 g of either CBT or placebo. Forty-two pouches of either CBT or placebo were provided to each randomized participant at visit 1 (week 0 ± 3 days), visit 2 (week 2 ± 3 days), visit 3 (week 4 ± 3 days) and visit 4 (week 6 ± 3 days). Each participant took a pouch three times a day before meals for 8 weeks.

2.4. Measurements

Primary outcome measure studied for efficiency was change in the inflammatory lesion count from baseline to the end of the trial. Secondary outcome measures studied were changes in the non-inflammatory lesion counts, number rating scale (NRS), investigator global assessment (IGA) scores for facial acne vulgaris, severity score on the Korean acne grading system (KAGS), and clinical laboratory tests (serum cortisol and dehydroepiandrosterone-sulfate [DHEA-S] levels). We considered black and white head comedones as non-inflammatory
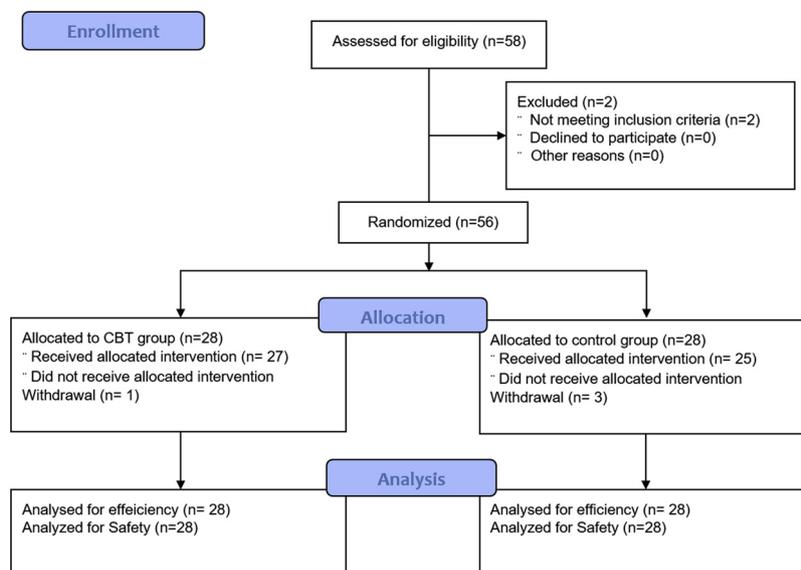
Fig. 1. Flow chart of the study.

lesions and the inflammatory papules, pustules and cysts as inflammatory lesions.

For sub-analysis, we used pattern diagnosis instrument and digital infrared thermal imaging (DITI). Pattern diagnosis instrument of acne is composed of eighteen items which reflect on nine subjective and nine objective characteristics related to acne symptoms.[5] We calculated the weights of each item by Delphi expert analysis.[7] This instrument is divided into four patterns: *Wind-Heat* pattern (WHP, 風熱型), *Dampness-Heat* pattern (DHP, 濕熱型), *Phlegm-Stasis* pattern (PSP, 痰瘀型) and *Disharmony of the Thoroughfare and Conception Vessels* pattern (DTCVP, 衝任不調型).[5,7] DITI is a non-contact infrared spectrum imaging technique to detect the infrared emissions from the objects. It generally evaluates the body temperature and is used for the assessing the depth of burn wounds, sports-related injuries, or as an adjunctive screening method for breast cancer.[9] For DITI, we photographed the front and both sides of the participant's face using a Lumix DMC-LX2 digital camera. We selected six points for detecting the skin temperature. These points were Ex-HN2, GV26, and right/left ST3 and ST7.

2.5. Sample size

To determine the sample size for this trial, we referred to a similar randomized controlled trial which was based on the effect size of the primary outcome, mean percent change of inflammatory acne lesion counts from baseline to week 8.[10] The calculated Cohen's effect size was 0.39 (α = 0.05, 1-β = 0.8, two-tailed test). Assuming a 20% dropout rate, and an allocation ratio of 1, we calculated the necessary sample size to be 56 participants (28 in each group).

2.6. Randomization & blinding

An independent statistician generated random numbers using the block-randomization method of a software program (version 3.2.0; The R Foundation for Statistical Computing). Using a block randomization, the 56 eligible participants were randomly allocated in a 1:1 ratio either to the CBT or control group in blocks of 4. A light-proof sealed envelope was used for allocation to conceal the randomization lists and was kept by the independent statistician.

Participants, investigators, and outcome assessors were blinded to the treatment allocation throughout the course of the study. The CBT and placebo granules were packaged and labelled identically. The blinding code was retained till the end of the study except in case of serious adverse events.

2.7. Adverse events and safety monitoring

The participants reported all unexpected adverse events related to CBT or the placebo to the investigator and investigator wrote on the individual case report form. Safety was assessed by the reporting of clinical laboratory tests and adverse events. Clinical laboratory tests, including AST / ALT and creatinine, were performed at screening and week 8 (the end of the trial). Each participant was monitored for adverse events (pain at acne lesions or other sites, nausea/vomiting, fatigue, allergic reaction, and any adverse events related to intervention) after each visit.

2.8. Statistical analysis

Statistical analysis was carried out on both intension-to-treat (ITT) and per-protocol (PP) bases using SPSS statistical analysis software version 20.0 (IBM Corporation, Armonk, NY, USA) with a 95% confidence interval. We analyzed the primary outcome and safety outcome using the intent-to-treat principle. Secondary outcomes were analyzed on both the ITT and PP populations. The "last observation carried forward principle" was used to compensate for missing data. The primary outcome, mean percentage change of the inflammatory lesion counts at baseline and at the end of the trial (at week 8) between the CBT treatment and placebo control groups, was evaluated using the independent *t*-test. Secondary outcomes, including the mean percentage change of the inflammatory or non-inflammatory lesion counts, the temperatures of the DITI points on the face, sebum level, serum cortisol, DHEA-S, NRS, IGA, and safety outcomes (AST, ALT and creatinine), were analyzed using the independent *t*-test, an analysis of covariance (ANCOVA) test, a Chi-square test or Fisher's exact test according to the statistical analysis plan mentioned in our study protocol.[8] In sub-analysis, lacking samples, non-parametric statistics (Mann-Whitney U test) were used.

3. Results

3.1. Demographic data

A total of 56 participants with acne were screened for eligibility. One participant (missing follow-up) in the CBT group and three participants (missing follow-up, symptom worsening, personal circumstances) in the control group were drop-outs (Fig. 1).

The baseline characteristics of the participants are shown in Table 2.

Table 2
Demographics and baseline characteristics.

	CBT group, n = 28	Control group, n = 28	p-value
Demographics			
Age, y, mean (SD)	22.64 (2.91)	24.57 (6.55)	0.160
Female, n (%)*	11 (39.2)	19 (67.9)	0.032
Body mass index, kg/m², mean (SD)	22.20 (2.60)	22.06 (2.37)	0.834
Clinical assessments			
Inflammatory lesion counts, mean (SD)*	31.57 (18.02)	23.64 (9.53)	0.046
Non-inflammatory lesion counts, mean (SD)	36.78 (24.99)	27.93 (18.40)	0.137
NRS, mean (SD)	6.54 (1.84)	6.11 (2.11)	0.421
IGA			
2, mild, n (%)	2 (7.1)	1 (3.6)	
3, moderate, n (%)	16 (57.1)	21 (75.0)	
4, severe, n (%)	10 (35.8)	6 (21.4)	0.366
KAGS			
1.2.	15 (53.6)	12 (42.9)	
3,4	11 (39.3)	15 (53.6)	
5,6	2 (7.1)	1 (3.6)	0.527
DITI (SD)	33.01 (0.94)	33.18(0058)	0.449
Cortisol, µg/dℓ, mean (SD)	13.77 (8.73)	12.42 (5.55)	0.494
DHEA-S, µg/dℓ, mean (SD)	240.03 (68.86)	259.98 (114.01)	0.432

There was no significant (P > 0.05) difference in age and body mass index. The placebo group had more female participants than the CBT group (p = 0.032). There were differences between the CBT and placebo groups in inflammatory lesion counts (CBT group vs. placebo group: 31.57 ± 18.02 vs. 23.64 ± 9.53, p = 0.046). Therefore, we only used percentage changes from baseline to compare the primary outcome.

Independent *t*-test for continuous variables (Age, Body mass index, Inflammatory lesion counts, Non-inlammatory lesion counts, NRS, DITI, Cortisol and DHEA-S) and chi-squared test for discrete variables (Female, IGA, KAGS) were performed. CBT group: Cheongsangbangpoong-tang group; NRS: Number Rating Scale; DITI; Digital infrared thermal imaging; KAGS: severity score on the Korean Acne Grading System; DHEA-S: dehydroepiandrosterone sulfate; IGA: investigator global assessment; p-value obtained by independent *t*-test or Chi-square test, *: p < 0.05.

3.2. Primary outcome

As there were significant difference between CBT group and control group in baseline inflammatory lesion count and gender, we conducted ANCOVA test with inflammatory lesion count and gender as covariates. There were significant differences between two groups in inflammatory lesion count. (CBT group vs. placebo group: 21.79 ± 13.67 vs. 23.18 ± 11.93, F = 11.453, p = 0.001). In reduction percentage, the CBT group showed increased reduction percentage from baseline (CBT

Table 3
Changes in secondary outcomes from baseline.

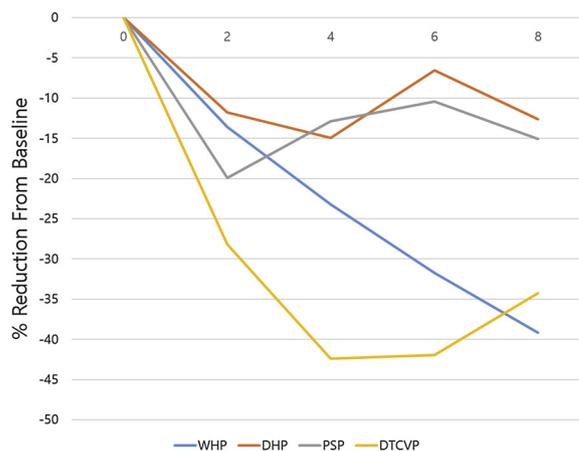|	CBT group, n = 28	Placebo group, n = 28	p-value
IGA improvement, n (%)	10 (35.7)	8 (28.6)	0.775
KAGS improvement, n (%)	19 (67.9)	17 (60.7)	0.781
NRS	−2.82 (1.52)	−2.32 (2.11)	0.313
Cortisol, µg/dl, mean (SD)	−1.56 (6.97)	0.75 (6.95)	0.219
DHEA-S, µg/dl, mean (SD)	27.61 (52.38)	1.65 (55.41)	0.077

Fig. 3. The percentage change of inflammatory lesions according to pattern identification. WHP: Wind-Heat pattern; DHP: Dampness-Heat pattern; PSP: Phlegm-Stasis pattern; DTCVP: Disharmony of the thoroughfare and conception vessels pattern.

group vs. placebo group: -29.54 ± 26.95 vs. -1.23 ± 37.14, p = 0.002, Cohen's *d* = 0.872). The difference between the two groups was also noted in the 2 and 4 weeks of assessment (Fig. 2).

3.3. Secondary outcome

In the CBT group, there was a diminution in the percentage of the non-inflammatory lesions. However, there were no significant differences between the two groups at each point (CBT group vs. placebo group: −19.67 ± 53.46 vs. −13.78 ± 62.85, p = 0.706) (Fig. 2). Ten (35.7%) and eight (28.57%) participants in the CBT and placebo groups showed improved IGA scores; however, there was no significant difference between these 2 groups (p = 0.775). There were also no significant differences in the changes noted in the KAGS, NRS, and clinical laboratory tests (Table 3).

CBT group: Cheongsangbangpoong-tang group; NRS: Number Rating Scale; KAGS: severity score on the Korean Acne Grading System; DHEA-S: dehydroepiandrosterone sulfate; IGA: investigator global assessment; p-value obtained by independent *t*-test or Chi-Square test,
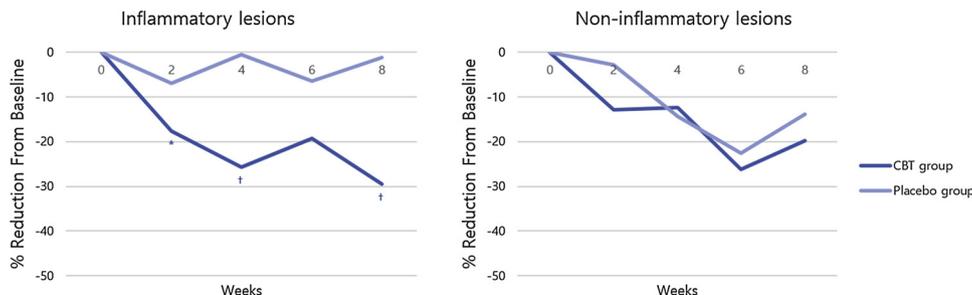

Fig. 2. The percentage changes of inflammatory and non-inflammatory lesions in the *Cheongsangbangpoong-tang* (CBT) and placebo groups. *p < 0.05, †p < 0.01 between the CBT and placebo groups.
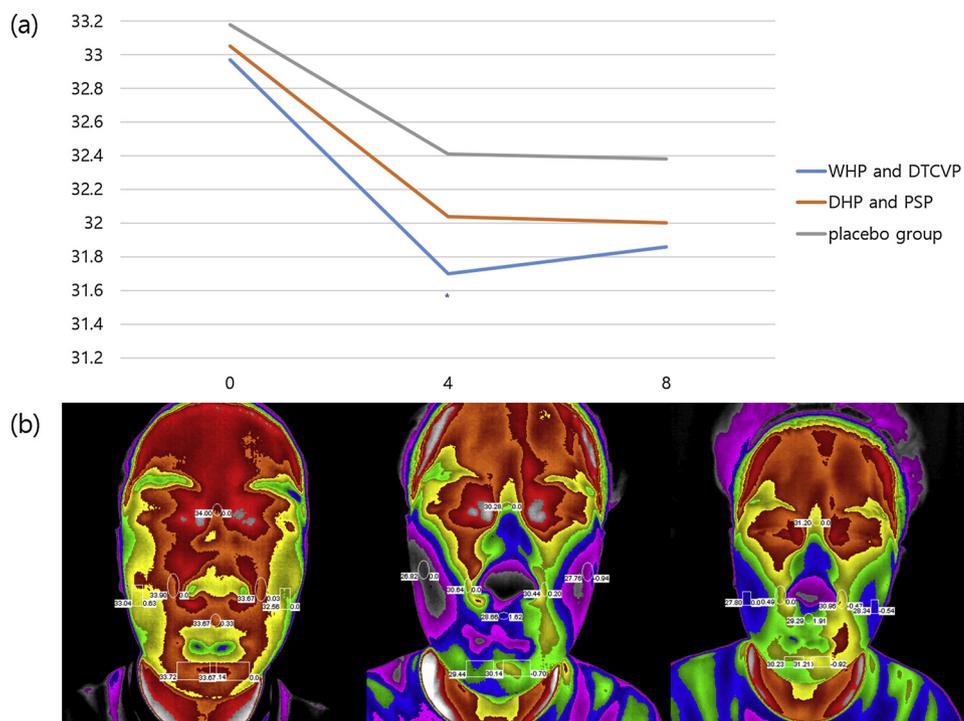
(a)

(b)

Fig. 4. Change in facial temperature by digital infrared thermal imaging (DITI) following CBT administration. (a) change in total facial temperature among the subgroups. (b) a case example of temperature change by DITI, from left: first visit, 4 weeks later, and 8 weeks later. *differences between WHP and DTCVP, and placebo group. p = 0.033, Mann-Whitney U test.

3.4. Sub-analysis

We divided the acne patterns into the following four types, based on an earlier study: WHP, DHP, PSP, and DTCVP. The group sizes in CBT group were 8, 4, 11 and 5, respectively. The sample size was too small for statistical data analysis, and they did not show differences in percent change of inflammatory lesion count (p = 0.875). However, the WHP and DTCVP groups tended to show a reduction in inflammatory lesion count (Fig. 3). Most of the subjects showing more than 40% reduction in the inflammatory lesion count belonged to the WHP or DTCVP groups (80%)

There were no differences in the facial temperatures between the CBT and control groups, as assessed by DITI. (CBT group vs. control group: 31.88 ± 1.19 vs. 32.41 ± 0.96 at 4 weeks, p = 0.072; 31.93 ± 1.08 vs. 32.38 ± 1.01 at 8 weeks, p = 0.116) However, when the CBT group was subdivided into WHP and DTCVP versus DHP and PSP groups, WHP and DTCVP groups showed a greater reduction in the facial temperature as compared to the control group at 4 weeks (WHP and DTCVP group vs. control group: 31.70 ± 0.80 vs. 32.41 ± 1.11, p = 0.026, Fig. 4(a)) However, there was no significant difference at 8 weeks. (WHP and DTCVP group vs. control group: 31.85 ± 1.11 vs. 32.38 ± 1.01, p = 0.144, Fig. 4(a)). The facial heat at baseline in the WHP and DTCVP recovered significantly to normal state after CBT administration, when compared with other acne patterns. (We presented a case example in Fig. 4(b).)

3.5. Safety

Three participants complained of digestion discomfort during treatment. At the endpoint, abnormalities were reported in the AST/ALT levels of 2 participants (one in the CBT group [AST/ALT; 64/46], one in the placebo group [AST/ALT: 45/48]); no abnormality was reported in the creatinine value. There were no severe adverse events.

4. Discussion

In TCM and KM, '*Heat*'(熱) is a pathogenic factor that causes '*Heat*' pattern (熱證).[11] This pathogenic heat results in a hyper-response such

as fever and an increased metabolic rate. The '*Heat*' pattern involves not only local inflammation but also the general body functions of the patient, in an attempt to correct maladjustments.[12] TCM includes herbal formulations that focus on the '*Heat*' pattern as a therapeutic target for treating inflammatory skin disease such as acne vulgaris. Therefore, we selected the therapeutic herbal formulation CBT, which cools off the '*Heat*' by stabilizing the elevated "upper energizer pathogenic heat (上焦熱)", for treating acne vulgaris.

Our findings indicate that CBT reduced the mean percentage of inflammatory lesions at 8 weeks. However, there were no significant (P > 0.05) differences in other outcome measures (non-inflammatory lesions, IGA score, NRS, and KAGS). Based on these results, we can hypothesize that clearing the pathogenic heat in upper energizer in TCM and KM may have an anti-inflammatory effect.[6] Most of the herbs in CBT are classified under Exterior-Releasing Medicinal (解表藥) and Heat-Clearing Medicinal (淸熱藥).[13] The herbs in these groups tend to have anti-inflammatory effects. In fact, some individual herbs showed anti-inflammatory effects in dermatitis.[14–17] In a *vitro* study, CBT showed anti-inflammatory effect through modulation of NF-κB activation and mitogen-activated protein kinase(MAPK) phosphorylation.[18] On the other hand, CBT had no effect on the cortisol and DHEA-S levels.

We evaluated pattern identification before trials to verify the pattern in which CBT is more appropriate. As a result, WHP showed the best effect among them. DTCVP also showed valid effect. However, the sample size was too small to evaluate the difference among the patterns. We can only show the tendency of the effect.

A few earlier studies have used DITI for detecting skin inflammation.[9,19,20] We assessed the effectiveness of DITI in diagnosing acne as it is related to inflammation. There were no differences significant (P > 0.05) between the CBT group and placebo group in our study. However, there were a few interesting findings. The facial heat at baseline in the WHP and DTCVP recovered significantly to normal state after CBT administration, when compared with other acne patterns. These findings suggest that CBT is more effective in some acne patterns and that the effectiveness of CBT is related to its action in stabilizing the upper heat.

There are some limitations in this study. First, in sub-analysis, we

found that pattern identification may be useful to improve the effect, but we evaluated the effect only with non-parametric statistical tests. Based on our pilot trial findings, further studies utilizing pattern identification are needed. Second, we faced unintended bias in random assignment with sex and primary outcome baseline levels. Hence, the results should be interpreted with caution. In primary outcome, we used ANCOVA and additionally percent change of inflammatory lesions to assess the difference. However, we did not correct for sex difference. As androgen affects the sebum secretion, sex difference may be an important factor in acne vulgaris.[21],[22] The main action of CBT is anti-inflammatory; however, there are no significant differences in cortisol and DHEA-S levels, and non-inflammatory lesion counts. These results suggest that CBT may not play a role in hormone changes, and hence the influence of sex difference may not be significant. Also, we did not consider the impact of dairy intakes and psychological factors such as stress, anxiety and sleep quality on our findings.[23],[24]

Despite these limitations, to our knowledge, this study was the first to investigate the effectiveness and safety of CBT and to conduct a sub-analysis using pattern identification, to focus on the therapeutic goals of CBT in TCM and KM.

5. Conclusion

Our findings demonstrate that CBT is more effective in relieving inflammatory than non-inflammatory lesions. Further, DITI may be a meaningful tool in determining the treatment course in TCM and KM clinical practice.

Author disclosure

All the listed authors have read and approved the submitted manuscript. All authors confirm that the data presented and their interpretation are reliable and free from bias. This study is not under consideration for publication elsewhere.

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Conflict of interest

The authors have no conflicts of interest to declare.

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