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A Study on the Mechanisms of Action of Jumihaidokuto for Patients with Acne: The Relationship between the Antioxidative Effect of Jumihaidokuto and Acne Improvement

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Abstract

Background: Drugs with various mechanisms of action such as antimicrobial agents, adapalene, and benzoyl peroxide are used to treat acne worldwide. In Japan, Kampo medicines have also traditionally been used for acne, including the medicine Jumihaidokuto (JHT). The mechanisms of action of Kampo medicines such as JHT have not been fully clarified, but it has been pointed out that oxidative stress is involved in the development of acne. Therefore, the author focused on the antioxidative effect of JHT and examined its relationship with acne improvement.

Methods: JHT (9 g/day) was administered for 3 weeks to 53 patients with acne, followed by measuring the diacron-reactive oxygen metabolites (d-ROMs) value as an indicator of oxidative stress, the biological antioxidant potential (BAP) value as an indicator of antioxidative potency, and the numbers of inflammatory and non-inflammatory skin rashes occurring before and after JHT administration. After the administration of JHT, the following results were observed.

Results: 1) The d-ROMs values of subjects who had a high baseline d-ROMs value were significantly reduced and the BAP values of those who had a low baseline BAP value were significantly increased; 2) there were significant reductions in the numbers of inflammatory and non-inflammatory skin rashes; 3) there was a significant correlation between the d-ROMs value and the number of non-inflammatory skin rashes; 4) the d-ROMs values of patients who rated their acne as "improved" by questionnaire were significantly reduced.

Conclusion: The above results suggest that an antioxidative effect is one of the mechanisms by which JHT contributes to acne improvement.

Keywords: Jumihaidokuto (Shi-Wei-Bai-Du-Tang); Kampo medicine; Acne vulgaris; d-ROMs; BAP; Oxidative stress

Introduction

Kampo medicine is a traditional Japanese medicine made by combining several kinds of medicinal herbs. It has spread widely as a treatment used in modern medical care in Japan and there are many Kampo medicines that are used for treating acne. On the other hand, drugs with various mechanisms of action such as antimicrobial agents, adapalene, and benzoyl peroxide have been developed as modern acne treatments and are being used around the world. However, the authors have come across patients whose acne was not improved by administration of such drugs. In our hospital, good results have been obtained by the oral intake of Jumihaidokuto (JHT) Kampo medicine in such cases [1]. Topically applied drugs are used as the basic treatments for acne, but it is considered that the oral administration of JHT has a systemic acne-improving effect that differs from the localized effects of topically applied drugs.

JHT is composed of 10 kinds of herbal medicines and can be widely applied to skin diseases such as acne, urticaria, and atopic dermatitis for its anti-inflammatory, antibacterial, pus discharging, and antipruritic actions. Previous research found that cherry bark, one of the constituent herbal medicines of JHT, had an estrogen production inducing effect, and suggested that estrogen healed acne by antagonizing testosterone, which is an exacerbator of sebum secretion [2]. The author uses JHT mainly to female acne patients, so that estrogen receptor expresses higher in female, and JHT is said to improve acne in female more effectively [3]. However, JHT is considered to have other mechanisms of action in addition to its estrogen production inducing effect, since it was observed to be equally effective in women of different ages and in menstruating and non-menstruating women in a previous survey conducted by the author [1]. Among these potential mechanisms of action, the authors focused on the antioxidative effect reported for antibacterial drugs such as minocycline [3] that are also taken orally as medicines for acne.

The involvement of oxidative stress in the development of acne has been pointed out before. Some reports have shown that xanthine oxidase, which mediates the generation of reactive oxygen species, and malondialdehyde, a marker of lipid peroxidation, were present at higher concentrations in the blood circulation of acne patients compared with healthy individuals [4,5]. In addition, the abundance of superoxide dismutase, an endogenous antioxidant enzyme, was found to vary depending on the severity of acne [6]. These reports suggested that oxidative stress is a causative factor in the development and/or exacerbation of acne.

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Therefore, the authors focused on the involvement of oxidative stress in acne to reveal a new mechanism of action for JHT as a treatment for acne and studied the relationship between acne improvement and the antioxidative effect of JHT [7].

Methods

Participants

Fifty-three adult females aged 20-47 years (mean age 33 ± 8 years) with a diagnosed of acne vulgaris, participated in this study. The study was set at Nomoto Mayumi Skincare Clinic (Niigata-ken, Japan) between January 2014 and January 2015. The severity grade of acne by counting the inflammatory rashes [8] before the study was as follows: mild, 45 patients; moderate, 8 patients. Although these patients had only few rashes, they had strong inflammation and tend to recur. So, they are considered as a recalcitrant acne vulgaris patients who did not improve by standard acne treatments in other hospitals before.

The study was approved by the Ethics Committee of the Niigata University of Pharmacy and Applied Life Sciences (reference: H25-008). Data were collected from patients whose written consent was obtained after a complete explanation of the study procedures was provided to them.

Intervention

A fine granular JHT extract obtained from Kracie Pharmaceutical, Ltd. was used as the study drug. The dose of 9 g/day, which corresponds to 1.5 times the normal dose, was divided into 3 administrations per day and was orally administered before or between meals for 3 weeks. The use of drugs other than JHT was prohibited for patients during the study. The author set the dose and duration with reference to the report of Takemura [9] which found that the dose of 9 g/day produced an improvement in the acne of patients with recalcitrant acne vulgaris for which the normal dose of JHT (6 g/day) was not sufficiently effective. In addition, a previous report by Nomoto [1] showed that administering 1.5 times the normal dose of JHT for 3 weeks resulted in an improvement in the acne of 79.5% (97/122) of cases with recalcitrant acne vulgaris.

Six grams of fine granular JHT extract contains 3.9 g of powdered extract obtained by hot water extraction after mixing the following 10 types of herbal medicines together: *Bupleurum* root (2.5 g), *Platycodon* root (2.5 g), *Cnidium* rhizome (2.5 g), *Poria* sclerotium (2.5 g), *Saposhnikovia* root (2.5 g), *Glycyrrhiza* root (1.5 g), Ginger (1.0 g), *Schizonepeta* spike (1.5 g), *Aralia* rhizome (1.5 g), and Pruni cortex (cherry bark) (2.5 g). The three-dimensional (3D) high performance liquid chromatography (HPLC) analysis of JHT is shown in Figure 1.

Outcomes measures

The primary outcome for this study was to evaluate the effect of JHT on oxidative stress and antioxidative potency in acne patients. For secondary outcome, improvements of inflammatory and non-inflammatory rashes were evaluated.

Blood was collected at the start and end of the study, and then the diacron-reactive oxygen metabolites (d-ROMs) value of each sample

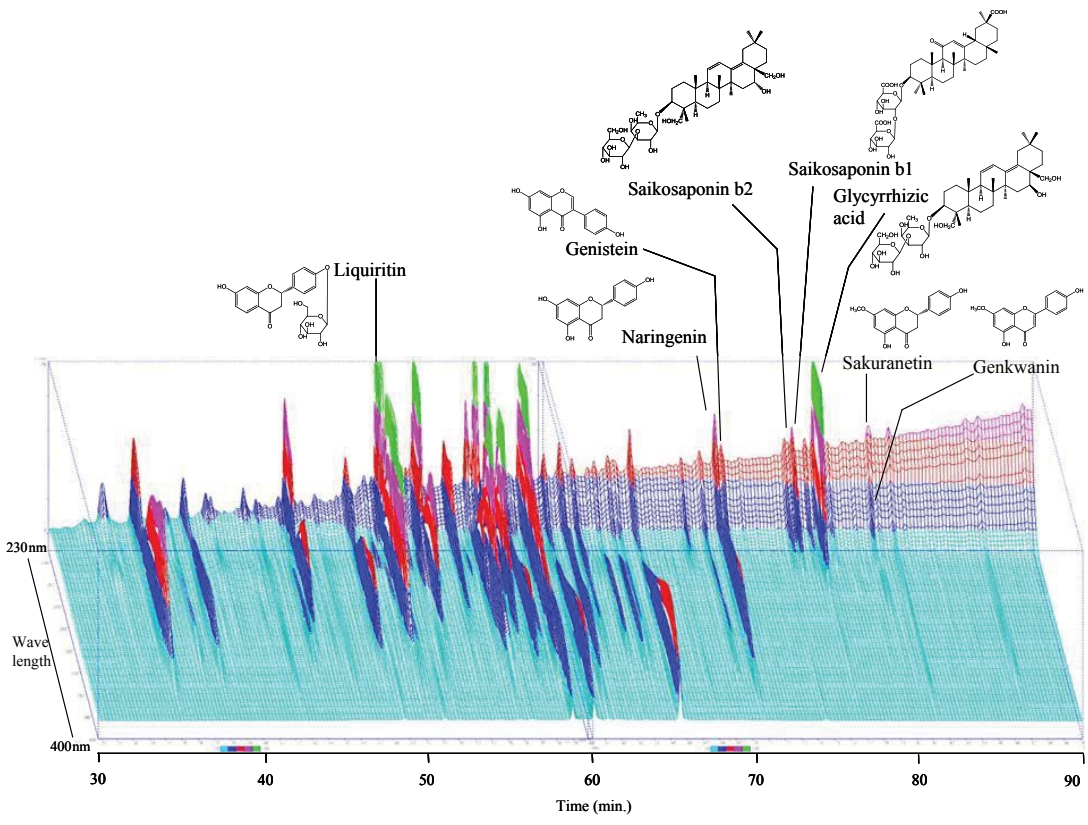

Figure 1: Typical 3D-HPLC chromatogram of JHT.

was measured as an indicator of oxidative stress and the biological antioxidant potential (BAP) value was measured as an indicator of antioxidative potency. The d-ROMs test measures the amount of hydroperoxide (R-OOH), which is a metabolite produced by active oxygen species and free radicals, in the sample via the colorimetric change of a chromogen. The d-ROMs value is represented by an arbitrary unit, U.CARR. The BAP test measures the ability of a sample to reduce trivalent iron ions (Fe^{3+}) to divalent iron ions (Fe^{2+}) and is represented by the unit μM. The degrees of oxidative stress corresponding to each range of d-ROMs values are as follows: normal, 200-300 U.CARR; borderline, 301-320 U.CARR; mild, 321-340 U.CARR; moderate, 341-400 U.CARR; high, 401-500 U.CARR; severe, ≥ 501 U.CARR [10]. The degrees of antioxidative potency corresponding to each range of BAP values are as follows: normal, ≥ 2200 μM; borderline, 2200 μM to 2000 μM; slightly low, 2000 μM to 1800 μM; low, 1800 μM to 1600 μM; very low, 1600 μM to 1400 μM; extremely low, ≤ 1400 μM [11]. Patients were classified into subgroups according to their d-ROMs and BAP values as follows. Based on their d-ROMs value at the start of the study, patients were divided into a d-ROMs normal group (≤ 320 U.CARR) and a d-ROMs high group (>320 U.CARR). Based on their BAP value at the start of the study, patients were also divided into a BAP normal group (>2000 μM) and a BAP low group (≤ 2000 μM).

Moreover, the numbers of inflammatory and non-inflammatory rashes at the start and end of the study were measured as an indicator of acne improvement. The changes in each measured value between the start and end of the study were indicated as "Δd-ROMs" for the change in d-ROMs value, "ΔBAP" for the change in BAP value, "Δnumber of inflammatory skin rashes" for the change in the number of inflammatory skin rashes, and "Δnumber of non-inflammatory skin rashes" for the change in the number of non-inflammatory skin rashes. Correlation analyses of Δd-ROMs and ΔBAP with Δnumber of inflammatory skin rashes and Δnumber of non-inflammatory skin rashes were performed to examine the relationships of the degree of oxidative stress and the degree of antioxidative potency with the improvement of acne rashes.

Furthermore, the patients were asked to grade their feelings about the changes in their acne symptoms by selecting from the choices of "improved", "no change", and "worsened" at the end of the study, compared with their feelings at the start of the study.

Statistical analysis

Analysis was conducted based on non-parametric tests, since the data could not be confirmed to be normally distributed. All the results are represented by the median ± interquartile range. Utilizing Statcel 3 software (OMS Inc., Saitama, Japan) for statistical analysis, Wilcoxon's signed rank test was used for the evaluation of the d-ROMs values, BAP values, and the number of rashes before and after the administration of JHT, and Spearman's rank correlation test was used for correlation analyses. A probability value of less than 5% was considered significant.

Results

Patient characteristics

The patient characteristics are shown in Table 1.

Effect of JHT administration on the d-ROMs and BAP values

d-ROMs value: In the analysis of all 53 cases, a significant reduction in the mean d-ROMs value was observed, with a change from 324 U.CARR at the start of the study to 313 U.CARR at the end of the study ($p<0.05$). The d-ROMs normal group showed no significant difference in the mean d-ROMs value between the start and end of the study, but the d-ROMs high group showed a significant reduction in the mean d-ROMs value at the end of the study compared with the value at the start of the study ($p<0.05$; Figure 2).

Sex	**No. of cases**	**%**	**Concomitant drugs**	**No. of cases**	**%**
Male	0	0	Nil	53	100
Female	53	100	**Treatment history**	**No. of cases**	**%**
Age	**No. of cases**	**%**	Present	11	20.8
20-29	24	45.3	Nil	42	79.2
30-39	14	26.4	Tretinoin gel 0.05%	3	5.7
40-49	15	28.3	Adapalene gel 0.1%	17	32.1
The main development site of acne	**No. of cases**	**%**	Clindamycin phosphate lotion 1%	12	22.6
Entire face	7	13.2	Nadifloxacin cream 1%	3	5.7
Face line*	27	50.9	Clobetasone butyrate ointment 0.05%	1	1.9
Lower jaw	16	30.2	Sulfur and camphor lotion	1	1.9
Perioral	7	13.2	Minocycline	25	47.2
Buccal region	9	17	Clarithromycin	4	7.5
Forehead	5	9.4	Tosufloxacin	2	3.8
Nasal region	2	3.8	Doxycycline	1	1.9
Temple	1	1.9	Levofloxacin	1	1.9
Scalp	1	1.9	Roxithromycin	1	1.9
Chest	2	3.8	Vitamin C, calcium pantothenate formulation	3	5.7
Back	4	7.5	Tranexamic acid	1	1.9
*From the lower jaw to the neck			Low dose pill	1	1.9
			Tokishakuyakusan#	2	3.8
The presence or absence of premenstrual worsening	**No. of cases**	**%**	Keishibukuryogan#	1	1.9
Present	26	49.1	Keishibukuryogankayokuinin#	1	1.9
Nil	12	22.6	Jumihaidokuto#	1	1.9
Unknown	15	28.3	Seijobofuto#	1	1.9
			#These are Kampo medicines		

Table 1: Patient characteristics.

BAP value: In the analysis of all 53 cases, no significant difference in the mean BAP value was observed, with a change from 2117 μM at the start of the study to 2144 μM at the end of the study (p=0.6). The BAP normal group showed no significant difference in the mean BAP value between the start and end of the study, but the BAP low group showed a significant increase in the mean BAP value at the end of the study compared with that at the start of the study (p<0.05; Figure 3).

Effect of JHT administration on the numbers of skin rashes

A significant decrease was observed in the numbers of inflammatory and non-inflammatory skin rashes at the end of the study, compared with the corresponding numbers at the start of the study (p<0.01 and p<0.05, respectively; Figure 4).

Correlation analyses of the d-ROMs and BAP values with the numbers of skin rashes

A significant correlation was observed between Δd-ROMs and Δnumber of non-inflammatory skin rashes (rs=0.61, p<0.01; Table 2).

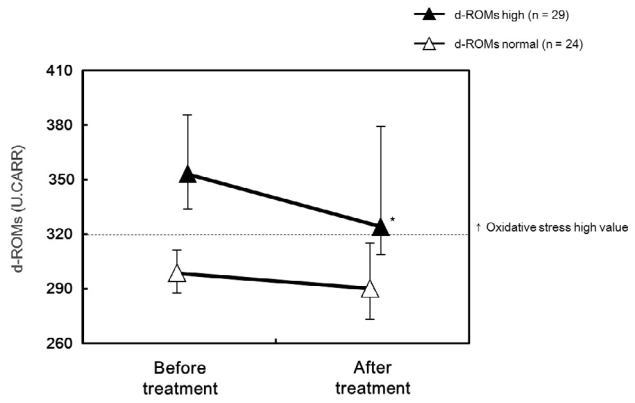

Figure 2: Effect of JHT administration on d-ROMs (oxidative stress). The cases were divided into 2 groups (d-ROMs high and d-ROMs normal) and were evaluated for change in the d-ROMs values before and after the administration of JHT. Results are presented as median ± interquartile range. Statistical analysis was performed using Wilcoxon's signed rank test (*p<0.05, *vs* before treatment).

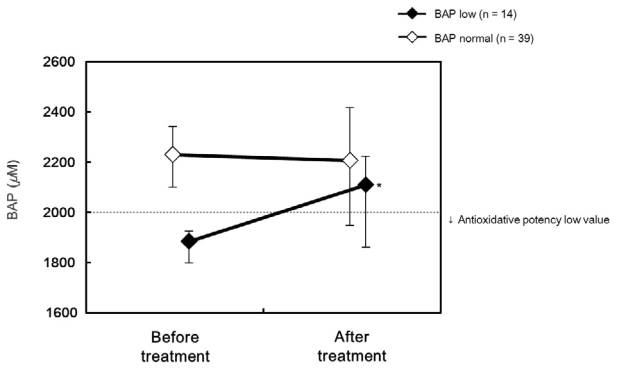

Figure 3: Effect of JHT administration on BAP (anti-oxidative potency). The cases were divided into 2 groups (BAP low and BAP normal) and were evaluated for change in the BAP values before and after the administration of JHT. Results are presented as median ± interquartile range. Statistical analysis was performed using Wilcoxon's signed rank test (*p<0.05, *vs* before treatment).

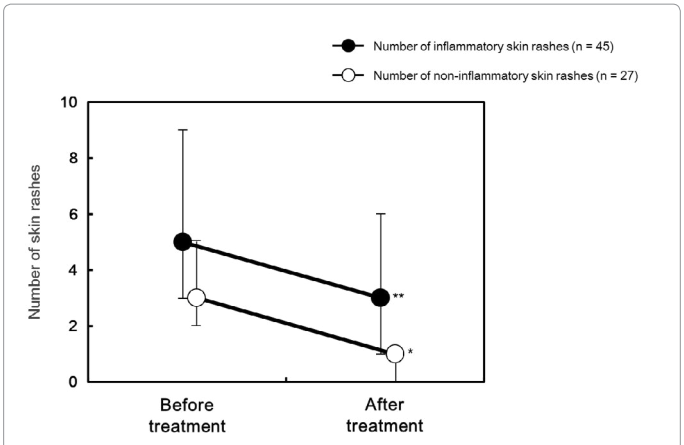

Figure 4: Effect of JHT administration on the numbers of skin rashes. The change of the number of inflammatory skin rashes and non-inflammatory rashes before and after the administration of JHT was evaluated. Results are presented as median ± interquartile range. Statistical analysis was performed using Wilcoxon's signed rank test (*p<0.05, **p<0.01, vs before treatment).

Relationship between the subjective degree of improvement of acne and the d-ROMs value after the administration of JHT

Among all, 48 patients were able to evaluate their grade of feelings. The group of subjects who rated their acne as "improved" at the end of the study showed a significant decrease in the mean d-ROMs value at the end of the study, compared with that at the start of the study (p<0.01; Figure 5).

Discussion

The antibacterial effect of JHT against *Propionibacterium acnes* (*P. acnes*) has been reported before [12], and it has been mainly used to treat acne due to its antibacterial property. Moreover, it has been reported that cherry bark, an herbal medicine that has recently begun to commonly be blended into JHT, has the ability to bind estrogen receptor β and can also enhance estradiol production by dermal fibroblasts [3,13]. That is, JHT blended with cherry bark locally enhances estrogen secretion in skin and acts antagonistically with respect to testosterone. There is a study that JHT and cherry bark suppressed the promotion of sebum secretion induced by testosterone *in vitro* [14]. Furthermore, clinical data was reported for 44 female patients with acne. In those cases, improvements in the symptoms of red papules, white papules, and pustules were observed after a 12-week combined treatment with JHT extract and a topical antimicrobial drug, resulting in a 77.3% cumulative improvement rate [3].

An effect that differs from those of the topical treatment drugs primarily used for acne treatment can be expected from JHT, since it is considered to be effective for acne due to its antibacterial effect and its systemic estrogen production inducing effect. One of the effects considered is a beneficial change in the constitution of subjects who are vulnerable to acne development [1]. The estrogen induction promoting effect of JHT might contribute to the inhibition of sebum secretion at the early stage of acne development, but JHT is considered to have other effects in addition to inducing estrogen production, since its effectiveness was observed regardless of the age and menstruation status of female subjects in a previous survey conducted by the authors [1].

Acne has a significant emotional impact in addition to its physical symptoms, since it tends to develop on the faces of the younger

Spearman's rank correlation test	Δd-ROMs	ΔBAP
ΔNumber of inflammatory skin rashes	0.07	0.04
ΔNumber of non-inflammatory skin rashes	0.61**	-0.24

Table 2: Correlation analyses of the d-ROMs and BAP values with the numbers of skin rashes. Correlation analyses of the changes in the d-ROMs and BAP values (Δd-ROMs and ΔBAP) and the changes in the numbers of inflammatory and non-inflammatory skin rashes (Δnumber of inflammatory skin rashes and Δnumber of non-inflammatory skin rashes) before and after administration of JHT. Statistical analysis was performed using Spearman's rank correlation test (**p<0.01, rs).

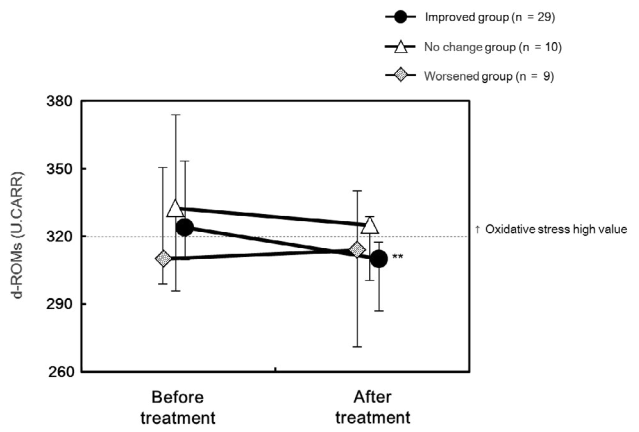

Figure 5: Relationship between the degree of subjective improvement of acne and the d-ROMs value after the administration of JHT. The patients were divided into 3 groups ("improved", "no change", and "worsened") based on their subjective ratings of the degree of improvement in their symptoms of acne, and the changes in their d-ROMs values before and after JHT administration were evaluated. Results are presented as median ± interquartile range. Statistical analysis was performed using Wilcoxon's signed rank test (**p<0.01, vs before treatment).

generation, who are concerned about their appearance [15]. It is considered that oxidative stress is closely related to acne since prolonged acne leads to psychological stress, which promotes the generation of active oxygen species [16] and reduces the activity of antioxidants [17].

The experience of the authors that JHT was effective for the treatment of acne in cases where the involvement of psychological stress was suggested indicates that JHT might correct the heightened oxidative stress typical of acne and contribute to acne improvement partly via a systemic antioxidative effect. Focusing on oxidative stress, this study produced the following results: the d-ROMs high group showed a significant reduction in the mean d-ROMs value after the administration of JHT, while the BAP low group showed a significant increase in the mean BAP value. Kampo medicines have traditionally been used to correct disturbances in immune function [18], the autonomic nervous system [19], and the endocrine balance of living organisms [20], and the present results suggest that JHT, via its antioxidative effect, can correct the heightened oxidative stress that typically occurs in patients with acne. JHT has previously been found to have an antioxidative effect by in vitro and in vivo studies [21,22]. According to the *in vivo* study, numerous polyphenols of JHT, such as genistein and liquiritigenin are prone to inhibit dermatitis via antioxidative effect [22]. However, the present study is the first to have revealed that JHT administration has an impact solely on patient groups in which abnormalities of oxidative stress level and antioxidative potency were observed in the blood circulation at baseline. On the other hand, no significant changes were observed in the d-ROMs normal and BAP normal groups between before and after JHT administration. However, acne vulgaris is a chronic inflammatory disease, and the degree of oxidative stress that people experience is expected to be constantly changing in modern society. Even if the degree of oxidative stress of a patient is normal when it is measured, continuous administration of JHT might help to control the fluctuations of oxidative stress that occur as a result of environmental stresses.

Another novel finding in this study was the observation of a significant correlation between the change in the d-ROMs value and the number of non-inflammatory skin rashes between before and after the administration of JHT. There have been some reports confirming a relationship between oxidative stress and inflammatory skin rashes [4,23], but the level of knowledge about the relationship between oxidative stress and non-inflammatory skin rashes is sparse. The accumulation of sebum in hair follicles that is observed with non-inflammatory skin rashes (pimples) involves several processes such as 1) enhancement of sebum secretion by testosterone, 2) reduction in the concentration of linolenic acid in sebum, 3) production of lipid peroxides by oxidation of sebum components such as squalene, 4) production of inflammatory cytokines such as interleukin (IL)-1α by lipid peroxides, and 5) dyskeratosis of the hair follicle funnel due to the effects of inflammatory cytokines [24,25]. In this series of processes, increased oxidative stress is suggested to be related to the oxidation of sebum components. For example, a previous report stated that squalene, a component of sebum, is susceptible to oxidation by oxygen and ultraviolet rays, and that squalene peroxide promotes pimple formation [26]. It has been also reported that squalene enhances the keratinization of the skin [27]. These reports suggest that squalene present in sebum and its peroxide are involved in the development of acne. Therefore, it can be inferred that JHT may improve pimples by inhibiting the oxidation of sebum via its antioxidative effect.

In the present study, the authors focused on the antioxidative effect of JHT, but antioxidative effects have also been reported for other acne treatment drugs. For example, vitamin C preparations for external and internal use and oral antibiotics such as minocycline have been revealed to have antioxidative effects [4]. Additional research is required in the future to identify the differences in the antioxidative effect of these drugs and JHT, but it can be inferred that JHT, a medicinal preparation consisting of multiple herbal components, has a unique mechanism of action, such as an ability to act against abnormally high levels of oxidative stress and to improve non-inflammatory skin rashes. Moreover, minocycline is mainly used for inflammatory skin rashes, and its administration at the pimple stage, which is the initial condition of acne, is not recommended since it can induce bacterial antimicrobial resistance of bacteria [28]. In contrast, JHT does not have any comparable problem of inducing bacterial resistance [12], and it has the advantage that its oral intake can be continued for a long time. Also, based on the findings of the present study, which revealed that a reduction of oxidative stress helps to reduce the number of pimples, JHT might contribute to a change in the constitution of treated patients towards greater resistance to acne by maintaining a normal level of oxidative stress through its continuous oral intake.

On the other hand, the present study showed a significant decrease in the number of inflammatory skin rashes following the administration of JHT, but no correlation with the decrease in oxidative stress was observed. The reasons for this are considered to be as follows. The direct cause for the development of inflammatory skin rashes is the stimulation of skin by active oxygen species and inflammatory cytokines derived from neutrophils that have migrated

and been activated by *P. acnes* [4]. Therefore, the administration of an antioxidant for removing the active oxygen species is considered to be effective in improving inflammatory skin rashes. In fact, it has been reported that skin rashes were reduced when metronidazole, which has an antioxidative effect but no antibacterial effect, was administered to patients with inflammatory acne [29]. In contrast, the reason why there was no correlation between the reduction of oxidative stress in the blood due to JHT and the improvement of skin rashes is considered to be that processes such as the increased amounts of sebum secretion, lipid peroxidation, dyskeratosis, *P. acnes*, and free fatty acid occur before activated oxygen species are released from the neutrophils. JHT and its constituent herbal medicines have been reported to have various effects such as estrogen secretion enhancing effect, 5α-reductase inhibiting effect, antibacterial effect against *P. acnes*, lipase inhibiting effect, and toll-like receptor (TLR) 2 suppressing effect [12,13,30,31], in addition to the antioxidative effect revealed in this study. Therefore, it is presumed that not only its antioxidative effect, but also the various other effects of JHT comprehensively contribute to the improvement of inflammatory skin rashes.

In addition, in this study, a survey of the subjective degree of acne improvement was performed by interviewing the patients as well. The results showed a significant reduction in the mean d-ROMs value of the patient subgroup who felt that their acne was "improved" after JHT administration. This may be because a decrease in the level of oxidative stress in the blood was caused by a reduction in the patient's psychological stress, whereas there is also the possibility that the reduction in oxidative stress resulted in the improvement of acne.

The authors would like to further investigate the mechanisms of action of JHT in the future using a comprehensive digital skin image analysis system (VISIA Evolution, Canfield Scientific, Fairfield, NJ, USA).

Conclusions

The findings of this study indicate that the Kampo medicine Jumihaidokuto can be expected to improve acne via a systemic antioxidative effect that cannot be obtained using topical acne treatment drugs, and also to alter the constitution of patients to make them less vulnerable to the development of acne.

References

1. Nomoto M (2015) The Effect of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) Containing Cherry Bark (Pruni cortex) on Refractory Acne Vulgaris: Short-term, High-Dose Administration. Nishinihon J Dermatol 77: 259-263.
2. Tohno H, Horii C, Fuse T, Okonogi A, Yomoda S (2010) Evaluation of estrogen receptor Beta binding of pruni cortex and its constituents. Yakugaku Zasshi 130: 989-997.
3. Takemura T, Tohno H, Yomoda S, Okubo T (2014) Mechanism of Action of Cherry Bark-containing Jumihaidokuto (Shi-Wei-Bai-Du-Tang) and Its Clinical Benefit in Patients with Acne Vulgaris. Nishinihon J Dermatol 76: 140-146.
4. Akamatsu H, Horio T, Hattori K (2003) Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. Int J Dermatol 42: 366-369.
5. Sarici G, Cinar S, Armutcu F, Altinyazar C, Koca R, et al. (2010) Oxidative stress in acne vulgaris. J Eur Acad Dermatol Venereol 24: 763-767.
6. Perihan O, Ergul KB, Neslihan D, Filiz A (2012) The activity of adenosine deaminase and oxidative stress biomarkers in scraping samples of acne lesions. J Cosmet Dermatol 11: 323-328.
7. Abdel Fattah NS, Shaheen MA, Ebrahim AA, El Okda ES (2008) Tissue and blood superoxide dismutase activities and malondialdehyde levels in different severities of acne vulgaris. Br J Dermatol 159: 1086-1091.
8. Adityan B, Kumari R, Thappa DM (2009) Scoring systems in acne vulgaris. Indian J Dermatol Venereol Leprol 75: 323-326.
9. Takemura T (2011) The Effect of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) Containing Cherry Bark (Pruni cortex) on Female with Acne Vulgaris: High-Dose Administration study. Phil Kampo 34: 18-19.
10. Seki Y (2009) Evaluation of total oxidative stress by d-ROMs testing. J Anal Bio Sci 32: 301-306.
11. Tanaka I, Kitagawa M (2014) Changes in oxidative stress and antioxidative potency during pregnancy period. J Jpn Acad Midwif 28: 51-59.
12. Higaki S, Nakamura M, Morohashi M, Hasegawa Y, Yamagishi T (1996) Activity of Eleven Kampo Formulations and Eight Kampo Crude Drugs against Propionibacterium acnes Isolated from Acne Patients: Retrospective Evaluation in 1990 and 1995. J Dermatol 23: 871-875.
13. Tohno H, Yomoda S, Takemura T (2014) Significance of cherry bark-formulation in Jumihaidokuto (Shi-Wei-Bai-Du-Tang) for acne vulgaris treatment. BIO Clinica 3: 124-131.
14. Shinohara K, Fujita N (2016) The Effect of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) and Cherry Bark (Pruni cortex) on sebum synthesis. Jpn J Med Pharm Sci 73: 579-583.
15. Hayashi N, Higaki Y, Kawamoto K, Kamo T, Shimizu S, et al. (2004) A cross-sectional analysis of quality of life in Japanese acne patients using the Japanese version of Skindex-16. J Dermatol 31: 971-976.
16. Atanackovic D, Brunner-Weinzierl MC, Kröger H, Serke S, Deter HC (2002) Acute Psychological Stress Simultaneously Alters Hormone Levels, Recruitment of Lymphocyte Subsets, and Production of Reactive Oxygen Species. Immunol Invest 31: 73-91.
17. Tochio T, Morichi E, Hirose O, Nakata S, Kuze J (2008) Makeup Inhibits Reduction of Reactive Oxygen Scavenging Enzyme Activity Induced by Mental Stress. J Soc Cosmet Chem Jpn 42: 121-127.
18. Kobayashi H, Ishii M, Takeuchi S, Tanaka Y, Shintani T, et al. (2010) Efficacy and Safety of a Traditional Herbal Medicine, Hochu-ekki-to in the Long-term Management of Kikyo (Delicate Constitution) Patients with Atopic Dermatitis: A 6-month, Multicenter, Double-blind, Randomized, Placebo-controlled Study. eCAM 7: 367-373.
19. Okahara K, Ishida Y, Hayashi Y, Inoue T, Tsuruta K, et al. (2010) Effects of Yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 34: 532-536.
20. Okamoto M, Sakakibara H, Yoshida H, Fukazawa Y, Takashima K, et al. (2010) Effects of Saireito on the ovarian function of patients with polycystic ovary syndrome. Reprod Med Biol 9: 191-195.
21. Nakanishi T, Inoue K (2011) Antioxidant Potential of Jumihaidokuto. Kampo New Ther 20: 89-91.
22. Matsumoto T, Matsubara Y, Mizuhara Y, Sekiguchi K, Koseki J, et al. (2015) Plasma Pharmacokinetics of Polyphenols in a Traditional Japanese Medicine, Jumihaidokuto, Which Suppresses Propionibacterium acnes-Induced Dermatitis in Rats. Molecules 20: 18031-18046.
23. Arican O, Kurutas EB, Sasmaz S (2005) Oxidative stress in patients with acne vulgaris. Mediators Inflamm 2005: 380-384.
24. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, et al. (2009) New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 18: 821-832.
25. Kurokawa I (2014) The Role of Hyperkeratinization. Pathogenesis and Treatment of Acne and Rosacea 3: 71-76.
26. Saint-Leger D, Bague A, Lefebvre E, Cohen E, Chivot M (1986) A possible role for squalene in the pathogenesis of acne. II. In vivo study of squalene oxides in skin surface and intra-comedonal lipids of acne patients. Br J Dermatol 114: 543-552.
27. Motoyoshi K (1983) Enhanced comedo formation in rabbit ear skin by squalene and oleic acid peroxides. Br J Dermatol 109: 191-198.
28. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, et al. (2009) New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. J Am Acad Dermatol 60: S1-S50.
29. Oguchi M, Akamatsu H, Asada M, Kubo K, Namura S, et al. (1987) Treatment of acne with oral metronidazole. Skin Res 29: 995-1000.
30. Higaki S, Hasegawa Y, Toyomoto R, Miyazaki K, Masaaki M, et al. (1993) The Anti-lipase Activities of Jumi-Haidoku-To and Minocycline Against Propionibacterium acnes. Jpn J Dermatol 103: 33-37.
31. Kaneko A, Sekiguchi K, Osegi J, Nishimura H, Hattori T, et al. (2014) Multi Targeting Action of Jumihaidokuto (Shi-Wei-Bai-Du-Tang) against Acne Vulgaris. J New Rem Clin 63: 38-49.