Efficacy of Non-Steroidal Topical Medications in the Treatment of Chronic Hand Eczema: A Systematic Review

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Abstract

Hand eczema (HE) is dermatitis that occurs on hands or wrists with a yearly prevalence of more than 10%. Topical corticosteroids are the primary treatment options in treating HE, however, long-term use can cause local and systemic side effects. This calls for the use of steroid-free topical medications in the treatment of HE. There have been only a few studies done on CHE using alternative topical medications. This study aims to compare the efficacies of alternative topical non-steroidal medications to that of topical corticosteroids in treating CHE. Methodology: A systematic review was conducted by collecting and analyzing data from PubMed, Scopus, and Cochrane Central from inception till June 2022 by using the following keywords: *(*chronic or chronic disease) AND (hand or hands) AND (eczema or dermatitis) AND (topical or topically) AND (treatment or therapy) AND (randomized controlled trial or controlled clinical trial). The search term would be based on the Cochrane Highly Sensitive Search Strategy. Result: A total of six articles with 229 participants (258 samples) were included in the systematic review. Overall, the alternative topical treatments have comparable efficacy to topical corticosteroids in most of the studies. Conclusions: This review demonstrated that non-herbal steroid-free single topical treatments have comparable efficacy to that of topical corticosteroids whereas most of the herbal topical treatments were not as effective as topical corticosteroids. Therefore, our systemic review suggests that non-herbal single topical treatments may be alternative options for treating CHE patients who are suffering from side effects of topical corticosteroids and those who are afraid to use them.

***Keywords*:** efficacy, non-steroidal, topical medications, chronic hand eczema, systematic review

1. Introduction

Hand eczema (HE) is dermatitis occurring on the hands or wrists and can be caused by various etiologies. It is called acute HE when the duration of the disease is less than 3 months, whereas if the disease lasts for longer than 3 months, it is called chronic hand eczema (CHE) (Agner & Elsner, 2020). The duration of disease may last for more than 10 years with frequent recurrence (Quaade et al., 2021).

There are several different outcome assessment tools for HE including objective tools like Hand Eczema Severity Index (HECSI), Physician's Global Assessment (PGA) (Duman & Uzunali, 2015), Hand Eczema Extent Score (HEES) (Carlsson et al., 2017), Dyshidrotic Eczema Area and Severity Index (DASI) (Schnopp et al., 2002), Eczema Area and Severity Index(EASI) (Jowkar et al., 2011), subjective scoring measures like Visual Analogue Scale (VAS), Patient's Global Assessment (PaGA) (Bissonnette et al., 2010) and questionnaire-based Dermatology Life Quality Index(DLQI) score (Mehrpooya et al., 2020).

Currently, a variety of treatment options are available such as topical, systemic, and phototherapy depending on the type and severity of CHE (Elsner & Agner, 2020). It is important to identify and avoid the causes of HE like irritants and allergens together with following the protection measures like wearing gloves and applying barrier creams (Diepgen et al., 2015).

It has been more than 50 years since topical preparations of high-potency steroids have been used as the centerpiece treatment for HE as they can reduce inflammation, mitotic activity, and immune activity (Dubin et al., 2020; Elsner & Agner, 2020). However, the use of topical corticosteroids for a long time can cause skin thinning, atrophy, telangiectasia, and adrenal insufficiency (Diepgen et al., 2015). This leads to a

real need for alternative topical treatments for chronic hand eczema apart from topical corticosteroids (Diepgen et al., 2007).

Steroid-free topical medications from non-herbal sources that are under trials for use in HE include topical calcineurin inhibitors (TCIs),calcipotriol, and topical delgocitinib (Elsner & Agner, 2020; Worm et al., 2020). TCIs are immunomodulatory agents and they are already approved for atopic eczema therapy (Elsner & Agner, 2020). Topical calcipotriol is derived from vitamin D and it inhibits the abnormal proliferation of cells and enhances the differentiation of keratinocytes (Juntongjin & Pongprasert, 2019). Topical delgocitinib is a novel therapy and it deters inflammation by inhibiting all Janus Kinase (JAK)enzymes (Nakagawa et al., 2020).

In addition to this, steroid-free topical herbal alternative treatments such as fumaric acid cream, Nigella ointment, pumpkin ointment, and almond ointments are also under trial to treat CHE. Topical fumaric acid is an extract from the *Fumaria Paviflora* plant and it has immune modulatory action, preventing T cell functions and cytokine release (Jowkar et al., 2011). Similarly, Nigella modulates the immune system and it was used traditionally to treat atopic diseases(Kalus et al., 2003; Yousefi et al., 2013). Another herbal product called topical pumpkin ointment as well as almond oil offer an anti-inflammatory and moisturizing activity (Khademi et al., 2020; Zeichner et al., 2018).

There were some reviews about the treatment of chronic hand eczema. However, the efficacy of steroid-free single topical treatments compared with topical corticosteroids in the treatment of CHE has not been properly summarized yet. For this reason, the objective of this study is to systematically review the efficacy of alternative single topical treatments to topical corticosteroids for the treatment of CHE.

2. Objectives

To systematically review the efficacy of alternative topical applications to topical corticosteroids for the treatment of chronic hand eczema.

3. Methodology

A systematic review was performed by searching through electronic databases such as PubMed, Scopus, and Cochrane Central from inception until June 2022. Depending on types of the databases, various search strategies, search terms, and keywords such as (chronic or chronic disease) AND (hand or hands) AND (eczema or dermatitis) AND (topical or topically) AND (treatment or therapy or therapeutics) AND (randomized controlled trial or controlled clinical trial) were used to search data. The search terms were based on Cochrane Highly Sensitive Search Strategy. Both male and female patients from all age groups with CHE diagnosed by any criteria were included in the study. Moreover, data from studies with any single topical treatment in the intervention group and all kinds of topical corticosteroids in the control group were also extracted. However, only studies with randomized controlled trials were included in this systematic review regardless of the various types of outcome measures. The inclusion and exclusion criteria of this systematic review are described in Table 1. Data analysis was performed using the Review Manager 5 software.

4. Results and Discussion

4.1 Results

Initially, there were altogether 733 studies with 104 from Pubmed,384 from Cochrane central, and 245 from Scopus. There was a systematic review done on the treatment of HE and it was focused on all types of topical and systemic treatments. After removing the duplicated papers, and screening based on title, abstracts, and full-text review,6 articles were selected. The studies in this systematic review involve 2 intra-individual studies, 2 studies with a comparison between two groups, 1 three-parallel-group study, and 1 four-parallel-group trial. Based on the search term, total 229 patients (258 samples) with chronic hand eczema are included in this systematic review. The detailed selection of studies was described in Figure 1 as a flow diagram.

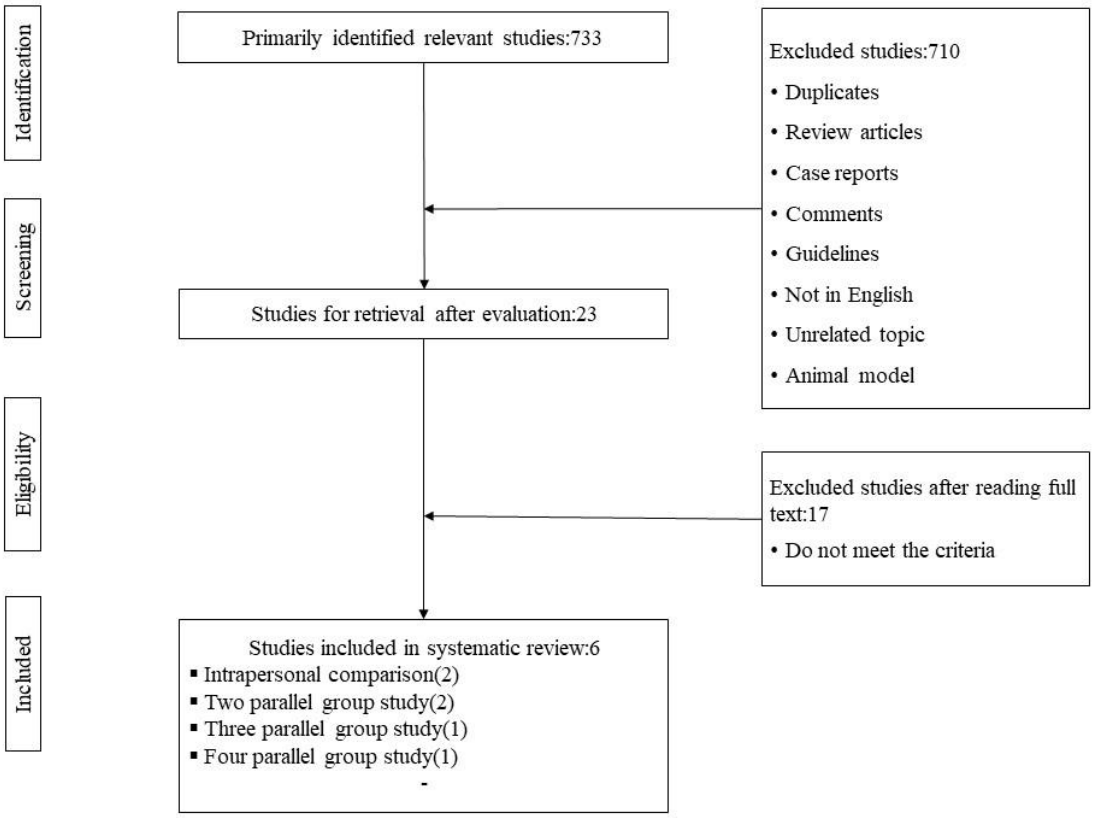

Figure 1 Flow diagram for data selection

The studies can be categorized into treatments not derived from plants and treatments derived from plants. In the non-herbal group, there were 3 studies in which the treatments include topical tacrolimus and topical calcipotriol whereas there were 3 studies in herbal-derived groups, see Table 2.

Among studies with non-herbal interventions, there were two studies that used the topical tacrolimus in the intervention group. Schnopp et al (2002) showed that after 4 weeks of treatment in patients with dyshidrotic HE, a significant decline in DASI score was seen in both topical tacrolimus treated side and topical mometasone furoate treated side, with the former from (18± 12.68) to (9) and the latter from (18.5±6.9) to (7.5) with (p value-<0.001) respectively. However, no significant difference in DASI score reduction between two sides was found (p=0.559), see Table 2 ,3 and 4 (Schnopp et al., 2002).

Similarly, Katsarou et al (2012) researched on patients with allergic contact HE using 0.1% tacrolimus and topical 0.1% mometasone furoate with 15 participants in each group. The result pointed out that VAS score that measure clinical signs such as redness, infiltration, vesiculation, desquamation, cracks, and pruritus decreased significantly in both groups with ($p<0.05$) respectively. The two groups were not significantly different in decreasing the clinical signs after 12-week-treatment ($p>0.05$), see Table 2 ,3 and 4 (Katsarou et al., 2012).

In 2019, an intra-individual study comparing the calcipotriol ointment with topical corticosteroid was conducted on 13 participants. It showed that after 8weeks of treatment, the mean HECSI score of both calcipotriol ointment treated sides and desoximetasone treated sides were declined significantly, with the former from (36.00 ±13.54) to (8.69±7.25), and the latter from (34.46±14.22) to (8.3±6.93), with (p value-0.001) respectively, see Table 2, and 3. Interestingly, no statistically significant difference was seen between

the two groups at every visit (p=0.84) (Juntongjin & Pongprasert, 2019), see Table 4. In addition to this, all participants completed the trial, (Juntongjin & Pongprasert, 2019).

There were three articles that the interventions were derived from plants or leaves. In 2014, a study was done on 30 participants using 5% fumaric acid and using 0.1% triamcinolone on 28 participants for 4 weeks. A significant decline in the EASI score was seen in the fumaric acid group as well as in the corticosteroid group with the former from (43.4) to (3) and the latter from (75.4) to (1.2) with ($p < 0.001$) respectively. However, triamcinolone caused a decline in EASI score significantly better than topical 5% fumaric acid with ($p<0.001$) (Jowkar et al., 2014), see Table 2,3 and 4.

The three-arm research which lasted for 4 weeks was conducted on 52 participants by using Nigella ointment, Eucerin, and 0.1% betamethasone. A significant HECSI score reduction was seen all three groups with topical 2%Nigella ointment group from (39.89±34.85) to (8.78±12.83), with topical 0.1% betamethasone group from (42±33.27) to (7.82±4.75), and with Eucerin group from (31.22±18.63) to (19.33±16.86) with ($p<0.05$) respectively. The severity score reduction of Eucerin was significantly lower than that of both betamethasone and Nigella ointment with (p=0.012), and (p=0.003) respectively. There were 8 participants who lost the follow up with no serious adverse effects reported. No statistically significance difference between Nigella and betamethasone was found in terms of mean HECSI score reduction (p=0.99) (Yousefi et al., 2013).

Lastly, a four-parallel-group study was conducted for 4 weeks on CHE patients with 15 participants in each group. A significant reduction in HECSI score was found in all four groups with betamethasone from (66.27±26.29) to (10.54±9.05), with pumpkin ointment from (64.82±12.72) to (38.72±4.51), with almond ointment from (58.45±13.39) to (44.09±8.2), and with Eucerin from (58.3±9.69) to (49.8±3.11), with ($p <0.05$) respectively. Moreover, it described that betamethasone ointment significantly improved HE greater than pumpkin ointment, almond ointment, and Eucerin ($p<0.001$) respectively (Khademi et al., 2020), see Table 2,3 and 4.

4.2 Discussion

HE is one of the most common skin diseases with a yearly prevalence of more than 10%. It was said that about one-third of HE patients were facing problems with their working capacity, and working hours due to HE and leading to financial problems (Juntongjin & Pongprasert, 2019). In addition to this, due to the frequent, chronic, and relapsing nature of CHE, the patients suffer from not only physical but also mental burdens in the long run.

Even though topical corticosteroids can reduce inflammation, and proliferation, the use of them for long term can induce both local and systemic side effects. For this reason, the efficacies of non-herbal and herbal topical alternative treatments have been studied through many trials till now.

Table 1 Characteristics and outcomes of studies based on non-herbal and herbal interventions

Studies, Year	Types of CHE	Interventions	Assessment	Before		After		MD	P value
				(mean±SD)	N	(mean±SD)	N	(Before-After)	
Non-herbal interventions									
Schnopp, 2002	Dyshidrotic HE	0.1%Tacrolimus ointment	DASI	18± 12.68	16	9	16	9	<0.05
Katsarou, 2012	Patch test positive CHE	0.1%Tacrolimus ointment	VAS	Erythema-1.9 Infiltration-0.97 Vesiculation-0.6 Desquamation-1.5 Cracks-1.12 Itching-2.07	15	Erythema-0.82 Infiltration-0.5 Vesiculation-0.22 Desquamation-0.3 Cracks-0.20 Itching-0.6	15	1.08 0.47 0.38 1.2 0.92 1.47	0.001 0.004 0.013 0.001 0.002 0.001
Jungtongjin, 2019	Mild-moderate CHE	0.005%Calcipotriol ointment	HECSI	36±13.54	13	8.69±3.25	13	27.31±13.92	0.001
Herbal interventions									
Jowkar, 2014	CHE	5%Fumaric acid cream	EASI	43.4	30	3	30	40.4	<0.001
Khademi, 2020	58.30 ±9.69	Pumpkin ointment	HECSI	64.82±12.72	15	38.72±4.51	14	26.1±13.5	0.012
	58.45 ±13.39	Almond ointment		58.45±13.39	15	44.09±8.2	13	14.36±15.7	<0.01
	64.82 ±12.72	Eucerin		58.3±9.69	15	49.8±3.11	13	8.5±10.18	<0.01
Yousefi, 2013	HE due to AD or ID or occupational dermatitis	Nigella ointment	HECSI,	39.89±34.85	18	8.78±12.83	18	31.11±1.30	<0.001
		Eucerin ointment		31.22±18.63	19	19.33±16.86	19	11.89±0.67	<0.01

Table 2 Characteristics and outcomes of studies based on topical corticosteroids

Studies, Year	Types of CHE	Type of topical corticosteroid	Assessment	Before		After		Mean difference (before-after)	P value
				(mean±SD)	N	(mean±SD)	N		
Schnopp, 2002	Dyshidrotic HE	0.1%Mometasone furoate ointment	DASI	18.5±6.9	16	7.5	16	11	<0.001
Katsarou, 2012	Patch test positive CHE	0.1%Mometasone furoate ointment	VAS	Erythema-1.74 Infiltration-0.84 Vesiculation-0.64 Desquamation-1.37 Cracks-0.87 Itching-2	15	Erythema-0.6 Infiltration-0.37 Vesiculation-0.27 Desquamation-0.13 Cracks-0.2 Itching-0.47	15	1.14 0.47 0.37 1.24 0.67 1.53	<0.001 0.004 0.013 <0.001 0.003 <0.001
Jungtongjin, 2019	Mild-moderate CHE	0.25% Desoximetasone ointment	HECSI	34.46±14.22	13	8.3±3.42	13	26.16±14.63	0.001
Jowkar, 2014	CHE	0.1%Triamcinolone cream	EASI	75.4	28	1.2	28	74.2	<0.001
Khademi, 2020	58.30 ±9.69	0.1% Betamethasone ointment	HECSI	66.27±26.29	15	10.54±9.05	13	55.73±27.80	0.002
Yousefi, 2013	HE due to AD or ID or occupational dermatitis	0.1% Betamethasone ointment	HECSI,	42±33.27	15	7.82±4.75	15	34.18±33.60	<0.001

Table 3 Comparison of HE severity reduction efficacy between topical non-steroidal interventions and topical corticosteroids

Study, Year	Type of non-steroidal interventions	Topical non-steroidal Intervention	Topical corticosteroid	Mean difference between intervention and topical corticosteroid	P value
		Mean Difference	Mean Difference		
Schnopp,2002	0.1%Tacrolimus ointment	9	11	-2	0.559
Katsarou,2012	0.1%Tacrolimus ointment	Erythema-1.08	Erythema-1.14	-0.06	>0.005
		Infiltration-0.47	Infiltration-0.47	0.00	
		Vesiculaton-0.38	Vesiculaton-0.37	0.01	
		Desquamation-1.2	Desquamation-1.24	-0.04	
		Cracks-0.92	Cracks-0.67	0.25	
		Itchiness-1.47	Itchiness-1.53	-0.06	
Jungtongjin,2019	0.005%Calcipotriol ointment	27.31	26.16±14.63	-1.15	0.84
Jowkar,2014	5%Fumaric acid cream	40.4	74.2	-33.8	<0.001
Khademi,2020	Pumpkin ointment	26.1±13.5	55.73±27.80	-29.63	<0.001
	Almond ointment	14.36±15.7	55.73±27.80	-41.37	<0.001
	Eucerin	8.5±10.18	55.73±27.80	-47.23	<0.001
Yousefi, 2013	Nigella ointment	31.11±1.30	34.18±33.60	-3.07	0.7
	Eucerin ointment	11.89±0.67	34.18±33.60	-22.29	0.012

Regarding non-herbal topical alternative treatments, topical calcineurin inhibitors like tacrolimus ointment have already received approval for the treatment of AD (Schnopp et al., 2002). Diepgen et al (2015) suggested that they should be considered to use alternatively or together with topical corticosteroids in CHE to reduce the side effects of steroids (Diepgen et al., 2015). This review suggests that topical 0.1%tacrolimus ointment can be used alternatively with topical corticosteroid in long-standing dyshidrotic palmar HE as well as in allergic HE(Katsarou et al., 2012; Schnopp et al., 2002).

Topical vitamin D analogue is an already used treatment for psoriasis due to its antiproliferative action and modulation of keratinocyte differentiation function (Juntongjin & Pongprasert, 2019). There were two previous studies using vitamin D analogue treatment on HE. Egawa confirmed that treating with topical vitamin D analogues for 2-8 weeks was promising and effective for hyperkeratotic palmoplantar HE (Egawa, 2005). In another study done in 2015, combined calcipotriol with betamethasone ointment showed excellent therapeutic response in treating refractory CHE after 5-24 weeks of treatment(Yang & Chang, 2015). The result of our systematic review showed that topical vitamin D analogue was useful as the substitute of topical steroids in treating CHE especially hyperkeratotic HE, and future long-term research with a large number of participants should be conducted (Juntongjin & Pongprasert, 2019).

Regarding plant-derived topical steroid-free treatments, fumaria parviflora extract has immune modulatory activity and a study done in 2005 showed that the use of oral fumaric acid esters was effective in the treatment of severe psoriasis (Harries et al., 2005).In 2011, a study proved that the efficacy of 4% fumaria parviflora cream was superior to that of placebo in treating HE after 4 weeks of treatment (Jowkar et al., 2011). However,our systematic review showed that improvement in HE caused by 5% fumaric acid was not comparable to that of topical 0.1% triamcinolone cream and this lead to a suggestion for more trials using a higher concentration of fumaric acid (Jowkar et al., 2014).

Regarding another herbal topical treatment, Kalus (Kalus et al., 2003) described that Nigella oil was useful in subsiding the symptoms related to allergies such as atopic dermatitis (AD), rhino conjunctivitis, and asthma. There was only a single study conducted on CHE patients using Nigella ointment and it was included in our systematic review. The result showed that Nigella ointment can improve the HE as comparable as topical corticosteroid with no adverse effect and the efficacy of Nigella ointment was superior to that of Eucerin (Yousefi et al., 2013). For this reason, more trials using Nigella ointment should be conducted in the future.

Lastly, the efficacies of pumpkin ointment as well as almond ointment were assessed together with betamethasone ointment and Eucerin in a four-parallel trial conducted by Khademi et al (Khademi et al., 2020). There was no previous study using those ointments in treatment of CHE before. Based on our study result, it can be regarded that pumpkin ointment had better efficacy in reducing the severity of HE then almond ointment and Eucerin. However, the efficacy of pumpkin ointment was not as comparable to that of topical betamethasone in treating CHE. Therefore, further trials are needed as there was only a single study assessing the efficacy of pumpkin ointment and almond ointment.

In this systematic review, there were two studies that used Eucerin as a type of intervention without mentioning exactly about the type and contents of Eucerin. As the data from the corresponding authors are not accessible, we conducted the systematic review by using only the available data of Eucerin in those studies.

5. Conclusion

This review demonstrated that non-herbal steroid-free topical treatment had comparable efficacy to topical corticosteroids, whereas most of the herbal steroid-free topical treatments were not as effective as topical corticosteroids. Therefore, our systemic review suggests that non-herbal single topical treatments may be the other options for the treatment of CHE.

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7. References

Agner, T., & Elsner, P. (2020). Hand eczema: epidemiology, prognosis and prevention. *Journal of the European Academy of Dermatology and Venereology*, *34*, 4-12. https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/jdv.16061?download=true

Bissonnette, R., Worm, M., Gerlach, B., Guenther, L., Cambazard, F., Ruzicka, T., Maares, J., & Brown, T. (2010). Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *British Journal of Dermatology*, *162*(2), 420-426.

Carlsson, A., Svensson, Å., Anderson, C. D., Baranovskaya, I., Hindsén-Stenström, M., Holt, I., Meding, B., Stenberg, B., Stenlund, H., & Gånemo, A. (2017). Scoring of hand eczema: good reliability of hand eczema extent score. *Acta Dermato-Venereologica*, *97*(2), 193-197.

Diepgen, T. L., Agner, T., Aberer, W., Berth-Jones, J., Cambazard, F., Elsner, P., McFadden, J., & Coenraads, P. J. (2007). Management of chronic hand eczema. *Contact Dermatitis*, *57*(4), 203-210.

Diepgen, T. L., Andersen, K. E., Chosidow, O., Coenraads, P. J., Elsner, P., English, J., Fartasch, M., Gimenez-Arnau, A., Nixon, R., Sasseville, D., & Agner, T. (2015). Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges*, *13*(1), e1-22. https://doi.org/10.1111/ddg.12510_1

Dubin, C., Del Duca, E., & Guttman-Yassky, E. (2020). Drugs for the Treatment of Chronic Hand Eczema: Successes and Key Challenges. *Ther Clin Risk Manag*, *16*, 1319-1332. https://doi.org/10.2147/tcrm.S292504

Duman, N., & Uzunali, E. (2015). Clinical assessment of the severity of chronic hand eczema: correlations between six assessment methods. *The European Research Journal*, *1*(2), 44-49.

Egawa, K. (2005). Topical vitamin D3 derivatives in treating hyperkeratotic palmoplantar eczema: a report of five patients. *The Journal of dermatology*, *32*(5), 381-386.

Elsner, P., & Agner, T. (2020). Hand eczema: treatment. *Journal of the European Academy of Dermatology and Venereology*, *34*, 13-21. https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/jdv.16062?download=true

Harries, M. J., Chalmers, R., & Griffiths, C. (2005). Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *British Journal of Dermatology*, *153*(3), 549-551.

Jowkar, F., Jamshidzadeh, A., Yazdi, A. M., & Pasalar, M. (2011). The effects of fumaria parviflora L extract on chronic hand eczema: a randomized double-blind placebo controlled clinical trial. *Iranian Red Crescent Medical Journal*, *13*(11), 824.

Jowkar, F., Saki, N., Mokhtarpour, A., & Saki, M. R. (2014). Comparison of fumaric acid 5% cream versus triamcinolone 0.1% cream in the treatment of hand eczema [Comparative Study; Journal Article; Randomized Controlled Trial]. *Acta medica Iranica*, *52*(7), 528-531. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00999261/full

Juntongjin, P., & Pongprasert, R. (2019). Calcipotriol ointment shows comparable efficacy to topical steroids in chronic hand eczema [Article]. *Dermatologic Therapy*, *32*(4), Article e12956. https://doi.org/10.1111/dth.12956

Kalus, U., Pruss, A., Bystron, J., Jurecka, M., Smekalova, A., Lichius, J. J., & Kiesewetter, H. (2003). Effect of Nigella sativa (black seed) on subjective feeling in patients with allergic diseases. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *17*(10), 1209-1214.

Katsarou, A., Makris, M., Papagiannaki, K., Lagogianni, E., Tagka, A., & Kalogeromitros, D. (2012). Tacrolimus 0.1% vs mometasone furoate topical treatment in allergic contact hand eczema: A prospective randomized clinical study [Article]. *European Journal of Dermatology*, *22*(2), 192-196. https://doi.org/10.1684/ejd.2011.1615

Khademi, A., Mansuri, P., Pahlevan, D., Bozorgi, M., Nasiri, M., Hejazi, S., Azizian, Z., & Shirbeigi, L. (2020). Efficacy of Pumpkin Ointment in Treatment of Chronic Hand Eczema: A Randomized, Active-Controlled, Double Blind Clinical Trial. *Iran J Public Health*, *49*(7), 1339-1347. https://doi.org/10.18502/ijph.v49i7.3588

Mehrpooya, M., Ghaed-Amini, F., Firozian, F., Mohammadi, Y., & Alirezaei, P. (2020). Beneficial effects of adding topical atorvastatin 5% cream to topical betamethasone 1% ointment on chronic hand eczema [Article]. *Archives of Iranian Medicine*, *23*(9), 605-613. https://doi.org/10.34172/aim.2020.71

Nakagawa, H., Nemoto, O., Igarashi, A., Saeki, H., Murata, R., Kaino, H., & Nagata, T. (2020). Long-term safety and efficacy of delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with atopic dermatitis. *The Journal of dermatology*, *47*(2), 114-120.

Quaade, A. S., Simonsen, A. B., Halling, A. S., Thyssen, J. P., & Johansen, J. D. (2021). Prevalence, incidence, and severity of hand eczema in the general population–A systematic review and meta-analysis. *Contact Dermatitis*, *84*(6), 361-374. https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/cod.13804?download=true

Schnopp, C., Remling, R., Möhrenschlager, M., Weigl, L., Ring, J., & Abeck, D. (2002). Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: A randomized, observer-blinded trial [Article]. *Journal of the American Academy of Dermatology*, *46*(1), 73-77. https://doi.org/10.1067/mjd.2002.117856

Worm, M., Bauer, A., Elsner, P., Mahler, V., Molin, S., & Nielsen, T. S. (2020). Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. *British Journal of Dermatology*, *182*(5), 1103-1110.

Yang, M., & Chang, J. M. (2015). Successful treatment of refractory chronic hand eczema with calcipotriol/betamethasone ointment: A report of three cases. *Experimental and Therapeutic Medicine*, *10*(5), 1943-1946.

Yousefi, M., Barikbin, B., Kamalinejad, M., Abolhasani, E., Ebadi, A., Younespour, S., Manouchehrian, M., & Hejazi, S. (2013). Comparison of therapeutic effect of topical Nigella with Betamethasone and Eucerin in hand eczema [Comparative Study; Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't]. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *27*(12), 1498-1504. https://doi.org/10.1111/jdv.12033

Zeichner, J. A., Berson, D., & Donald, A. (2018). The Use of an Over-the-Counter Hand Cream With Sweet Almond Oil for the Treatment of Hand Dermatitis. *Journal of drugs in dermatology: JDD*, *17*(1), 78-82.