



Effects of Herbal Medicines on the Prevention and Treatment of Contact Dermatitis: A Systematic Review

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Abstract

Background: Contact dermatitis (CD) is a common inflammatory disease of the skin. CD has a complex and multifaceted treatment, and one of the main components of CD treatment is inflammation management. We summarized the clinical trials exploring the effects of herbal medicine on patients with CD.

Methods: A systematic review was performed by searching four databases. Clinical trials in English investigating the effect of herbal medicines on CD prevention and treatment published from 2010 to 2020 were reviewed. This study was conducted based on the PRISMA guidelines.

Results: Nine clinical trials examining the effects of herbs on CD were identified. A total of 450 patients participated in these studies. Herbal medicines used in the reviewed studies were in various forms. Almost all the studies showed that these herbs were useful in preventing and treating CD. Regarding the side effects of the herbal medicines, few complications such as erythema and papules as well as positive chronotropic effects were reported.

Conclusion: Evidence showed that herbal medicines were effective in preventing and treating CD by reducing the inflammation level and increasing antioxidant defense. However, the number of clinical trials was low to draw definitive conclusions. Moreover, the studies were not homogeneous and differed regarding methodology, evaluation tools, and quality. Also, in these studies, the interactions and safety of the herbal medicines were not considered adequately. Therefore, well-designed evidence is required to draw definitive conclusions in this regard.

Keywords: Contact dermatitis; Herbal; Systematic review; Prevention



Introduction

Contact dermatitis (CD) is a common inflammatory disease of the skin characterized by pruritic skin lesions and erythematous after contact with a foreign object. This disease can be divided into two main routes, irritant or allergic (1), and may occur in both acute and chronic forms (2).

Irritant contact dermatitis (ICD) predominates about 75-85% of all CD cases while allergic contact dermatitis (ACD) accounts for the remaining 15-25% (1,2). The difference between the two forms of CD is based on their pathogenesis: immunologic versus non-immunologic mediation. An allergic reaction is defined as the inducing substance that needs sensitization and can occur only in a genetically specific host capable of being sensitized to that given antigen. In contrast, an irritant reaction is nonspecific, does not need previous sensitization, and may occur in any antigens (1,3). The disruption of skin barriers is the first CD pathogenesis step created by mechanical stress, prolonged contact with detergents or water, and exposure to harmful chemicals. It exposes the skin to penetration by pathogens, allergens, and irritants (4).

Despite their differing pathogenesis, ACD and ICD may be impossible to differentiate clinically, particularly in their chronic forms (5). CD signs and symptoms can vary depending on the causes, such as acute or chronic dermatitis, stimulating or allergenic nature, and dermatitis localization (6). The acute CD is characterized by erythematous papules with vesicles and weeping. Subacute CD presents with erythema, scaling, and a severe exúdate. Finally, chronic CD is associated with epidermal hyperkeratosis, lichenification, and fissuring (5).

Identifying and avoiding relevant allergens and irritants is the first line of treatment to reduce inflammation in patients with CD. However, it is mostly impossible to differentiate between ACD and ICD, and sometimes it is a mix of both conditions. If it is impracticable to avoid allergens and irritants or if the causal substance cannot be

determined, topical treatment with creams/ointments, corticosteroids, and other immune-modulating treatments can be useful. Also, artificial barriers to prevent the passage of sensitizing antigens or harmful irritants may help epidermal healing (3,6).

CD treatment is complex and multifaceted, but a core component of treatment for both ACD and ICD is to manage inflammation with topical corticosteroids (6). However, the treatment has side effects such as cutaneous atrophy, striae, telangiectasia, tachyphylaxis, and adrenal suppression (7).

CD management is often unpleasant, and CD recurrence is expected. Therefore, many patients suffering from CD intend to try complementary and traditional medicine (CTM), mainly herbal medicines. Many studies have assessed the effects of different plants on CD (8–11).

No systematic review has been conducted on the effects of herbal medicine as one of CTM on CD treatment. This systematic review aimed to summarize evidence from interventional human studies examining the effects of herbal substances on CD treatment.

Methods

Study protocol and registration

The review protocol was registered (CRD42020197630 PROSPERO) and established based on the rules of the preferred reported items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement (12).

Ethical Approval

This study is taken from the dissertation thesis entitled "Determination of efficacy and safety of *Portulaca oleracea* product on clinical signs of mild to moderate chronic dermatitis" which has been approved by the Ethics Committee of the Vice Chancellor for Research and Technology of Shahid Beheshti University of Medical Sciences

and has been registered in the Iranian Registry of Clinical Trials with registration number IRCT20200707048040N1.

Eligibility criteria

We included all types of clinical trials investigating the effect of herbal medicine interventions on CD prevention or treatment with keywords, mesh words, and synonyms between January 2010 and December 2020.

Information sources

This search was conducted in the Embase, Web of Science, Scopus, Pubmed databases from January 2010 to December 2020 to identify relevant publications.

Search strategy

Two professional healthcare librarians (M.S. and A.S.) started a comprehensive search of four English databases on 01/05/2020 and updated the search on 06/12/2020 to provide a comprehensive evidence base. The search strategy is available upon request. After obtaining the full texts of the articles, reference lists were hand-searched and additional publications were identified to be used in the review.

Data management

Titles, abstracts, and keywords were searched in the articles detected in the four databases, and finally 206 clinical trials published between 2010 and 2020 were selected.

Duplicate articles were first removed from the records. Then, irrelevant articles, review articles, articles on unclassified dermatitis, plant-induced dermatitis, and articles related to acupuncture and Ayurveda were removed. Finally, 11 articles that met the eligibility criteria were evaluated. Howev-

er, two more articles were excluded from the study since their full texts were not available and they had insufficient abstract information. Therefore, nine articles, including eight full texts and one abstract, were reviewed. The Jadad scale (13) and Cochrane Risk of Bias tool (14) were used to evaluate the quality of the reviewed articles.

Selection process

Two persons (S.R. and S.P.) independently reviewed titles, abstracts, and keywords of the articles to find studies that meet the eligibility criteria. Disagreements were resolved after discussing issues with a third author (G.H.) and reaching a consensus.

The details of the study selection method are summarized in the PRISMA-compliant flow chart (Fig. 1).

Data collection process

The main characteristics of the nine selected studies are summarized in Table 1. The articles were published from 2010 to 2020 (10,15–22). Three of the studies were performed in Iran (10,18,22), two of them were conducted in America (16,17), and the others were performed in Sweden, China, Thailand, and Italy (15,19–21).

Data items

Study specifications were as follows: author's name, publication year, sample size, size of experimental and control groups, age, type of study, disease category, interventions, prevention or treatment, intervention method, intervention duration, follow-up duration, conclusion after treatment, and intervention side effects.

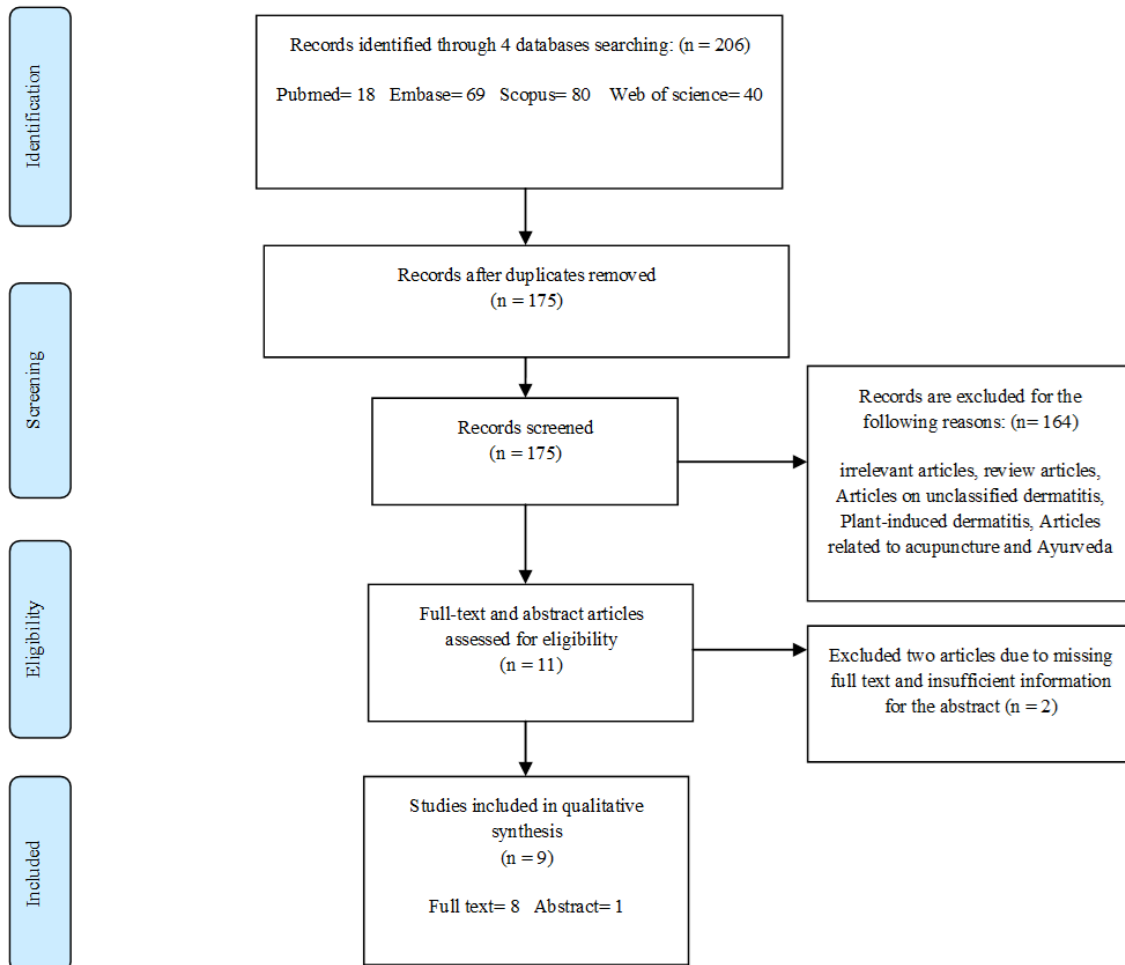


Fig. 1: PRISMA flow chart of the study selection process

Table 1: Study specifications of included controlled trials

Author's name	Interventions	Sample size	Duration of intervention and follow-up	Age (yr)	Disease category	Side effects
M. Niazi, et al (10)	IG: Topical henna (<i>Lawsonia inermis</i> L.) CG: Topical placebo	N= 95 IG= 37 CG= 37	Treatment for a while 2 weeks (every night)	12-70	CD	No serious adverse effect was reported
Ding Lei, Wang Bo (15)	IG: TGP capsules with halometasone cream CG: Halometasone cream only	N=102 IG= 50 CG= 52	Treatment for a while 4 weeks	Mean age of IG: 55.21 ± 9.28 Y Mean age of CG: 56.48 ±	ACD	No report

Vicki Motz et al(17)	A.	According to a random sequence, 6 areas exposed to Poison Ivy were treated by: 1. (Control) distilled water, 2. fresh plant (<i>I. capensis</i>) mash, 3. An extract of <i>I. capensis</i> containing saponin, 4. a concentrate with double strength from the same infusion, 5. Natural and Pure Lye soap and 6. Jewelweed Soap	N= 23	Rash development was followed-up 18 days after being exposed to Poison Ivy	18-65	ICD (Poison ivy induced dermatitis)	May positive chronic effects of the extract contain saponin.
Vicki Motz et al (16)	A.	Protocol 1: (Randomized sequence) squares treated with 1. (Control) single water wash, 2. Double wash water, 3. fresh plant (<i>I. capensis</i>) mash, 4. aqueous extract of <i>I. capensis</i> , 5. lawsone solution, 6. jewelweed soap Protocol 2: PI exposed squares treated with 1. (Control) single water wash, 2. mash of <i>I. balsamina</i> , 3. <i>I. balsamina</i> extract, 4. <i>I. balsamina</i> soap, 5. Soap containing <i>I. capensis</i> , 6. Dawn's dish soap	N= 40 Protocol 1= 25 Protocol 2= 15	Followed-up 24h, 48h, and 96 h and 7 days after being exposed to Poison Ivy (protocol 1) Followed-up 96 h, 7 and 10 days after being exposed to Poison Ivy (protocol 2)	18-65	ICD (Poison ivy induced dermatitis)	No report
S. Trakanwittayarak, J. Meephan-san (20)		IG: Pre-treated with an emulsion containing astaxanthin CG: Pre-treated with an emulsion without astaxanthin	N= 13	Followed-up on Day 2, 3, and 7 after the application of 1% p-phenylenediamine in petrolatum.	20-70	ACD	Not serious adverse effects
J. Wal-lengren (19)		IG: The effect of tea tree oil, camphor, zinc oxide, ichthammol, clobetasone butyrate, and menthol on CD caused by nickel and benzalkonium chloride patch test CG: physiological saline	N= 21	24 hours after applying 120 µl tea tree oil and 150 mg of the substances in petrolatum on the ventral part of lower arms	mean age 48 , range 25-73	ICD ACD	No report

		and Petrolatum on CD caused by nickel and benzalkonium chloride patch test					
M. A. Ebrahim-zadeh et al (22)		IG: Treatment with topical solution of palmoline (5% fruit extract of <i>S. ebulus</i> in 70% ethanol) 3 times a day CG: Using topical solution of 70% ethanol and topical hydrocortisone ointment 3 times a day	N= 62 IG= 33 CG= 29	All patients were visited or questioned every 12 hours to 48 h Only 2 patients needed to continue treatment for more than 48 hours	<20 y =9 20-40 y= 30 >40 y=23	ICD	No report
F. Jowkar et al (18)		IG: Treatment with 4% cream of <i>Fumaria parviflora</i> CG: Using vehicle cream	N= 44	Treatment twice a day for 4 weeks.	mean age 13.3 , range 13-58	ICD ACD AD Pompholyx	Erythema and population (one patient)
T. Ma-grone et al (21) (Abstract)		IG: Treatment with 300 mg of Polyphenolic extract red grape seed orally on ACD by nickel CG: Using placebo for ACD by nickel	N= 50 IG= 25 CG= 25	3 months after starting treatment	Unknown due to lack of full text	ACD	Unknown due to lack of full text

Abbreviations:

IG: Intervention Group

CG: Control group

N: Number

CD: Contact Dermatitis

TGP: Total glucosides of paeony

ACD: Allergic Contact Dermatitis

ICD: Irritant Contact Dermatitis

PT: Pre-Treatment

Results

Prevention or Treatment

Nine clinical trials examined the effects of various forms of herbal products, such as fresh herbs, creams, capsules, solutions, emulsions, injections, and soaps on CD. Among them, 5 studies evaluated the therapeutic measures (10,15,18,21,22) and 4 studies evaluated the preventive measures on CD (16,17,19,20).

Participants

A total of 450 patients had enrolled in these studies (10,15–22).

Sample size

The sample sizes varied between 13 and 102 (Table 1).

Intervention method

In 5 studies, eligible participants were allocated into two groups (intervention and control) (10,15,18,21,22) whereas in 4 studies, the intervention and control were used in two different areas of the same body (16,17,19,20).

Results measurement tool

To show the effect of product, measurement of biomarkers was used in 2 studies (15,21) while in 7 studies clinical sign scoring system was applied (10,16–20,22).

Duration of follow-up

The treatment duration varied between 12 hours and 3 months. The follow-up duration in the prevention studies ranged from 24 hours to 18 days (Table 1).

Side effects

Among the articles reviewed in this manuscript, four studies evaluated the side effects of herbal medicines (10,17,18,20), while two studies reported the side effects. Since using herbal products itself may cause contact dermatitis and side effects, this subject has been neglected (17,18).

Type of CD

Three studies have been performed on ACD (15,20,21), three studies on ICD (16,17,22), and three studies on both (10,18,19). In addition, in five studies, Patch tests were used to create dermatitis, having the advantage of differentiating between different types of CD (16,17,19–21).

Interventions

Lawsonia inermis L

Niazi et al. investigated the topical henna (*Lawsonia inermis* L.) product in CD patients using limb prosthesis (10). Their results showed a significant improvement in CD symptoms in the intervention group compared to the placebo group; though skin redness increased significantly in the henna group. In Niazi et al. study, the topical formulation of henna proved to be a useful medication for improving CD symptoms in patients using lower limb prostheses. Lack of using an objective method to assess the symptoms of dermatitis, not using a patch test to differentiate types of CD, and a short follow-up period were the limitations of their study. The number of patients was appropriate (95 patients) (10).

Total glucosides of paeonyZS

Lei et al. evaluated the efficacy of total glucosides of paeony (TGP) on interleukin-33 (IL-33) and interleukin-18 (IL-18) mRNA expressions in ACD patients (15). The results showed that the expression levels of IL-33 and IL-18 mRNA in the intervention group were remarkably decreased compared to before the intervention. According to the results of their study, TGP can help treating ACD by inhibiting pro-inflammatory cytokines. The positive points of this study were the use of biomarkers to evaluate the effect of herbal medicine on dermatitis, and a one-month follow-up period. The number of patients was appropriate (one hundred and two patients). However, one limitation of this study was that side effects were not assessed (15).

Saponin

Motz et al. evaluated the efficacy of one of the components of *Impatiens capensis* Meerb., saponin in prevention of CD induced by urushiol (17). Both extracts containing saponins and soaps effectively decreased toxic ivy dermatitis. They suggested that the saponin contents had the potential to prevent poison ivy rash. However, it should be noted that saponin-containing extracts may have positive chronotropic effects. The advantages of this study were the use of different concentrations of the drug, various forms of medicine to evaluate the effect of herbal product in the prevention of dermatitis, a follow-up period of eighteen days and using patch test. In addition, this study investigated and reported the side effects. The limitation of this study was the small number of volunteers (23 people) (17).

jewelweed, lawson

Motz et al. investigated the efficacy of jewelweed, *Impatiens capensis*, the related cultivar *I. balsamina* and the content, lawson (The claimed effective factor in the preparation of jewelweed) in prevention of CD which induced by poison ivy (16). Jewelweed mash was effective in managing dermatitis induced by poison ivy. Although soaps with jewelweed extract were effective in managing dermatitis, they did not show more efficacy compared to soaps without extract. In addition,

the *Lawsonia* content showed no effect on reducing rash development. The advantage of this study was the use of different concentrations of the drug and different forms of medicine in the intervention. The limitation of this study was the small number of participants for each protocol. In almost half of the participants no significant poison ivy dermatitis developed, and data analysis was performed in protocol one with 15 patients and protocol two with 7 patients. Furthermore, the maximum duration of follow-up was ten days (16).

Astaxanthin

Trakanwittayarak et al. evaluated the effect of astaxanthin on ACD created by p-phenylenediamine. The use of astaxanthin emulsion pre-treatment decreased the allergenic reaction to p-phenylenediamine-containing hair color. The advantage of this study was the evaluation of side effects, while its limitations were the small number of participants (13 people) and the short follow-up period (20).

Tea tree oil

In another study, the positive effect of tea tree oil, camphor, zinc oxide, ichthammol, clobetasol butyrate, and menthol on CD was caused by nickel and benzalkonium chloride patch test, was investigated (19). The anti-dermatitis effect of tea tree oil was more than clobetasol butyrate and zinc oxide. The effectiveness of tea tree oil was only on ACD. The limitations of this study were short follow-up period (24 to 48 hours), small number of participants (21) and difficulty in scoring of itching due to proximity of patch tests on patients' backs (19).

Sambucus ebulus

Ebrahimzadeh et al. evaluated the effect of *Sambucus ebulus* lotion on *Paederus* dermatitis (22). Five percent topical solution of the *S. ebulus* fruit was more effective in controlling the inflammation and infection, drying the wound, reducing burning sensation and acceleration of healing. Only the anti-itching effect of this solution was similar to the control group. This study had sev-

eral advantages such as sufficient number of patients (62) and short recovering time of symptoms (24 to 48 hours). The limitation of this study was the lack of investigation for possible side effects (22).

Fumaria parviflora L

Jowkar et al. investigated the effectiveness of *Fumaria parviflora* L. extract on the treatment of chronic hand dermatitis. *F. parviflora* L. alcoholic extract improved various types of hand dermatitis, including CD, compared with placebo, which indicated the existence of immunomodulatory principles in *F. parviflora* L. The positive points of this study were the assessment and report of side effects such as erythema as well as the number of participants (44) and the follow-up period of 4 weeks (18).

Red grape seed polyphenols

Magrone et al. evaluated the effect of orally administering red grape seed polyphenols on improving ACD caused by nickel (21). The IL-4, IFN- γ , PTX3, IL-17, and NO levels decreased, while the IL-10 level increased in the intervention group patients. Laboratory data show that polyphenols have anti-inflammatory, antioxidant, and anti-allergic properties. The advantage of this study was using patch tests in two parallel groups as well as measurement of biomarkers. Side effects and limitations were unknown due to the lack of access to the full text. The number of participants was 50. There were also 7 dropouts in each group (21).

The specifications of the controlled trials are given in Table 1.

Risk of bias in individual studies (quality assessment)

The Jadad scale and Cochrane risk of bias tool were used to evaluate the quality of the reviewed studies. According to the Jadad scale, the items of randomization, randomization method, blinding, blinding method, and exclusion with a minimum score of 1 and a maximum score of 5 were measured (13). Based on the Jadad checklist, three studies (33.3%) received the maximum score

(score 5) (10,18,22) and four studies (44%) received a score of 3 (15–17,19). A total of seven studies (78%) received scores equal to or greater than 3 (10,15–19,22). One study received a score of 1 (20). The score of another study was reported to be uncertain due to insufficient information and unavailability of the full text (21). According to this scale, the items of randomization, randomization method, blinding, blinding method, and exclusion have been adequately reported in seven (78%), seven (78%), three (33%), three (33%), and nine (100%) clinical trials, respectively. Therefore, the best score was related to the exclusion item whereas the lowest score was related to the blinding and blinding method. The evaluation results of the quality of the clinical tri-

als with the Jadad scale are given in Table 2. Based on the Cochrane risk of bias tool, the items of random sequence generation (selection bias), allocation concealment (selection bias), blinding (participants and personnel; performance bias), blinding (outcome assessment; detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) were measured (14). Concerning the random sequence generation of selection bias, there were six low-risk of bias studies (67%) (10,16–19,22), one high-risk of bias study (11%) (20), and two unclear risks of bias studies (22%) (15,21). The summary of the risk of bias profile according to the Cochrane criteria is given in Table 3.

Table 2: Evaluating the quality of clinical trial articles by Jadad scale

<i>Authors, year</i>	<i>Randomization</i>	<i>Method of randomization</i>	<i>blinding</i>	<i>Method of blinding</i>	<i>Exclusion from the study</i>	<i>Total score</i>	<i>Quality assessment</i>
M. Niazi, et al. 2020 (10).	1	1	1	1	1	5	HQ
Ding Lei, Wang Bo 2019 (15).	1	1	0	0	1	3	LQ
Vicki A. Motz et al. 2015 (17).	1	1	0	0	1	3	MQ
Vicki A. Motz et al 2012 (16).	1	1	0	0	1	3	MQ
S. Trakanwittayarak, J. Meephansan 2019 (20).	0	0	0	0	1	1	LQ
J. Wallengren 2010 (19).	1	1	0	0	1	3	MQ
M. A. Ebrahimzadeh et al 2014 (22).	1	1	1	1	1	5	HQ
F. Jowkar et al 2011 (18).	1	1	1	1	1	5	HQ
T. Magrone et al 2020 (21). abstract	Unknown	Unknown	Unknown	Unknown	1	Unknown	Unknown

Abbreviations:

HQ: High Quality

LQ: Low Quality

MQ: Medium Quality

Table 3: Summary of risk of bias profile according to the Cochrane criteria

<i>Authors, year</i>	<i>Selection bias Random sequence generation</i>	<i>Selection bias Allocation concealment</i>	<i>Performance bias Blinding (participants and personnel)</i>	<i>Detection bias Blinding (outcome assessment)</i>	<i>Attrition bias Incomplete outcome data</i>	<i>Reporting bias Selective reporting</i>
M. Niazi, et al. 2020 (10).	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ding Lei, Wang Bo 2019 (15).	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk
Vicki A. Motz et al. 2015 (17).	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk
Vicki A. Motz et al 2012 (16).	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk
S. Trakanwit-tayarak, J. Meephanan 2019 (20).	High risk	High risk	High risk	High risk	Low risk	Low risk
J. Wallengren 2010 (19).	Low risk	Low risk	High risk	High risk	Low risk	Low risk
M. A. Ebrahim-zadeh et al 2014 (22).	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
F. Jowkar et al 2011 (18).	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
T. Magrone et al 2020 (21). Abstract	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

Discussion

The current attempt was a systematic review of clinical trials on the effects of herbal medicines on prevention and treatment of CD. In general, there were few clinical trials conducted in this field.

Heterogeneity

Despite substantial heterogeneity being evident in the design of studies, materials and methods, number of patients, follow-up period, tools for measuring results and quality of the studies, the results of these nine clinical trials showed that most herbal medicines are very effective in the treatment and prevention of CD.

Side effects

Given that only four studies investigated the side effects and the follow-up duration was varied in

those studies, the comparison of studies was difficult (Table 1). If the follow-up time in two studies which reported the side effects (10,20) was longer, assessment of side effects could be more accurate.

Quality assessment

The quality of studies was assessed by the Jadad scale and accordingly, three studies were of high-quality, three studies were of medium-quality, two studies were of low-quality and the last one could not be evaluated since the full text was unavailable (Table 2). Many scales have been used to assess the methodological quality of RCTs, but most of them have not been satisfactorily developed and tested for validity and reliability. The Jadad Scale has been reported as the best scale for evaluating the methodological quality of RCTs (23). Seven studies were randomized while blinding was performed in only 3 studies (Table

2). The lowest quality clinical trial belonged to Trakanwittayar et al., with a small number of volunteers and a short follow-up period (20). The sample size was appropriate in 3 studies, moderate in 2 studies, and small in 4 studies (Table 1); and there was a large variety of follow-up period in the studies. In 3 studies, follow-up period was appropriate while in other studies, follow-up period was short (Table 1). It seems that more accurate results could be obtained with longer follow-up periods. We used the Cochrane Criteria to evaluate the risk of bias (Table 3). Consequently, Niazi, et al study, as well as Jowkar et al study showed the lowest risk of bias in all items such as random sequence generation, allocation concealment, blinding, outcome assessment, and selective reporting (10,18).

Type of intervention

In most of the studies, herbal preparation was used topically (10,16–20,22). Although topical medications appear to cause fewer side effects, it is not possible to make an accurate assessment because about half of the mentioned studies did not report side effects. Moreover, there was substantial heterogeneity in the method and analysis of the studies. On the other hand, since dermatitis is a systemic disorder, it seems the use of systemic medications may be more effective in its prevention and treatment, although in our study, systemic herbal medicine was used in only 2 studies (15,21). Hence, it is not possible to compare the effectiveness as well as side effects between systemic and topical interventions.

Different results

Despite the positive results of herbal medicines in the treatment of the CD, several articles have shown the opposite results. Henna showed a positive effect in management of CD in Niazi et al. study with no report of serious side effects (10). However, in several studies, Henna has been introduced as causative agent in dermatitis (24–27). It is possible that the complications of Henna would appear if the follow-up period in the study of Niazi et al. was longer (10). The Henna side effects can be attributed to para-

phenylenediamine (PPD) (25,27), daiminotoluenes, and diaminobenzenes which are added to henna dye (24). There are few reports on the contact sensitivity of pure Henna showing low allergenic potential (26); However, more studies are needed to draw accurate conclusions.

Wallengren's study (19), showed the positive effect of tea tree oil in the prevention of CD with report of no side effects. Still, several studies have introduced the tea tree oil as a causative agents in dermatitis (28,29). Maybe this difference is related to the difficulty of itching assessment due to proximity of patch tests on patients' backs or the short follow-up period in Wallengren's study. On the other hand, people who use low concentrations of this oil on healthy skin (28), as well as people who use fresh oil, show almost no allergies (29). It seems that excessive oil application, especially on damaged skin (28) as well as usage of oxidized oils, increases the risk of ACD (29). According to the results of this study, herbal medicines can be considered valuable potential medications for prevention and treatment of CD with report of no serious side effects. In future studies, some factors can be considered for determination of the effectiveness and safety of herbal medicines such the use of two parallel groups of intervention and control, the use of objective tools such as patch tests to determine the type of dermatitis, drug preparation in different doses and different forms, the appropriate number of participants and appropriate follow up to evaluate side effects of herbal medicines and use of biomarkers to investigate effects of herbal interventions on prevention and treatment of CD.

Strengths and Limitations

One of the study's strengths is that due to the high prevalence of dermatitis, high recurrence of the disease, high side effects of common chemical drugs, and people's growing tendency to use herbal medicines, this study can provide valuable information about herbal medicines that have been studied in humans. The study may also provide constructive and useful ideas for researchers and pharmacists to develop effective and safe

herbal medicines to prevent and treat dermatitis. Another strength of the study is using the Jadad scale and the Cochrane risk of bias tool to evaluate the quality of the clinical trials. The review has also several limitations. The ability to compare the clinical trials was limited due to the heterogeneity in the design of studies, materials, and methods, the number of patients, follow-up time, the tool for measuring results, and the quality of the studies. Moreover, there was a flaw in the method in 2 of the clinical trials. There was no access to the full text of one clinical trial.

Conclusion

The existing but limited human evidence showed that herbal medicines were effective in preventing and treating CD by reducing the inflammation level and increasing antioxidant defense. Moreover, the studies were not homogeneous in methodology, evaluation tools, and quality. Also, the interactions and safety of the herbal medicines were not considered adequately. Therefore, well-designed evidence is required to draw definitive conclusions in this regard.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

No conflicts of interest.

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