

Original Article / 원저

# Efficacy of Herbal Medicines for the Treatment of Seborrheic Dermatitis : Systematic Review

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## 지루성 피부염의 한약 치료 효과에 대한 체계적 문헌고찰

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### Abstract

**목적** : 체계적 문헌고찰을 통하여 지루피부염에 한약복용의 효과와 연구의 질을 평가하기 위함.

**방법** : OASIS, NDSL, EMBASE, Pubmed, Cochrane Library, CINAHL, CNKI, WANFANG, CiNii, J-STAGE를 이용하여 검색하였다. 검색은 2018년 6월 21일에 시행되었으며 P는 지루성 피부염, I는 한약 복용으로 진행하였다. 두 명의 연구자가 독립적으로 연구를 평가하고 선정하였으며, 의견이 다를 경우 제 3자가 개입하여 다수결로 결정하였다.

**결과** : 중복 검색을 제외하고 총 952개의 연구가 검색되었으며 제목과 초록을 검토한 결과 897개의 연구가 제외되었다. 나머지 55개 연구의 전문을 검토한 결과 4개의 RCT연구가 최종 선정되었다. 선정된 연구는 발행연도, 대상, 중재법, 평가방법, 효과, 부작용, RoB를 통해 평가하였다. 한약 복용을 한 치료군에서 대조군에 비해 유의하게 호전을 보였으며 중대한 부작용은 없었다.

**결론** : 지루성 피부염에 있어 한약 복용은 효과적이며 안전성이 있는 하나의 치료법이다. 향후 다양하고 체계적인 RCT의 시행이 요구된다.

**Key words** : seborrheic dermatitis; herbal medicine; Korean medicine; intake; systematic review

## I .Introduction

Seborrheic dermatitis is an eczematous dermatitis that occurs in areas of sebaceous glands are prominent. It is characterized by the redness and scales on the skin. It affects areas of the scalp, eyebrows, sternum, axillae, breast, umbilicus, groin, and wrinkles of buttocks and has repeat episodes.

Incidence is 1-3% of the total population and 3-10% of the general adult population. Infants aged 3-4 months and men aged 40-70 are frequently affected, and is associated with oily skin. It is common in patients with neurological disorders, neuroleptic medication, endocrine disorders which cause obesity, alcoholics, and AIDS patients<sup>1)</sup>. Recently, patients are increasing regardless of gender and age, due to stress and the change of lifestyles such as having instant meal and meat<sup>2)</sup>.

The cause is unclear and there are various hypotheses such as sebaceous hypersecretion, malassezia yeast, abnormal metabolism of neurotransmitters(L-dopa), epidermal hyperplasia, AIDS, seasonal effects, food and drug disorders, and lifestyle, etc<sup>1)</sup>.

In general, the treatment of seborrheic dermatitis uses anti-inflammatory and antifungal agents as a topical treatment, and *fluconazoles* focusing on *Malassezia* yeasts are also used. If seborrheic dermatitis spreads to the entire body or does not respond to topical

treatment, oral therapy is used and there is an antifungal agent such as *ketoconazole*. However, due to side effects of medication and the chronicization of seborrheic dermatitis, alternative methods such as mud treatment are being sought due to the difficulties in using external or oral solutions<sup>7)</sup>.

Therefore, developing more effective and safe treatments than current methods for seborrheic dermatitis is needed. In the traditional Korean medicine literature, seborrheic dermatitis is referred to “baekseolpung(白屑風)”, “myeonyupung(面遊風)”, “yugupung(紐口風)”. Which occurs in the cephalic area is called “baekseolpung(白屑風)”, occurs in the face is “myeonyupung(面遊風)”, and that occurs in the chest is called “yugupung(紐口風)”<sup>3)</sup>.

As the prevalence of seborrheic dermatitis increase, research is actively underway in Korean medicine. Many studies using various herbal remedies for seborrheic dermatitis have been reported, including the treatment of pharmacopuncture and applying herbal medicine extract. However, the number of patients used in the study is small and most of the studies were case reports. Therefore, there is lack of enough organized evidence to confirm the validity of herbal medicine for seborrheic dermatitis. These clinical studies should be validated and justified in evidence-based medicine. As a part of the evidence-based medicine, systematic review of the effects of acupuncture and herbal medicine in various diseases is being conducted in Korean medicine<sup>20-23)</sup>.

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This study investigated the use of herbal medicine as an alternative treatment for seborrheic dermatitis by extensively reviewing related literatures. The purpose of this study is to evaluate the safety and efficacy of taking herbal medicine as seborrheic dermatitis treatment and to provide database for the further study including establishing clinical practise guidelines. Furthermore, this study is written in English in order to identify the global trends and provide reliable baseline data that so can be widely used in the field of alternative medicine worldwide in the future.

## II. Objectives and Methods

### 1. Objectives

From the start of search engine support to June 20, 2018, clinical research papers on herbal medicine intake to seborrheic dermatitis were reviewed.

### 2. Methods

The electronic databases that were surveyed for this review were:

Korean - OASIS (Oriental medicine Advanced Searching Integrated System, <http://oasis.kiom.re.kr>), NDSL (National Digital Science Links, <http://scholar.ndsl.kr>)

English - EMBASE (Excerpta Medica Database, <http://www.embase.com>), PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Cochrane library (<http://www.cochranelibrary.com>), CINAHL (Cumulative Index to Nursing and Allied Health Literature, [\[ebscohost.com/login.asp?profile=ehost&defaultdb=rzh\]\(http://ebscohost.com/login.asp?profile=ehost&defaultdb=rzh\)\)](http://search.</a></p></div><div data-bbox=)

Chinese - CNKI (China National Knowledge Infrastructure, <http://acad.cnki.net/kns/default.htm>), WANFANG (<http://www.wanfangdata.com.cn/>)

Japanese - CiNii articles (<http://ci.nii.ac.jp/>), J-STAGE (Japan Science and Technology information Aggregator, Electronic, <https://www.jstage.jst.go.jp/>).

The search terms P (patient) AND I (intervention) were used. Korean search terms were '지루 피부염', '지루성 피부염', english search terms were 'seborrheic dermatitis' for P, and 'herbal', 'traditional', 'medicine' for I. Chinese search terms used previous english terms as well as '脂溢性皮炎' for P, and '中药' for I. Also, japanese search terms used previous english terms and used '脂漏性皮膚炎' for P, '漢方薬' for I. After the search, the literature was organized.

### 3. Selection and Exclusion Criteria

The selection criteria:

- 1) A study of patients with seborrheic dermatitis
- 2) A randomized controlled trials(RCTs) using herbal medicine intake
- 3) A study involving outcome variables to determine whether seborrheic dermatitis improved

The exclusion criteria:

- 1) Combined treatment which cannot identify the efficacy of herbal medicine intake
- 2) A study except RCTs, such as nonrandomized controlled trials(non-RCTs), case control

study(CCT), single group trial, case report, in vivo, in vitro, literature review, letters

- 3) A study that did not include outcome variables to determine whether seborrheic dermatitis improved

#### 4. Study selection and data extraction

The study selection was undertaken by two review authors (KJY, JYW). The first selection was made after screening the title and abstract of articles found in the search, and after screening the full text, the second selection was done. The entire process was performed independently. The study was selected through the agreement between the two researchers, when the researchers failed to reach agreement, the third party intervened and decided by majority.

Data extraction was done by summarizing the year of publication, subject, treatment intervention procedure, evaluation method, treatment effect and side effect report.

#### 5. Risk of bias assessment

A bias is a systematic error, or deviation from the truth, in results or inferences. Different biases can lead to underestimation or overestimation of the true intervention effect.

Risk of bias was evaluated by the risk of bias (RoB) tool which was developed by the Cochrane group. The types of bias in the RCTs are selection bias, performance bias, detection bias, attrition bias and reporting bias.

The RoB tool uses seven areas of random sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Depending on the study, the risk is determined as “high risk of bias”, “low risk of bias”, “unclear risk of bias” for each questions<sup>15)</sup>.

Results were combined using Review Manager(RevMan) 5.3.

### III. Results

#### 1. Search results

Search results were OASIS 15, NDSL 79, EMBASE 256, Pubmed 553, Cochrane Library 6, CINAHL 7, CNKI 70, WANFANG 116, CiNii 13, and J-STAGE 5. A total of 952 studies were found, excluding duplicates.

After screening the title and the abstract, the studies which did not deal with seborrheic dermatitis or used intervention other than herbal medicine were excluded. Even if herbal medicine was used as intervention, it was excluded when it is unclear to identify the effects of herbal medicine solely from combined treatments. And the papers that did not focus on comparing the efficacy of taking herbal medicine, case reports, laboratory papers which did not cover the human body, and papers that only provided abstracts were excluded, only RCTs were included. Therefore, 4 papers that meet the criteria were finally selected(Fig. 1).

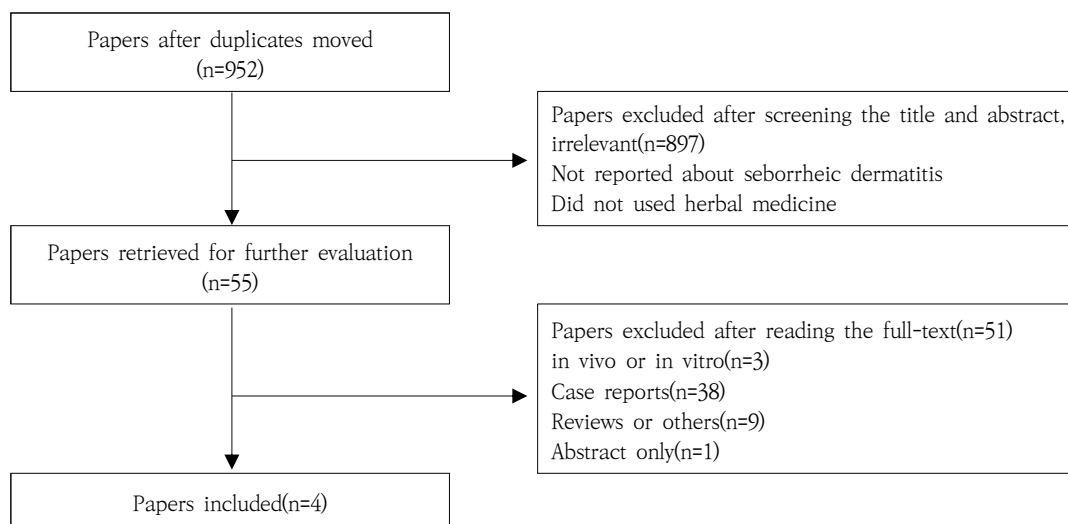


Fig. 1. Flow Diagram for Process of Literature Search.

## 2. Data extraction and analysis

A total of four studies were analyzed in the Table 1.

### 1) Publication year

The research included 1 in 2009<sup>9)</sup>, 1 in 2010<sup>8)</sup>, 1 in 2012<sup>11)</sup> and 1 in 2015<sup>10)</sup>.

### 2) Subject characteristics and baseline similarity

There were no significant differences between the treatment and control groups in all four studies on age, sex, and duration of illness. In only 1<sup>10)</sup> study, the statistically no significant difference between the treatment group and the control group was referred, and other studies<sup>8,9,11)</sup> did not mention the statistical figures but the similarity between the two groups.

There were no significant difference between the treatment and control groups on the

severity of the disease in two studies<sup>8,11)</sup>. Ma et al<sup>8)</sup> refers to the severity of disease as the erythematous type and scarring type which is similar in two groups, and Li<sup>11)</sup> refers to the similarity between the two group without presenting the classification of the severity.

### 3) Intervention

Of the 4 selected studies, 1<sup>11)</sup> study performed only herbal medicine in the treatment group, 1<sup>9)</sup> study with the combination of oral western medicine, 1<sup>10)</sup> study with the combination of topical western medicine, and 1<sup>8)</sup> study with the combination of both oral and topical western medicines.

Li<sup>11)</sup> used Cheongyeolliseubryanghyeol-tang (Qingrelishiliangxie-tang)(*Sophorae Radix*:苦参, *Lonicerae Flos*:金銀花, *Lithospermi Radix*:紫草, *Rehmanniae Radix*:生地黃, *Anemarrhenae Rhizoma*:知母, *Schizonepetae Spica*:荊芥, *Saposhnikovia Radix*:防風) orally, 1dose/day, 2times/day, for 2 weeks.

Table 1. Characteristics of Included Studies.

First author (year)	Subjects			Intervention	Results T/C	Adverse effect
	N (T/C)*	Mean age	Mean DI † (year)			
Zhang (2009)	104 (52/52)	T:23.12±12.54 C:22.92±11.85	T:(3.68+4.32) C:(3.86+4.23)	T:Herbal medicine with C C:Vitamin capsule	1) Cured 32/16(61.54%/30.77%) 2) Improve 14/18(26.92%/34.62%) 3) Invalid 6/18(11.54%/34.62%) 4) Total efficacy rate 88.46%/65.38%	Not mentioned
Ma (2010)	200 (100/100)	36(15~61)	2.9(0.1~10)	T:Herbal medicine with C C:Vitamin capsule, hasinide solution, glucose chlorhexidine ointment	1) 2weeks efficiency 41%/10% 2) 4weeks efficiency 73%/35% 3) 6weeks efficiency 89.5%/66.4% 4) Total efficiency 89.5%/66.4%	8 cases
Li (2012)	100 (50/50)	T:32(20~45) C:31(21~46)	T:1.2(0.2~4) C:1.3(0.3~3.8)	T:Herbal medicine C:Cetirizine, multivitamin B	1) Cured 35/24 2) Significant effect 9/7 3) Improvement 5/11 4) Invalid 1/8 5) Efficacy 88%/62% 6) Cure rate 70%/48%	No adverse effect
Ma (2015)	82 (42/40)	T:32.6(19~45) C:34.3(18~47)	T:0.84(0.3~5) C:0.76(0.3~6)	T:Herbal medicine with C C:0.1% Tacrolimus ointment	-Efficacy 1) Cured 30/25(71.4%/62.5%) 2) Significant effect 6/4(14.3%/10.0%) 3) Improved 5/4(11.9%/10%) 4) Invalid 1/7(2.5%/17.5%) 5) Total efficacy 41/38(97.5%/82.5%) -Recurrence rate 1) 2weeks 2/5(6.7%/20.0%) 2) 4weeks 4/12(13.3%/48.0%)	T:8 cases C:9 cases

\*T/C: Treatment group/Control group, †DI: Duration of illness

Ma<sup>10)</sup> applied 0.1% *Tacrolimus Ointment* on the affected area of the face in both groups, 1time/day, for 2 weeks, and took herbal medicine in the treatment group. *Tacrolimus* is a macrolide immunomodulator, whose mechanism of action prevents activation of T cells by inhibiting the activity of calcineurin, has potent anti-inflammatory effects, and also inhibits skin mast cells and basophils. The release of synthetic media has been shown to inhibit the activity of *Malassezia furfur*, making it safe and effective in the treatment of seborrheic dermatitis<sup>10)</sup>.

Prescribed herbal medicine was divided into two kinds of syndromes, according to the syndrome differentiation, syndrome of stirring wind and dryness due to intense heat; syndrome of blockage and retention of damp-heat. The former used Sopung-san gagam(Xiaofeng-san jiajian)(*Schizonepetae Spica*: 荊芥, *Saposhnikovia Radix*: 防風, *Cicadae Periostracum*: 蟬蛻, *Anemarrhenae Rhizoma*: 知母, *Sophorae Radix*: 苦參, *Atractylodis Rhizoma*: 蒼朮, *Arctii Fructus*: 牛蒡子, *Gypsum Fibrosum*: 石膏, *Angelicae Gigantis Radix*: 當歸, *Rehmanniae Radix*: 生地黃, *Cimicifugae Rhizoma*: 升麻, *Carthami Flos*: 紅花, *Campsis Flos*: 凌霄花), and in the later used Sahwang-san gagam (Xiehuang-san jiajian)(*Pogostemi Herba*: 藿香, *Eupatorii Herba*: 佩蘭, *Poria*: 茯苓, *Coicis Semen*: 生苡薏仁, *Lonicerae Folium*: 茵陳, *Alismatis Rhizoma*: 澤瀉, *Mori Folium*: 桑葉, *Chrysanthemi Flos*: 菊花, *fried Coptidis Rhizoma*: 炒黃連, *fried Scutellariae Radix*: 炒黃芩, *Notopterygii Rhizoma*: 羌活).

Herbs were added according to symptoms. In

case of lots of dry scale and severe itching, *Aconiti Racemulosi Tuber*: 首烏, *Sesami Semen*: 胡麻仁, *Rehmanniae Radix*: 生地黃, *Cynanchi Paniculati Radix*: 徐長卿 were added. Plenty of effusion accompanied by pustule added *fried Gentianae Radix*: 炒龍膽草, *fried Phellodendri Cortex*: 炒黃柏, *Lonicerae Flos*: 金銀花, *fried Sanguisorbae Radix*: 炒地榆 : on constipation *Rhei Rhizoma preparata cum vinum*: 酒大黃, *fried Ponciri Fructus Pericarpium*: 炒枳殼. In case of high fever *Calcitum*: 寒水石, *Oldenlandiae Diffusae Herba*: 白花蛇舌草 were added. And if the lesion accompanies vulva, umbilicus, and nipple area added *Bupleuri Radix*: 柴胡, *Gardeniae Fructus*: 梔子, *Curcumae Radix*: 鬱金, *Gentianae Radix*: 龍膽草. The medicine was treated for 1dose/day, 2weeks.

Ma et al<sup>8)</sup>. put *Vitamin Capsules* 2cap/day, *Halcinonide solution* on the head, and *Glucose chlorhexidine ointment* on the rest of the lesion 1time/day in both groups. Herbal medicine were prescribed to the treatment group.

As a prescription for herbal medicines, Meinuoping-keli was used which consists of *Oldenlandiae Diffusae Herba*: 白花蛇草, *Scutellariae Radix*: 黃芩, *Gypsum Fibrosum*: 石膏, *Lonicerae Flos*: 金銀花, *Forsythiae Fructus*: 連翹, *Moutan Cortex*: 丹皮, *Paeoniae Radix Rubra*: 赤芍, *Mori Radicis Cortex*: 桑白皮, *Gleditsiae Semen*: 皂角刺 3times/day, 6g/time.

*Vitamin Capsules* is a derivative of retinoic acid that regulates and controls epithelial cell differentiation and growth, reduces sebum secretion, inhibits the growth of *Propionibacterium*, and regulates immune and

anti-inflammatory effects.

*Glucose chlorhexidine ointment* is a cationic surface-active preservative. Its mechanism of action is to change the permeability of bacterial cell membranes, has a broad-spectrum antibacterial effect, and improves the inflammatory response on the skin surface<sup>8)</sup>.

Zhang<sup>9)</sup> treated the orally three times a day with a *vitamin capsule* on both groups, and only the treatment group took the herbal medicine additionally.

Herbal medicine prescription is Bihaesamsseup-tang *gagam*(Bibishenshi-tang *jiajian*)(*Coicis Semen*:苡仁, *Tokoro Rhizoma*:革薜, *Phellodendri Cortex*:黄柏, *Poria*:茯苓, *Moutan Cortex*:丹皮, *Alismatis Rhizoma*:澤瀉, *steamed Plantaginis Semen*:車前子(包), *Cynanchi Paniculati Radix*:徐長卿, *Dictamni Radicis Cortex*:白蘚皮, *Sophorae Radix*:苦參, *Glycyrrhizae Radix*:生甘草, *Akebiae Caulis*:通草), twice a day in the morning and evening, total of 500mL was orally administered for 2 months.

In case of severe fever added *Forsythiae Fructus*:連翹, *fried Scutellariae Radix*:炒黃芩, *fried Gardeniae Fructus*:炒山梔, *Sophorae Radix*:苦參. In subacute, chronic stage with the symptoms of spleen deficiency added *Atractylodis Rhizoma Alba*:白朮, *Dioscoreae Rhizoma*:山藥.

#### 4) Evaluation method

In selected four studies, the severity of symptoms was divided into three or four stages, of which 2<sup>10,11)</sup> studies used calculation

method to evaluate the final efficacy. And all the studies presented guidelines or literatures on the basis of the evaluation of symptoms.

Li<sup>11)</sup> evaluated the symptoms refer to 《Standards of Diagnosis and Therapeutic Effect for Diseases and Patterns in Chinese Medicine (中医病症诊断疗效标准)》, efficacy index was calculated as (number of lesions before treatment - number of lesions after treatment) / (total number of lesions before treatment) × 100%. The efficacy was evaluated as 'cured' for efficacy index > 90%, 'significant effect' for > 60%~89%, 'improvement' for > 30%~59%, and 'invalid' for < 30%.

'Cured' corresponds to the cure rate and efficacy is calculated by combining 'cured' and 'significant effect'. Evaluated 2 weeks after the treatment.

Ma<sup>10)</sup> refer to 《China Clinical Dermatology (中国临床皮肤病学)》, 《Dermatology:Diagnosis and Treatment of Chinese Medicine(皮肤病中医诊疗学)》 evaluating using 4-point scale, and 0 to 3 were scored for no, mild, moderate, severe to grade skin lesions, itching, and skin lesion areas. Lesions were classified as mild(erythema, scales), moderate(erythema, scales, infiltration), and severe(erythema, scales, infiltration, exudate, crusting). Efficacy index is calculated as (total score before treatment - total score after treatment) / total score before treatment × 100%.

The efficacy was evaluated as 'cured' for efficacy index > 90%, 'significant effect' for 60%~90%, 'improved' for 20%~59%, and < 20% for 'invalid'. It was evaluated after 2 weeks, and recurrence was evaluated at 2 weeks and 4



weeks after the end of treatment.

Ma et al<sup>8)</sup> refer to 《Clinical disease diagnosis based on cure improvement criteria(临床疾病诊断依据治愈好转标准)》, 'cured' for skin lesions disappear, returned to normal, 'improve' for most of the lesions disappeared and occasionally new skin appeared, and 'invalid' for no significant changes in lesions before and after treatment. Evaluated for 2 weeks, 4 weeks, and 6 weeks.

Zhang<sup>9)</sup> refer to 《Standard of Diagnosis and Assessment of Treatment Effects of Dermatological Conditions in Chinese Medicine·mianyounfeng(中医皮肤科病证诊断疗效标准·面游风)》 issued by the State Administration of Traditional Chinese Medicine. 'Cured' for the skin lesions disappeared more than 95% and the subjective symptoms disappeared, 'improve' for more than 30% of skin lesions subsided, subjective symptoms reduced, and 'invalid' for no change in symptoms, or improvement of less than 30%. 'Cured' and 'improve' were combined to calculate the total efficacy rate. Evaluated after 4 weeks.

## 5) Treatment effect

In all four selected studies, the treatment group treated with herbal medicine was more effective than the control group without herbal medicine treatment to improve symptoms of seborrheic dermatitis. Statistical significance was presented in three<sup>8,10,11)</sup> studies, but not in the other<sup>9)</sup> studies.

Ma et al<sup>8)</sup>'s study showed the total effect at 2 weeks, 4 weeks, and 6 weeks. In the 2 week treatment effect, 41% of the treatment group

and 10% of the control group showed the effect. In the 4 week treatment, 73% of the treatment group, 35% of the control group showed the effect. In the 6 weeks treatment, 89.5% of the treatment group, 66.4% of the control group showed the effect, and the total efficacy was 89.5% at the treatment group, 66.4% at the control group, that the difference was statistically significant( $P < 0.05$ ).

In the study of Li<sup>11)</sup>, the efficacy index was calculated by the number of lesions before and after treatment, and it was presented as four stages of 'cured', 'significant effect', 'improvement', and 'invalid' according to the score. 'Cured' and 'significant effect' were higher in the treatment group than in the control group, and 'improvement', 'invalid' were higher in the control than the treatment group. There was statistically significant difference for the 'cured' which is the cure rate. ( $X^2 = 5.00, P < 0.05$ ) Efficacy which was calculated as the sum of 'cured' and 'significant effect' and there was statistically significant difference. ( $X^2 = 9.01, P < 0.01$ )

According to Zhang<sup>9)</sup>'s study, 'cured', 'improve', and 'invalid' were indicated according to skin lesion and subjective symptoms. In 'cured' and total efficacy rate were higher in the treatment group than in the control group, and in the 'improve' and 'invalid' the control group was higher than the treatment group. There was a significant difference between the two groups, but no statistical value was presented.

In Ma<sup>10)</sup>'s study, the score of the lesion was graded as 'cured', 'significant effect',

'improved', and 'invalid' according to the result of the calculation which compares the total points before and after treatment. 'Cured', 'significant effect' and 'improved' were higher in the treatment group than in the control group, and the control group was higher than the treatment group in the 'invalid'. As a result, the total efficacy rate was higher in the treatment group than in the control group, and the difference between the two groups was statistically significant ( $P < 0.05$ ). This study also evaluated the recurrence rate at 2 weeks and 4 weeks after treatment. The recurrence rate was investigated into 30 patients in the treatment group and 25 patients in the control group, compared with 42 patients in the treatment group and 40 patients in the control group at the start of the study. At 2 and 4 weeks, the recurrence rate was higher in the control group than in the treatment group, which was statistically significant ( $P < 0.05$ ).

### 6) Side effect report

Three of the four selected studies reported side effects. One<sup>11)</sup> study in which only the herbal medicine was administered to the treatment group reported no side effects. Among the two<sup>8,10)</sup> studies in which the both group were applied with topical western medicine, the study<sup>8)</sup> that both group were treated with vitamin showed skin redness, peeling, and dry mouth at 3 of the treatment group, 5 of the control group. It is reported topical agents were discontinued and took only oral medications. In the other<sup>10)</sup> study, 8

patients in the treatment group and 9 patients in the control group reported mild erythema and fever, but did not applied any treatment or discontinuing medication, and did not affect the treatment. However, in Zhang<sup>9)</sup>'s study, there was no report of side effects.

### 3. Risk of bias assessment

The results of the risk of bias assessment for the four studies are shown(Fig. 2,3).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Li 2012	?	?	?	?	+	+	+
Ma 2010	?	?	?	?	+	+	+
Ma 2015	?	?	?	?	?	+	+
Zhang 2009	-	?	?	?	+	?	+

Fig. 2. Risk of Bias Summary.

#### 1) Random sequence generation

Random sequence generation should be done by appropriate random assignment sequences such as coin, die roll, computer-like

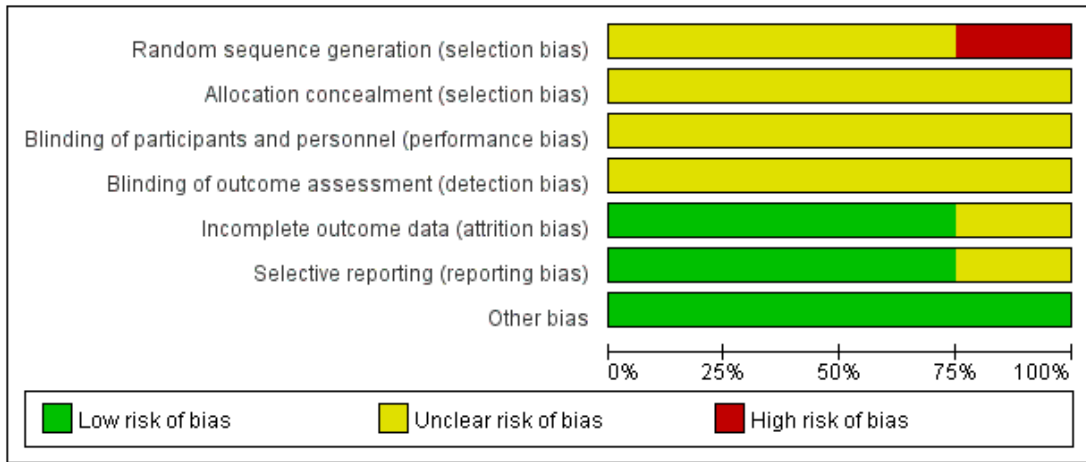


Fig. 3. Risk of Bias Graph.

method. Sequence generated by hospital record number, date of admission is non-random approach<sup>15)</sup>. One<sup>9)</sup> study was assigned randomly according to the order of treatment, which was regarded as 'high risk' due to non-random approach, and the other three<sup>8,10,11)</sup> studies only referred that it was randomly assigned, and no detailed method was mentioned, so it was evaluated as 'unclear risk'.

### 2) Allocation concealment

Even if the random sequence is well generated, if the allocation concealment is not performed, the order can be predicted and the effort to reduce the bias may not be effective<sup>15)</sup>. However, in all four studies was 'unclear risk' because it did not address the content.

### 3) Blinding of participants and personnel

Blinding is reducing the impact on outcomes and outcome evaluation by reducing the risk of knowing what interventions are being

received rather than intervention itself. If blindness to participant or personnel is not performed, difference in expectation of control group and different behaviors among intervention groups may affect research result<sup>15)</sup>. All four studies did not cover the item and were evaluated as 'unclear risk'.

### 4) Blinding of outcome assessment

If the outcome assessors is not properly blinded and knows the allocated interventions, it can affect the evaluation of the result<sup>15)</sup>. All four studies did not cover the content and were evaluated as 'unclear risk'.

### 5) Incomplete outcome data

If the outcome data are missing during the study or excluded during the analysis, the likelihood of attrition bias increases. In order to evaluate attrition bias, both the reason for missing and the number of missing should be considered<sup>15)</sup>. There was no missing in three studies. In one study, there was missing data

at follow up after the end of treatment and no reason for missing is not mentioned, which was evaluated as ‘unclear risk’.

### 6) Selective reporting

Reports may be biased if some results were selectively omitted, select only some of the results, or report only some of the analyzes using the same data. There are several ways to identify bias: if there is a protocol, the outcome of the protocol can be compared with the outcome of the published paper. If there is no protocol, the results in the method can be compared with the variables in the reported outcome. If there are no key findings that are usually collected in similar studies in the field, it may not have been reported<sup>15)</sup>. There were no protocols in all three studies, but the risk of selective reporting was assessed to ‘low risk’ because all results were reported according to previously designed studies. In one study, the significance level (P value) was not indicated only the significance is mentioned, evaluated as ‘unclear risk’.

### 7) Other bias cluster-randomized design

In the case of cluster randomized design, there is a risk of bias such as recruitment bias, baseline imbalance, loss of clusters, inaccurate statistical analysis, and comparability with individual randomized trials<sup>15)</sup>. All four studies reported similarity between the control and treatment group baseline values as the bias risk was assessed as ‘low risk’.

## IV. Discussion

Seborrheic dermatitis is a chronic superficial eczematous dermatitis that forms a pink or yellow plaque of various shapes and sizes with a dry or greasy scale, and it waxes and wanes, with mild itching<sup>4)</sup>.

The first record of seborrheic dermatitis in Korean medicine can be seen in 《The Great Compendium of External Medicine》 “Mostly, it occurs in the head, face, ear, neck, hair. It is slightly itchy at first, as it prolongs, white dandruff becomes flaky, which is peeled off and occurs again. It is caused by heat and wind on the skin, and it is the appearance of the heat and wind. *Geopunghwangihwan, okgigo, yungigo* should be used<sup>†</sup>.”, explaining symptoms, causes and methods of treatment<sup>5)</sup>. In 《The Golden Mirror of Medicine》 “This symptom occurs in the face, initially with swelling of the face and eyes, itching as if the worm is crawling, the skin becomes dry, and as the time goes, white dandruff occurs. After that, the nails are cracked. In case of severe heat and damp, yellow water comes out. In case of severe wind and dryness, blood comes out and the pain is very severe. It is caused by blood dryness, overeating spicy and oily food, and this is caused by the dampness heat of yin, yang and stomach meridian, which is affected by wind<sup>§</sup>.”, describing the symptoms in detail<sup>6)</sup>.

†《外科大成》白屑風生髮內及面目耳項。初起微痒。久生白屑。疊疊飛起。脫之又生。由肌熱當風。風熱之所化也。宜祛風換肌丸。玉肌膏。潤肌膏。

§《醫宗金鑑》此證生于面上。初發面目浮腫。痒若虫行。肌膚乾燥。時起白屑。此後極痒。抓破。熱濕盛者津黃水。風燥盛者津血。痛楚難甚。由平素血燥。過食辛辣厚味。以致陰陽胃經濕熱受風而成。

Treatment of seborrheic dermatitis in western medicine uses topical treatment (such as *selenium sulfide*, *tar*, *zinc pyrithione*, *steroid*, etc.) in order to inhibit cell proliferation and bacterial activity. In more severe cases, oral antibiotics are used. As seborrheic dermatitis is common chronic-recurrent disease, most of the therapeutic options aim to alleviate lesions, not the full recovery. However, long-term application of *steroids* leads to capillary vasodilatation, rosacea, acne, and skin atrophy, and there are many side effects in the use of antifungal agents<sup>1)</sup>.

Therefore, the development of effective Korean medicine treatment for seborrheic dermatitis is important.

Treating seborrheic dermatitis in traditional Asian medicine has a rich history and is now being featured as an alternative to the general limitations of treatment for seborrheic dermatitis. In this regard, various researches on therapeutic agents based on herbal ingredients have been conducted worldwide. *Aloe vera*<sup>13)</sup>, *Althaea officinalis L*<sup>14)</sup>, as well as *olive oil*<sup>6)</sup>, which has been used as single herbal medicines, has been shown to be highly effective in the treatment of seborrheic dermatitis, and studies on the application of single herbal extracts to various combination formulation have been actively conducted and proved to be effective<sup>12)</sup>. In animal experiments and cell-level experiments, it was reported that herbal medicines are a method for the treatment of seborrheic dermatitis<sup>18,19)</sup>. In Korea, it was found that the use of

*Cinnamomum zeylanicum oil* and *Mentha arvensis oil* are effective in treating and alleviating symptoms of seborrheic dermatitis<sup>17)</sup>.

In Korean medicine, seborrheic dermatitis occurs on the surface of the body, but the cause of the disease is inside, which is described as damp-heat. Moreover, recent researches on seborrheic dermatitis, reporting the effect of taking the herbal medicine takes majority. As a result, the purpose of this study was to investigate the effects of taking herbal medicine to external lesion which is seborrheic dermatitis, and to evaluate the quality of research. A total of 4 RCTs articles were collected from Korean and abroad patients with seborrheic dermatitis.

The search was done through various databases, but all of the selected studies were researched and published in China. Therefore, active research is needed in Korea.

As the intervention used in the selected study, herbal medicine such as Cheongyeo-lliseubryanghyeol-tang (Qingrelishiliangxie-tang), Sopung-san gagam (Xiaofeng-san jiajian), Sahwang-san gagam (Xiehuang-san jiajian), Meinuoping-keli, Bihaesamsseup-tang gagam (Bibishenshi-tang jiajian) were treated. There was traditional Korean medicine prescription, newly established prescription, and granule form of prescription. Although the prescriptions used were different, all four studies have noted that seborrheic dermatitis is caused by stress and dietary imbalance resulting in damp-heat developing external skin lesions. Therefore, the prescription was

used to eliminate and reduce damp-heat.

All four studies evaluated using different methods based on the number of lesions, the shape of the lesion, and subjective symptoms, etc. Currently, the seborrheic dermatitis is diagnosed by its distinguishing symptom of erythema and scale, and if necessary, serum zinc level, HIV test are examined for differential diagnosis<sup>1)</sup>. In the studies, different evaluation methods are being used. Standardized evaluation tools are needed for effective treatment and assessment of seborrheic dermatitis.

The Risk of Bias(RoB) assesses whether the RCTs is systematically performed without bias, and the process of evaluating the selected studies with these tools is important for quality assessment. However, in the final selection, there was no mention of selection bias, performance bias, and detection bias. For the further clinical trials, high quality study is required through clarifying the random sequence generation, allocation concealment, and blinding of participants and personnel.

As a result, it was concluded that the use of herbal medicine intake for seborrheic dermatitis could be a good alternative for the treatment of seborrheic dermatitis. In addition, it seems to be possible to increase the effectiveness treating seborrheic dermatitis through applying suitable for each individual by the differentiation of symptoms of Korean medicine. However, there was some limitation in the study design evaluated through RoB, so that reliable information was not obtained. Small numbers of studies finally selected, was

insufficient to support the results. The selected studies were all published in chinese, so that the language bias exists is the limitation of this study as well. Therefore, it is necessary to conduct high quality research through systematic protocol establishment with low risk research design. In Korea, case reports using various kinds of prescriptions to seborrheic dermatitis have been reported, and it seems that there is a sufficient possibility of a good RCTs on the effects of such herbal medicines on seborrheic dermatitis. Furthermore, in order to establish clinical practice guidelines, it is necessary to conduct studies that can provide a high level of evidence.

## V. Conclusion

The purpose of this study was to evaluate the effect of herbal medicine intake on seborrheic dermatitis and the quality of the study. The conclusions of this study are as follows.

1. The search has gone through Korean and abroad RCTs published up to date for herbal medicines intake as intervention for seborrheic dermatitis. Even the studies which used combined treatment that can compare the effect of herbal medicine in the treatment group compared to the control group are included. As a result, a total of four RCTs were selected and all were published in China.
2. Herbal medicine taken to treat seborrheic dermatitis are Cheongyeolliseubryanghyeol-tang

(Qingrelishiliangxie-tang), Sopung-san gagam (Xiaofeng-san jiajian), Sahwang-san gagam (Xiehuang-san jiajian), Meinuoping-keli, Bihaesamsseup-tang gagam(Bibishenshi-tang jiajian), all four studies have been focused on damp-heat inside body due to stress and dietary imbalance as the cause of seborrheic dermatitis.

3. All of the selected studies used different assessment scales which in need for standardized measures of diagnose and evaluation of seborrheic dermatitis.
4. The studies were comparative study of herbal medicine intake versus oral western medicine<sup>11)</sup>, combined treatment of herbal and western medicine intake versus western medicine only<sup>9)</sup>, combined treatment of herbal medicine intake, western topical treatment versus western topical treatment only<sup>10)</sup>, and combined treatment of herbal medicine and western topical·oral treatment versus western topical·oral treatment only<sup>8)</sup>, all of which had a significantly better effect on treatment group than the control group. Therefore, it was identified that herbal medicine intake is effective in reducing the number of lesions and the degree of subjective symptoms, and severity of seborrheic dermatitis.
5. There were no adverse effects in one study of 100 subjects, in a study of 82 subjects, 17 adverse effects were reported and in a study of 200 subjects, 8 adverse effects was reported. One study in which had no reports of side effects. The side effects described were mild which did not require

treatment, or stopped using western medicine and did not affect the results of the study. This confirms that the intake of herbal medicine for the treatment of seborrheic dermatitis is relatively safe.

6. In risk of bias assessment using RoB, there was lack of checking selection bias, performance bias, and detection bias. The quality of the RCTs should be improved by referring and confirming the items described in the further RCTs.
7. In the treatment of seborrheic dermatitis, intake of herbal medicines are considered to be a good alternative, and various well-designed RCTs of Korean researchers are needed in the future.

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