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Review Article

Review of Medicinal Remedies on Hand Eczema Based on Iranian Traditional Medicine: A Narrative Review Article

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Abstract

Background: Hand Eczema (HE) is a dermatological disorder with frequent relapses and multiple causes such as atopic, allergic and irritant contact dermatitis. The management is complex because of the wide range of different pathogenesis. Efficacy of some of available treatments is not well established and it can affect patients' quality of life significantly.

Methods: Reports on HE such as diagnosis, pathophysiology, pharmacological and nonpharmacological therapy that described in medieval Iranian medicine, were gathered and analyzed from selected medical and pharmaceutical textbooks of Iranian Traditional Medicine (ITM). The search of databases such as PubMed, EMBASE/Excerpta Medica, Science direct, Scopus, Google scholar, Web of science, Sid, Iran medex, Irandoc, was performed to reconfirm the efficacy of ITM remedies in conventional medicine from 1980-Jan-1 to 2015-Dec-30.

Results: According to their opinion, HE is highly associated with liver function. This disorder was categorized into two main types as wet and dry ones. Most Iranian textbook explained signs of HE, as excessive skin itching, redness, burning and dryness. Treatments recommended by Iranian scientists were lifestyle modification, dietary intervention and performing the rules of prevention as well as herbal therapy and special manipulations.

Conclusion: Iranian practitioners believed that, six essential principles, diet therapy and medicinal plants have high impact on treatment of HE. These remedies based on Iranian scholar's experiences might be useful for further studies to the management of HE.

Keywords: Hand eczema, Herbal medicine, Iranian traditional medicine, Medicinal remedies, Diet therapy, Lifestyle modification

Introduction

Hand Eczema (HE) is a common dermatological disorder. This complication is an inflammatory response of the skin has annual prevalence of 10% and may cover more than 4% of the population (1, 2). HE is a multifactorial disorder and its pathophysiology is not yet well understood. Evidences have suggested the impaired permeability barrier function of the skin in the pathogenesis of this disease (3-5). HE is typically presented by itching, erythema, papules, vesicles, fissures, scaling and hyperkeratosis accompanied with pain (6). Emollient and topical corticosteroids are the first line of treatment (7).

Interventions concerning the usage of complementary medicine are considerably high with a great tendency towards the use of complementary

medicine in dermatology. According to Iranian Traditional Medicine (ITM), internal factors as well as external factors has very important role on HE. Nowadays lots of information from remained manuscripts of traditional medicine, which can help dermatologists, exist in medieval Iranian manuscripts (8). Several skin diseases with similar symptoms of HE have been proposed in ITM texts. Dry skin, itching, and scaling are the main characteristics of these diseases (9, 10). During the medieval period, Iranian practitioners gathered the medical information from other civilizations and supplemented the received data with their own findings and experiments (11, 12).

Accordingly, medical and pharmaceutical manuscripts of Iranian scientists contain considerable information on various ailment and treatment strategies by lifestyle modification and the usage of medicinal plants. Among these, mentioned nutritional and pharmacological aspects of HE would be useful. Hence, the present article has been carried out to gather the most considerable medieval Iranian knowledge in HE as well as those therapeutic approaches.

Methods

Definition, classification, sign and symptoms and causes of HE as well as recommended treatments were collected. The whole process of collecting literatures was started by thorough; line-by-line reading of the extracted materials and key sentences. Then, concepts were defined and coded. In the next step, by constant comparison of data and codes, significant phrases about Saafe, Ghuba, Hekke and Taghashof-e-atraf such as classification, sign and symptoms and causes and treatments were identified and registered properly.

These manuscripts were found at Iranian college libraries. They were considered as the most important texts among manuscripts from medieval Persia. Whole aspects of this disease was derived from medical text books of ITM including the Kholasato-tajarob by Bahaodoleh Razi (10^{th}), Canon of medicine by Avicenna (11^{th}), Al-Aghraz-al-Tibbiyah by Jorjani (12^{th}), Tebbe- Akbari by Arzani (18^{th}) and Exir-e-Azam by Azam Khan (19^{th}).

Pharmacological treatment of HE in medieval period were gathered from Iranian pharmaceutical manuscripts containing the Canon of Medicine, Al-Havi (9^{th} and 10^{th}) and Makhzan al-advieh (18^{th}) (13-19). To find the exact scientific names of the plants, the other textbooks such as "Dictionary of Medicinal Plants" (20), "Dictionary of Iranian Plant Names" (21), "Popular Medicinal Plants of Iran" (22), "Matching the Old Medicinal Plant Names with Scientific Terminology" (23) were studied. PubMed, EMBASE/Excerpta Medica, Science direct, Scopus, Google scholar, Web of science, Sid, Iran medex, Irandoc were searched with all scientific names of plants separately from 1980-Jan-1 to 2015-Dec-30.

Besides, Searches through the references of articles retrieved, authoritative texts of dermatology and personal contacts with experts in ITM was performed. Inclusion criteria of all selected articles were any clinical, animal or in vitro evidence of the efficacy and pharmacological mechanisms on treatment of HE. Any studies which exhibited apparent efficacy or indirect effectiveness on HE were selected for this current research.. The publications without available full text, unpublished data, letters to the editor, case reports and experimental studies without proven biological effects, older studies (before 1980) were excluded from the study. Duplication was also avoided by excluding multiple copies of the same article in different databases. Finally, this research included the articles reviewed for more relevant studies and publication in English.

Results

Hand Eczema, current medicine

As a dermatological disorder, HE was first described in the 19th century by general manifestations of itching, redness, scaling, vesicles, hyperkeratosis, erosions and fissuring (24, 25). HE is a multifactorial disease includes both endogenous and exogenous factors. Accordingly, HE is divided into three types, irritant, allergic, and atopic

dermatitis (26-28). Irritant contact dermatitis, the most common type of hand dermatitis results from skin exposure to exogenous irritant agents including detergents, organic solvents (1) and water itself that damage or remove the protective layers of the upper epidermis. Allergic contact dermatitis is much less common than irritant contact dermatitis which is a delayed-type hypersensitivity (type IV hypersensitivity reaction) to some substances with high sensitizing potential like rubber, plastics, nickel, biocides, fragrance and topical antibiotics (24, 29, 30). Atopic dermatitis is a genetic or immune system defect of the skin barrier, facilitating sensitization to food or airborne allergens, as well as infections (31). However, HE classified based on morphology such ass fissured, vesicular, pulpitis, nummular, pompholyx and hyperkeratotic types (32-34). Genetic factors also play a role in HE (35, 36). Main clinical approaches in HE include lifestyle modification and systemic therapy to prevent and manage the complications (37).

Hand Eczema, medieval definition, etiology, categories and clinical manifestation

The terms "Saafe, Ghuba, Hekke and Taghashof-e-atraf" were used by early Iranian scientists to define and describe as eczema. The word eczema is a Greek word meaning "to boil out" first used by a physician in the Byzantine court in the sixth century (24, 38). In Iranian manuscripts HE is highly associated with liver function. The humor production in the liver was impaired and as a result, inappropriate humors cannot be absorbed into the target organs and enters beneath the skin by vessels therefore itching, rash, vesicles and cracking of the skin appears progressively (13, 17, 39). Furthermore, shifting of abnormal humors from internal organs into the skin was noted as another factor for this problem (17). Like the basic mechanisms of humoral theory (40) the disorder might have been resulted from an imbalance in the liver temperament as well as whole body. Therefore, treatment was based on temperament modification to reach the balanced state (41). Accordingly, Iranian medical practitioners categorized the disorder into two main types as wet and dry ones. The wet type or exudative eczema was reported to be accompanied by pruritus and discharge. This type is severe and a large area of the skin involved and it even may lead to ulcers. The dry type or non-exudative eczema, itching and erythema is without any discharge. This type is mild and limited to the skin surface (42). Iranian scientists remarked eczema results from mixing of abnormal yellow bile and black bile humors with blood. These abnormal humors change the blood quality. Hence, the expulsion of abnormal humors towards the skin can cause itching, burning, scales, crust and vesicles (13, 18). Based on Avicenna's view, human body is composed of four humors, blood or Sanguine, yellow bile or Safra, phlegm and black bile or Melancholic, produced in the liver and their correct ratio and the specific balance of humors based on their quality and quantity is needed for health (43). Liver is the main source of humoral production according to all authoritative ITM such as Al-Havi and Canon of medicine (13, 15-18, 42). All management strategies and medications considered for the impaired liver should also be applied for this disorder, as it was mentioned by Iranian practitioners (13). Table 1 represents the classification of HE according to ITM. An overview and comparison between modern aspects of HE and medieval description of HE is represented in Table 2.

Clinical interventions

In reviewed manuscripts, there is an immense amount of information including recommendations and management strategies as well as preventive approaches for HE.

For health preservation and disease prevention issues, there are six essential principles (involving observation and optimization of six main parameters as climate, eating and drinking, retention and evacuation, repose and movement, sleep and wakefulness as well as sensual qualities) considered by early Iranian practitioners. These parameters are explained as lifestyle factors in conventional medicine and should be observed before any medications (37).

Table1: Medieval classification of hand eczema

Types of Hand Eczema	Etiology	Sign symptoms	Treatment
Wet	Wet dystemperament of liver		Life style modification, food ,herbal medications with cold temperament
Blood(Sanguine)		Redness, itching, burning, blood secretion, Severe redness, acute	
Phlegmatic		itching, White rash and wide, diluted blood secretion	
Dry	Dry dystemperament of liver		Life style modification, food , herbal medicine with wet temperament
Yellow bile(Safra)		Redness, severe pain and pruritus, burning, dryness, acute	
Black bile(Melancholic)		Low pain and pruritus, dark rash, Chronic	

Table 2: The comparison of hand eczema in current medicine and traditional medicine

	Traditional medicine	Current medicine
Definition	A disease which constitutes red rashes and excessive itching, developing more on the hands and between the fingers. (13, 17)	A common dermatological disorder an inflammation of the skin of the hands characterized by sever itching in hands.(3)
Signs/Symptoms Categorization	Redness, Itching, burning, secretion in wet type	Erythema, itching, dryness, vesicles, papules
Etiology	Dystemperament of liver, wet or dry	Irritants agents, allergy to a specific substance, endogenous factors (27)
Diagnosis	Clinical manifestations and signs and symptoms mentioned in medieval texts	Past personal and family history (exposure to irritants and allergens or atopic dermatitis), Physical examination, Patch testing, Prick tests and RAST(radioallergosorbent test) (44)
Prevention	Observing the six essential principles for the health maintenance. (climate, eating and drinking, retention and evacuation, repose and movement, sleep and wakefulness and sensual qualities)	Lifestyle modification, Avoidance of irritants (and allergens), frequent application of lipid-rich emollients (ointments), use of gloves (29, 45)
Interventions	Life style modification and Nutritional therapies, Herbal remedies (simple or compound medicaments), special physical manipulations (13, 16, 17)	Lifestyle changes and topical corticosteroids, Calcineurin Inhibitors (such as pimecrolimus), Phototherapy (PUVA), Systemic treatments (such as Alitretinoin, Acitretin, Systemic Corticosteroids) (1)

Medicinal manuscripts of ITM suggest plenty of natural remedies for the management of HE. Natural medicines were simple herbal medicines or in combination to other medicaments.

These approaches were presented in three main categories. The first approach was lifestyle modification based on diet therapy, which was the hallmark of the ITM treatment methodology and often suggested as the first line of treatment or as an adjuvant therapy with other modalities of treatment. In this condition, easily digestible food, hydrator and Heat-lowering temperament foods capable of producing a sufficient amount of pure blood in the body was administered (46). Accordingly, food or beverages such as pottage of mung bean (*Vigna radiata*) with fresh Spinach (*Spinacia oleracea*) and Zucchini (*Cucurbita pepo*), beer, barely soup, oxymel (a mixture of honey and vinegar), verjuice pottage and pomegranate pottage were applied for patients (17). The second approach is the administration of simple or compound herbal forms. Herbs like Will Fumitory (*Fumaria parviflora Lam*), Jujube (*Ziziphus vulgaris L.*), extract of pumpkin (*Cucurbita Pepo DC*), Cucumber (*Cucumis sativus L.*), Common Pursalane (*Portulaca oleracea L.*) seeds were suggested (13). Most cited natural medicines concerned to HE are shown in Table 3.

Table 3: Prevalent medicinal plant for the management of hand eczema

scientific name	Traditional name	part used in ITM	Current findings	
			Anti-inflammatory	**Immunomodulatory**
Apium graveolens L.	Karafs	Leaves	Ethanol-water extract of leaves exhibit anti-inflammatory (48).	
Bryonia dioica Jacq.	Fasherestin	Fruits	Triterpene glycosides of the roots of *Bryonia dioica* in mice showed anti-inflammatory effects, (49).	
Brassica oleracea L.	Karnab	Leaves	Cabbage juice exhibited anti-inflammatory via anti-inflammatory cytokine interleukin (IL)-10 and pro-inflammatory cytokine (50).	Suiforaphane stimulated humoral and cell mediated immune system with enhanced stem cell proliferation (51).
Brassica rapa L.	Shaljam	Leaves	Indole-containing fraction showed anti-inflammatory activity via inhibition of inducible nitric oxide synthase, tumor necrosis factor-α and interleukin-6.(52).	Different extract showed immunomodulatory activity in animal models of delayed-type hypersensitivity (53).
Convolvulus scammonia L.	Saghmunia	Dried juice of root		
Delphinium staphisagria L.	Zabibol-jabal	Fruits	Oral administration of alkaloids extracts of *Delphinium staphisagria* revealed paw volume in carrageenan-induced rat paw edema and experimental traumatism in rats (54).	Prepared total and Protein extracts of the plant showed a significant immunostimulatory activity (55).
Ecballium elaterium (L.) A.Rich.	Ghesaol-hemar	Fruits	Fruit juice of *Ecballium elaterium* and its triterpenoid constituent, cucurbitacin B, in mice showed inhibition of edema (56).	Lymphocytes treated by *Cucurbitacin E* isolated showed cytotoxic enhancement against two human cancer cell lines (57).
Lagoecia cuminoides L.	gherdamana	Fruits		
Lepidium sativum L.	Habol-reshad	Seeds	Dietary supplementation of seed oil increased ALA, EPA and DHA levels in the membrane lipids of immunocompetent Cells. (58).	Prepared total and Protein extracts of the plant tested using showed a significant immunostimulatory activity (55).
Linum usitatissimum L.	Katan	Seeds	Fixed oil inhibited rat paw inflammation (59).	
Lawsonia inermis L.	Henna	Leaves		Methanol extract of leaves was effective in the lymphocyte transformation assay. (60)
Moringa oleifera Lam.	baan	Seeds	Oral administration of the aqueous seed extract caused reduction in leukocyte migration. All of the doses tested showed effectiveness in reducing cell migration (61).	The production of the humoral antibody titer was significantly ameliorated by the ethanolic extract of seeds (62).
Melissa officinalis L.	Badran-jbooyeh	Leaves	Pretreatment with *Melissa officinalis L.* Aqueous extract significantly reduced inflammagen-induced paw edema in rats (63).	
Nerium oleander L.	Defli	Leaves	Ethanolic extract of flowerers possess activity in carrageenan- induced hind paw edema in mice (64).	Aqueous extract of leaves showed immunomudalatory activity in rabbits (65).
Nigella sativa L.	Shuniz	Seeds	Seed oil and its main constituent, thymoquinine, were effective in vitro and in vivo models (66).	The immunomodulatory effect of seeds and involved mechanisms were gathered in a review article wrote by Salem (66).
Portulaca oleracea L.	Baghlatol-hamgha	Leaves	10% ethanolic extract of aerial part inhibited inflammation in animal models (67).	
Rumex conglomeratus Murray.	Hommaaz	Root		
Ricinus communis L.	karchak	Seeds	The methanolic extract of the *Ricinuscommunis* root possess significant anti-inflammatory activity (68).	The isolated compound of R. communis showed predominantly significant activity on human neutrophils (69).
Reum rhabarbarum L.	Ribas	Seeds	Aloe- emodin exhibit anti-inflammatory activity on cell line. (70).	
Strychnos Nux vomica L.	Azaraghi	Seeds	Brucine N-oxide showed stronger inhibitory effect than brucine in carrageenan-induced rat paw edema (71).	S. nux-vomica showed suppressive activity on allergen-specific IgE antibody response (72).
Vitis vinifera L.	Enab	Fruits	That extract of *Vitis vinifera* was active against COX-I and COX-II (73)	Resveratrol, polyphenol found in grapes, can exert a dose-related regulatory effect on immune function (74)
Viola odorata L.	Banafsaj	Oil prepared from petals	Isolated polysaccharide inhibits inflammation in mice hind paw edema model (75).	
Zizyphus jujuba Mill.	Annab	Fruits, branches	Seed essential oil possesses anti-inflammatory effect on skin inflammation (76).	

In addition, to natural pharmacotherapy, special physical manipulations have also been applied by early Iranian practitioners as the third approaches. These approaches usually involved wet cupping (Hijamat), venesection (Fasd) and emetics (Ghey, moshel) applied regarding to the patient's dystemperament. Additionally, to physical manipulation, topical treatments were also recommended such as anointment of the skin and bathing skin with a traditional medical bath (abzan). They believed this procedure would tighten the skin (9, 47).

Discussion

Due to increasing industrial environment in the 21st century, it is important to find the exact etiology of HE and use appropriate preventive and treatment strategies (77). There are some similarities between the disorders of Saafe, Ghuba, Hekke and Taghashof-e-atraf and what is currently accepted as HE. Redness, pruritus, pain and burning sensation are the main similarities. Lifestyle has an important influence on occurrence of HE and patients may have no information about the relation between their disorder and food-induced eczema. Aeroallergens and food allergens are related factors of atopic eczema (78). Some foods like pizza, beef, fish, poultry pork, Garlic, cayenne pepper, onion, broccoli, cauliflower, potato, spices, and food additives may create contact eczema in occupational and non-occupational settings (79). The eczematous rash develops within 6–48 h and subsides within several days (80). With reference to the management of HE, many instructions about health maintenance were recommended by Iranian scholars (81). The six essential principles were highly emphasized by Iranian practitioners. Like these rules, current medicine has also significant recommendation in this field. Avoidance of air pollution (82, 83) appropriate exercise and sport (84), avoiding stress and psychological tensions (85), appropriate sleep (86) as well as eluding some special foods and drinks and proper nutritional regimen (79) have high impact on HE. Most considered mechanisms for these medieval herbs were anti-inflammatory and immunomodulatory effects. Iranian practitioners believed that there are differences between types of temperaments in patients. Hence, they differentiated HE regarding the patient's temperament and used the related medication. Conventional medicine also accept this fact as pharmacogenetics (87). Moreover, differences in temperaments can influence neuroendocrine and immune systems (88). Therefore, medication should be prescribed according to the patient's temperament. Since HE is composed of wet and dry types in ITM, different treatments have been recommended for each type of the disease and patients. We survey the knowledge of medieval Iranian scientists on HE and their pharmacological treatment approaches. Remedies reported in this study might be of beneficial use for further studies in the management of HE and related undesirable effects.

Conclusion

While the management of chronic HE is still inadequate (37) and traditional approaches have found experimental support over the centuries, some of these treatments may still be useful to modern medicine. Furthermore, these medications are natural and may have fewer side effects than synthetic compounds, leading to better patient compliance. These ancient texts showed that medieval physicians were aware of HE and possessed both etiological theories and treatment strategies for this problem. They believed that three basic steps; lifestyle modification, diet therapy and medicinal plants have high impact on treatment. In conclusion there is a need to prepare clinical trials according to ITM remedies in order to demonstrate effectiveness of traditional medicine in HE management.

Ethical 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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References

1. de Leon FJ, Berbegal L, Silvestre JF (2015). Management of Chronic Hand Eczema. *Actas Dermosifiliogr,* 106 (7): 533-44.
2. Thyssen JP, Johansen JD, Linneberg A, Menne T (2010). The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis,* 62 (2): 75-87.
3. Coenraads PJ (2007). Hand eczema is common and multifactorial. J Invest Dermatol, 127 (7): 1568-70.
4. Lan CC, Tu HP, Wu CS, Ko YC, Yu HS, Lu YW, Li WC, Chen YC, Chen GS (2011). Distinct SPINK5 and IL-31 polymorphisms are associated with atopic eczema and non-atopic hand dermatitis in Taiwanese nursing population. *Exp Dermatol,* 20 (12): 975-9.
5. Proksch E, Folster-Holst R, Jensen JM (2006). Skin barrier function, epidermal proliferation and differentiation in eczema. *J Dermatol Sci,* 43 (3): 159-69.
6. Coenraads PJ (2012). Hand eczema. *N Engl J Med,* 367 (19): 1829-37.
7. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, 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.
8. Landis ET, Davis SA, Feldman SR, Taylor S (2014). Complementary and alternative medicine use in dermatology in the United States. *J Altern Complement Med,* 20 (5): 392-8.
9. Aghili Khorasani S (2008). *Moalejate Aghili.* Institute for Islamic and Complementary Medicine,Tehran university of Medical Science; Tehran, pp.: 976-981.
10. Kermani NIE (2009). *Sharh al-Asbab va al-Alamat (Arabic*). Jalaleddin Publications, Qom, p:391.
11. Zargaran A, Zarshenas MM, Mehdizadeh A, Mohagheghzadeh A (2012). Oxymel in medieval Persia. *Pharm Hist (Lond),* 42 (1): 11-3.
12. Zarshenas MM, Zargaran A, Muller J, Mohagheghzadeh A (2013). Nasal drug delivery in traditional persian medicine. *Jundishapur J Nat Pharm Prod,* 8 (3): 144-8.
13. Avicenna (2005) *Al Qanun Fi Al-Tibb (Arabic).* Alaalami library, Beirut, P:158.
14. Avicenna (2005) *Al Qanun Fi Al-Tibb (Arabic).* Alaalami library, Beirut, PP: 393-6.
15. Jorjani S (2006). *Al-Aghraz al- Tibbva val Mabahess al- Alaiia.* University of Tehran, Tehran , P:172.
16. Arzani H (2008). *Tebb akbari.* 1st ed. Jalal al-Din, Qom, pp: 1156-7.
17. Azam Khan M (2004). *Aksir Azam (Persian).* The Institute for Medical History-Islamic and Complementary Medicine, Tehran University of Medical Sciences; Tehran, pp.: 270-5.
18. Razi M (2000). *Alhavi(Arabic).* Dar Al-Kotob Al- ilmiyah, Beyrouth- Lebanon, p.: 305.
19. Aghili M (2004). *Makhzan al adviye (Persian).* Sabz Arang, Tehran, pp.: 145- 450.
20. Soltani A (2004). *Dictionary of Medicinal Plants.* Arjmand. Tehran.
21. Mozaffarian V (2006). *Dictionary of Iranian Plant Names.* Farhang Moaser, Tehran.
22. Amin G (2005). *Popular Medicinal Plants of Iran.* The Institute for Medical History - Islamic and Complementary Medicine, Tehran University of Medical Sciences, Tehran.
23. Ghahraman A, Okhovvat A (2004). *Matching the Old Medicinal Plant Names with Scientific Terminology.* The Institute for Medical

History -Islamic and Complementary Medicine, Tehran University of Medical Sciences, Tehran.
24. Agarwal US, Besarwal RK, Gupta R, Agarwal P, Napalia S (2014). Hand eczema. *Indian J Dermatol,* 59 (3): 213-24.
25. Willan R. (1808). *On Cutaneous Diseases*. Johnson, London, England.
26. Sehgal VN, Srivastava G, Aggarwal AK, Sharma AD (2010). Hand dermatitis/eczema: current management strategy. *J Dermatol,* 37 (7): 593-610.
27. Arshah T, Shambesh M, Grera A, Albaccush M (2008). Eczema in north west of libya. *Libyan J Med,* 1;3(3):134-5.
28. Charan UP, Peter CV, Pulimood SA (2013). Impact of hand eczema severity on quality of life. *Indian Dermatol Online J,* 4 (2): 102-5.
29. Diepgen TL, Agner T, Aberer W, Berth-Jones J, Cambazard F, Elsner P, McFadden J, Coenraads PJ (2007). Management of chronic hand eczema. *Contact Dermatitis,* 57 (4): 203-10.
30. Heymann WR (2006). Hand dermatitis. *J Am Acad Dermatol,* 54 (6): 1078-80.
31. Cipriani F, Dondi A, Ricci G (2014). Recent advances in epidemiology and prevention of atopic eczema. *Pediatr Allergy Immunol,* 25 (7): 630-8.
32. King T, McKenna J, Alexandroff AB (2014). Alitretinoin for the treatment of severe chronic hand eczema. *Patient Prefer Adherence,* 25;8:1629-34.
33. Molin S, Vollmer S, Weiss EH, Weisenseel P, Ruzicka T, Prinz JC (2011). Deletion of the late cornified envelope genes LCE3B and LCE3C may promote chronic hand eczema with allergic contact dermatitis. *J Investig Allergol Clin Immunol,* 21 (6): 472-9.
34. Diepgen TL, Andersen KE, Brandao FM, Bruze M, Bruynzeel DP, Frosch P, Goncalo M, Goossens A, Le Coz CJ, Rustemeyer T, White IR, Agner T (2009). Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol,* 160 (2): 353-8.
35. Lerbaek A, Kyvik KO, Ravn H, Menne T, Agner T (2007). Incidence of hand eczema in a population-based twin cohort: genetic and environmental risk factors. *Br J Dermatol,* 157 (3): 552-7.
36. Bryld LE, Hindsberger C, Kyvik KO, Agner T, Menne T (2003). Risk factors influencing the development of hand eczema in a population-based twin sample. *Br J Dermatol,* 149 (6): 1214-20.
37. English J, Aldridge R, Gawkrodger DJ, Kownacki S, Statham B, White JM, Williams J (2009). Consensus statement on the management of chronic hand eczema. *Clin Exp Dermatol,* 34 (7): 761-9.
38. Hegde P, Hemanth DT, Emmi SV, Shilpa MP, Shindhe PS, Santosh YM (2010). A case discussion on eczema. *Int J Ayurveda Res,* 1 (4): 268-70.
39. Emtiazy M, Keshavarz M, Khodadoost M, Kamalinejad M, Gooshahgir SA, Shahrad Bajestani H, Hashem Dabbaghian F, Alizad M (2012). Relation between Body Humors and Hypercholesterolemia: An Iranian Traditional Medicine Perspective Based on the Teaching of Avicenna. *Iran Red Crescent Med J,* 14 (3): 133-8.
40. Bujalkova M, Straka S, Jureckova A (2001). Hippocrates' humoral pathology in nowaday's reflections. *Bratisl Lek Listy,* 102 (10): 489-92.
41. Rezaeizadeh H, Alizadeh M, Naseri M, Ardakani MS (2009). The traditional Iranian medicine point of view on health and disease. *Iran J Publ Health,* 38 (Suppl. 1): 169-72.
42. Razi B (2000). *Kholasat ol-Tajarob. (Persian).* The Institute for Medical History-Islamic and Complementary Medicine, Tehran University of Medical Sciences, Tehran, pp.: 134-153.
43. Fallahi F, Namdar H, Emaratkar E, Nazem E, Nikbakht Nasrabadi A, Choopani R, Movahhed M, Gooshah Gir AA (2013). Avicenna's view of reperfusion in

myocardial infarction. *Int J Cardiol,* 165 (2): 393-4.
44. Brasch J, Becker D, Aberer W et al. (2014). Guideline contact dermatitis: S1-Guidelines of the German Contact Allergy Group (DKG) of the German Dermatology Society (DDG), the Information Network of Dermatological Clinics (IVDK), the German Society for Allergology and Clinical Immunology (DGAKI), the Working Group for Occupational and Environmental Dermatology (ABD) of the DDG, the Medical Association of German Allergologists (AeDA), the Professional Association of German Dermatologists (BVDD) and the DDG. *Allergo j int,* 23 (4): 126-38.
45. Meding B, Wrangsjö K (2014). *Scope of the Problem: Epidemiology of Hand Eczema*. Textbook of Hand Eczema. Springer, pp 75-84.
46. Siahpoosh MB (2012). Six essential principles of Iranian traditional medicine for maintaining health from the Quran's point of view. *Quran and Medicine,* 1 (4): 101-07.
47. Baghdadi S (1998). *Al-moghni fi tadbirelamraz va marefatol ellal valaraz (Arabic).* Darroalnafaes, Beirut, pp.:217-218.
48. Mencherini T, Cau A, Bianco G, Della Loggia R, Aquino RP, Autore G (2007). An extract of Apium graveolens var. dulce leaves: structure of the major constituent, apiin, and its anti-inflammatory properties. *J Pharm Pharmacol,* 59 (6): 891-7.
49. Ukiya M, Akihisa T, Yasukawa K, Tokuda H, Toriumi M, Koike K, Kimura Y, Nikaido T, Aoi W, Nishino H, Takido M (2002). Anti-inflammatory and anti-tumor-promoting effects of cucurbitane glycosides from the roots of Bryonia dioica. *J Nat Prod,* 65 (2): 179-83.
50. Lin J-Y, Li C-Y, Hwang I-F (2008). Characterisation of the pigment components in red cabbage (Brassica oleracea L. var.) juice and their anti-inflammatory effects on LPS-stimulated murine splenocytes. *Food Chem,* 109 (4): 771-81.
51. Thejass P, Kuttan G (2007). Immunomodulatory activity of Sulforaphane, a naturally occurring isothiocyanate from broccoli (Brassica oleracea). *Phytomedicine,* 14 (7-8): 538-45.
52. Shin J-S, Yun CH, Cho Y-W, Baek N-I, Choi M-S, Jeong T-S, Chung H-G, Lee K-T (2011). Indole-containing fractions of Brassica rapa inhibit inducible nitric oxide synthase and pro-inflammatory cytokine expression by inactivating nuclear factor-κB. *J Med Food,* 14 (12): 1527-37.
53. Jafarian-Dehkordi A, Zolfaghari B, Mirdamadi M (2013). The effects of chloroform, ethyl acetate and methanolic extracts of Brassica rapa L. on cell-mediated immune response in mice. *Res Pharm Sci,* 8 (3): 159-65.
54. Faridi B, Zellou A, Touati D, Alaoui K, Cherrah Y (2014). Toxicité aiguë et activité anti-inflammatoire des graines de Delphinium staphysagria. *Phytothérapie,* 12 (3): 175-80.
55. Daoudi A, Aarab L, Abdel-Sattar E (2013). Screening of immunomodulatory activity of total and protein extracts of some Moroccan medicinal plants. *Toxicol Ind Health,* 29 (3): 245-53.
56. Yesilada E, Tanaka S, Tabata M, Sezik E (1989). Antiinflammatory effects of the fruit juice of Ecballium elaterium on edemas in mice. *Phytoth Res,* 3 (2): 75-76.
57. Attard E, Brincat MP, Cuschieri A (2005). Immunomodulatory activity of cucurbitacin E isolated from Ecballium elaterium. *Fitoterapia,* 76 (5): 439-41.
58. Diwakar BT, Ramaswamy Lokesh B, Naidu KA (2011). Modulatory effect of α-linolenic acid-rich garden cress (Lepidium sativum L.) seed oil on inflammatory mediators in adult albino rats. *Br J Nutr,* 106 (04): 530-9.

59. Kaithwas G, Mukherjee A, Chaurasia AK, Majumdar DK (2011). Anti-inflammatory, analgesic and antipyretic activities of Linum usitatissimum L. (flaxseed/linseed) fixed oil. *Indian J Exp Biol,* 49 (12): 932-8.
60. Mikhaeil BR, Badria FA, Maatooq GT, Amer MM (2004). Antioxidant and immunomodulatory constituents of henna leaves. *Z Naturforsch C,* 59 (7-8): 468-76.
61. Araújo LCC, Aguiar JS, Napoleão TH, Mota FVB, Barros ALS, Moura MC, Coriolano MC, Coelho LCBB, Silva TG, Paiva PMG (2013). Evaluation of cytotoxic and anti-inflammatory activities of extracts and lectins from Moringa oleifera seeds. *PLoS One*, 8(12):e81973.
62. Mahajan SG, Mehta AA (2010). Immunosuppressive activity of ethanolic extract of seeds of Moringa oleifera Lam. in experimental immune inflammation. *J Ethnopharmacol,* 130 (1): 183-6.
63. Birdane Y, Buyukokuroglu M, Birdane F, Cemek M, Yavuz H (2007). Anti-inflammatory and antinociceptive effects of Melissa officinalis L. in rodents. *Rev Med Vet,* 158 (02): 75-81.
64. Erdemoglu N, Küpeli E, Yeşilada E (2003). Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. *J Ethnopharmacol,* 89 (1): 123-29.
65. Al-Farwachi M (2007). In vivo and in vitro Immunmodulatory Activities of Nerium oleander Aqueous Leaf Extract in Rabbits. *J Anim Vet Adv,* 14 1047-50.
66. Salem ML (2005). Immunomodulatory and therapeutic properties of the Nigella sativa L. seed. *Int Immunopharmacol,* 5 (13): 1749-70.
67. Chan K, Islam M, Kamil M, Radhakrishnan R, Zakaria M, Habibullah M, Attas A (2000). The analgesic and anti-inflammatory effects of Portulaca oleracea L. subsp. sativa (Haw.) Celak. *J Ethnopharmacol,* 73 (3): 445-51.
68. Ilavarasan R, Mallika M, Venkataraman S (2006). Anti-inflammatory and free radical scavenging activity of Ricinus communis root extract. *J Ethnopharmacol,* 103 (3): 478-80.
69. Kumar A, Singh V, Ghosh S (2011). An experimental evaluation of in vitro immunomodulatory activity of isolated compound of Ricinus communis on human neutrophils. *Int J Green Pharm,* 5 (3): 201.
70. Hu B, Zhang H, Meng X, Wang F, Wang P (2014). Aloe-emodin from rhubarb (Rheum rhabarbarum) inhibits lipopolysaccharide-induced inflammatory responses in RAW264. 7 macrophages. *J Ethnopharmacol,* 153 (3): 846-53.
71. Yin W, Wang T-S, Yin F-Z, Cai B-C (2003). Analgesic and anti-inflammatory properties of brucine and brucine N-oxide extracted from seeds of Strychnos nux-vomica. *J Ethnopharmacol,* 88 (2): 205-14.
72. Duddukuri GR, Brahmam AN, Rao DN (2008). Suppressive effect of strychnos nux-vomica on induction of ovalbumin-specific IgE antibody response in mice. *Indian J Biochem Biophys,* 45 (5): 341-4.
73. Handoussa H, Hanafi R, Eddiasty I, El-Gendy M, El Khatib A, Linscheid M, Mahran L, Ayoub N (2013). Anti-inflammatory and cytotoxic activities of dietary phenolics isolated from Corchorus olitorius and Vitis vinifera. *J Funct Foods,* 5 (3): 1204-16.
74. Li T, Fan G-X, Wang W, Li T, Yuan Y-K (2007). Resveratrol induces apoptosis, influences IL-6 and exerts immunomodulatory effect on mouse lymphocytic leukemia both in vitro and in vivo. *Int Immunopharmacol,* 7 (9): 1221-31.
75. Drozdova I, Bubenchikov R (2005). Composition and antiinflammatory activity of polysaccharide complexes extracted from sweet violet and low mallow. *Pharmaceutical Chem J,* 39 (4): 197-200.

76. Al-Reza SM, Yoon JI, Kim HJ, Kim J-S, Kang SC (2010). Anti-inflammatory activity of seed essential oil from Zizyphus jujuba. *Food Chem Toxicol,* 48 (2): 639-43.
77. Elston DM, Ahmed DD, Watsky KL, Schwarzenberger K (2002). Hand dermatitis. *J Am Acad Dermatol,* 47 (2): 291-9.
78. Darsow U, Ring J (2000). Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol,* 25 (7): 544-51.
79. Lembo S, Lembo C, Patruno C, Balato A, Balato N, Ayala F (2014). Pizza makers' contact dermatitis. *Dermatitis,* 25 (4): 191-4.
80. Bahna SL (2004). Adverse food reactions by skin contact. *Allergy,* 59 Suppl 78 66-70.
81. Choopani R, Mehrbani M, Fekri A, Mehrabani M (2015). Treatment of Atopic Dermatitis From the Perspective of Traditional Persian Medicine: Presentation of a Novel Therapeutic Approach. *J Evid Based Complementary Altern Med,* 9. pii: 2156587215598610. [Epub ahead of print]
82. Kim J, Kim EH, Oh I, Jung K, Han Y, Cheong HK, Ahn K (2013). Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol,* 132 (2): 495-8.e1.
83. Lee SY, Chang YS, Cho SH (2013). Allergic diseases and air pollution. *Asia Pac Allergy,* 3 (3): 145-54.
84. Anveden Berglind I, Alderling M, Meding B (2011). Life-style factors and hand eczema. *Br J Dermatol,* 165 (3): 568-75.
85. Niemeier V, Nippesen M, Kupfer J, Schill WB, Gieler U (2002). Psychological factors associated with hand dermatoses: which subgroup needs additional psychological care? *Br J Dermatol,* 146 (6): 1031-7.
86. Camfferman D, Kennedy JD, Gold M, Martin AJ, Winwood P, Lushington K (2010). Eczema, sleep, and behavior in children. *J Clin Sleep Med,* 15;6(6):581-8.
87. Shastry BS (2006). Pharmacogenetics and the concept of individualized medicine. *Pharmacogenomics J,* 6 (1): 16-21.
88. Shahabi S, Hassan ZM, Mahdavi M, Dezfouli M, Rahvar MT, Naseri M, Jazani NH, Khalkhali HR (2008). Hot and Cold natures and some parameters of neuroendocrine and immune systems in traditional Iranian medicine: a preliminary study. *J Altern Complement Med,* 14 (2): 147-56.