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ACUPUNCTURE FOR THE TREATMENT OF ATOPIC ITCH - A SYSTEMATIC LITERATURE REVIEW

Rudolf Alexander Herbst

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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ACUPUNCTURE FOR THE TREATMENT OF ATOPIC ITCH - A SYSTEMATIC LITERATURE REVIEW

ACUPUNCTURA PARA O TRATAMENTO DO PRURIDO ATOPICO - REVISÃO SISTEMÁTICA DE LITERATURA

Dissertação de Candidatura ao grau de
Mestre em Medicina Tradicional Chinesa submetida
ao Instituto de Ciências Biomédicas de Abel Salazar
da Universidade do Porto.

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Resumo

Introdução: A dermatite atópica (AD) é uma doença de pele comum, crónica e multifatorial que acarreta um enorme custo para o paciente e directa e indirectamente, também para os serviços de saúde e sociedade de forma geral. Um dos principais sintomas, sinal clínico e que mais afecta a qualidade de vida dos pacientes com esta patologia, é o prurido. O prurido atópico está associada à carga inflamatória, caracterizada por uma multiplicidade de mecanismos. Esta patologia pode ser muito difícil de tratar e não responde bem aos medicamentos anti-histamínicos. Tal como acontece com muitas outras doenças crónicas e ou difíceis de tratar, os pacientes buscam ajuda desesperada em estratégias alternativas ou medicinas complementares, como a medicina tradicional chinesa (MTC). Existem vários relatos que o MTC, em geral, e a acupuntura em particular, podem ser úteis para o tratamento do prurido e / ou da dermatite atópica.

Objetivo: Realizar uma revisão sistemática de literatura sobre a acupuntura como uma medida terapêutica distinta para o tratamento do prurido associada à dermatite atópica, com base nos Critérios Principais Itens para Relatar Revisões sistemáticas e Meta-análises (PRISMA) para avaliar sua eficácia e segurança na prática clínica.

Métodos: Foi realizada pesquisa bibliográfica de ensaios controlados randomizados, (RCT) em 3 base de dados médicos: Pubmed, Web of Science e SCOPUS, com base em regras de pesquisa padronizadas. Foram incluídos estudos que compararam os efeitos da acupuntura com os de placebo, ou pseudoacupuntura, ou nenhuma intervenção, na intensidade, duração e / ou sinais e sintomas da Dermatite atópica.

Resultados: A pesquisa inicial produziu 104 artigos, dos quais 26 foram excluídos, uma vez que foram duplicados, e 67 após uma leitura cuidadosa do título e do resumo. 11 estudos foram selecionados para revisão detalhada de texto completo. Destes, apenas 2 descreviam o tratamento do prurido atópica em contextos clínicos; Um deles por acupressão, o outro por acupuntura. O último, no entanto, não era suficientemente controlado, portanto, excluído, assim como o primeiro, porque se tratava de auto-tratamento, através de acupressão. Em resumo, não encontramos nenhum estudo que fosse elegível para ser incluído nesta revisão sistemática.

Conclusão: Não encontramos estudos de alta qualidade sobre o tratamento do prurido atópica por acupuntura em contextos clínicos e, portanto, não podemos fazer recomendações baseadas em evidências, com base nesta revisão. No entanto, identificamos vários estudos que demonstraram a eficácia da acupuntura na indução de histamina e prurido induzido por alérgenos, em voluntários saudáveis e bem como em pacientes atópicos. Encontramos, também, evidências de que a acupuntura e a acupressão são capazes de modificar o prurido atópica, na prática clínica, no entanto, não em RCT e apenas em estudos com reduzido numero de pacientes. Portanto, concluímos que RCTs rigorosamente projetados e controlados para avaliar a eficácia da acupuntura no manejo da coceira atópica na prática clínica são necessários para esclarecer sua utilidade como monoterapia.

Palavras-chave: acupuntura, atópico, prurido, prurido

Abstract

Introduction: Atopic dermatitis (AD) is a common multifactorial chronic skin disease that causes immense disease burden on patients and enormous direct and indirect health care costs for societies. One of the main symptoms and the leading clinical sign but also one of the most quality of life affecting problems in AD is itch. Atopic itch is associated with the inflammatory burden and characterized by a multitude of mechanisms. It can be very difficult to treat and does not respond well to antihistaminic drugs. As with many other chronic and difficult to treat diseases or symptoms patients seek desperately help in alternative or complementary medicine strategies such as traditional chinese medicine (TCM) and others. There are various reports that TCM in general and acupuncture in particular can be helpful for the treatment of itch and / or AD.

Objective: To systematicallly review the literature on acupunture as one distinct therapeutic measure for the treatment of itch associated with atopic dermatitis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to evaluate its efficacy and safety in clinical practice.

Methods: Literature searches for randomized controlled trials (RCT) were conducted in three medical databases (Pubmed, Web of Science and SCOPUS) based on standardized searching rules. Included were studies comparing the effects of acupuncture with those of placebo- or pseudoacupuncture or no intervention on itch intensity, duration and/or signs and symptoms of AD.

Results: The initial search yielded 104 articles, 26 of which were excluded as they were duplicates and 67 after carefull reading of title and abstract. 11 studies qualified for detailed full text review. Only 2 of these described the treatment of atopic itch in clinical settings; one of them by acupressure, the other one by acupuncture. The latter was however not sufficiently controlled and therefore excluded as well as the first one because it was on self-applied acupressure. In summary we did not find any studies that were eligible to be included in this systematic review.

Conclusion: High quality studies on the treatment of atopic itch by acupuncture in clinical settings could not be identified and therefore no evidence-based recommendations can be made based on this review. However, several studies that demonstrated the effectiveness of acupuncture on histamine induced and allergen induced itch in healthy volunteers and atopic patients as well were identified. In addition, evidence that acupuncture and

acupressure are able to modify atopic itch in clinical practice were found, however not in a RCT and only with very small patient numbers. Therefore the conclusion of this review is that rigorously designed and controlled RCTs to assess the efficacy of acupuncture in the management of atopic itch in clinical practice are needed to clarify its usefullness as monotherapy.

Keywords: acupuncture, atopic, itch, pruritus

Dedicação

"O princípio da ciência é sabermos que ignoramos."

(A Hora do Diabo, Fernando Pessoa, ano desconhecido)

"Auch ein gelehrter Mann // Studiert so fort, weil er nicht anders kann."

(Faust II, Vers 6639, Johann Wolfgang von Goethe, 1832)

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My family.

List of Abbreviations

ACU:	acupuncture
AD:	atopic dermatitis
Attn score:	attention score
C:	controls
CAT:	complementary alternative treatment
CO:	cross over study design
CNS:	central nervous system
DLQI:	Dermatology Quality of Life Index
Dx Crit AD:	diagnostic criteria for the diagnosis of AD
EACU:	electroacupuncture
EASI:	Eczema Area and Severity Index
e.g.	for example
EIQ:	Eppendorf Itch Questionnaire
etc.:	et cetera (and so on)
F:	female
H:	liver conduit (meridian)
HT:	heart conduit (meridian)
IgE:	immunoglobulin E
K:	kidney conduit (meridian)
LI:	large intestine or crassintestinal conduit (meridian)
M:	male
NG:	not given
NI:	no intervention
OCT:	over the counter (without prescription available)
PC:	proportional cun (fingerwidth of the respective patient receiving acupuncture)
PLACU:	placebo-acupuncture (at non-acupoint(s)

PLPSEACU: placebo-pseudo-electroacupuncture (at non acupoint(s) and non penetrating)

PSACU: pseudoacupuncture (not penetrating but at acupoint(s)

PL-levocetirizine: placebo levocetirizine

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: randomized controlled trial

SCORAD: Severity Scoring of Atopic Dermatitis

SP: spleen or lienal conduit (meridian)

ST: stomach conduit (meridian)

T: treated

TCM: Traditional Chinese Medicine

VAS: visual activity score

WF-size: wheal/flare size

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(acupoint figures courtesy of the Heidelberg School of Traditional Chinese Medicine, with permission)

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1. INTRODUCTION

1.1 Atopic Dermatitis

Atopic dermatitis (AD) is a non-contagious, multifactorial chronic inflammatory skin disease occurring often in families with atopic diseases (namely: atopic dermatitis, bronchial asthma and/or allergic rhino-conjunctivitis). Manifestation factors are genetic predisposition factors on one hand and various internal and/or external triggers on the other (Werfel et al., 2014). The varying etiologic concepts of this disease have lead to a variety of different names that are or have been used for the condition, such as "atopic dermatitis or eczema", "neurodermatitis", "neurodermitis", "endogenous or constitutional eczema".

The atopic diseases are genetically linked, and the concordance ranges from 80% in monozygotic twins to 30% in dizygotic twins. Described genetic polymorphisms in AD involve mediators of atopic inflammation on a variety of chromosomes, some of these are also relevant for respiratory atopy. The strongest association has been demonstrated for mutations in the filaggrin gene that is also associated with ichthyosis vulgaris. This is a clear hint to the importance of a predisposing barrier defect in AD patients. The skin barrier dysfunction can be quantified by measuring the transepidermal water loss (Ring et al., 2012a).

The cumulative incidence of AD ranges between 11 and 21% in Northern Europe depending on age and region with a recorded point prevalence of e.g. 10–15 % in Germany. According to epidemiologic analyses about 23 % of babies and toddlers, 8 % of schoolchildren and 2-4 % of adults claim healthcare services because of AD in that country. AD can diminish over time but at least 30% of all children that suffer from atopic dermatitis will have eczema in adulthood.

AD is an eosinophilic and spongiotic inflammatory disease of the skin with characteristic age-dependent distribution patterns and morphology of lesions. There is no specific marker to diagnose AD so that the diagnosis should be made by using evaluated clinical criteria. This requires a medical history (including personal and family atopic history) and examination of the whole skin organ. Dermatohistopathologal examination of a skin biopsy can be necessary at times to rule out other inflammatory diseases (such as e.g.

cutaneous T cell lymphoma), but even then other eczematous diseases cannot always be distinguished. Most diagnostic criteria are based on cutaneous signs of atopy. Hanifin and Rajka's criteria include: pruritus, typical morphology and distribution, chronic or chronically relapsing course, and atopic personal or family history (3 of 4 necessary), in addition to three minor criteria among a list of 21 (Wollenberg et al., 2016).

Disease activity can be measured with a composite score assessing both objective signs and subjective symptoms, such as the so called SCORAD (Severity Scoring of Atopic Dermatitis) or the EASI (Eczema Area and Severity Index) (Chalmers et al., 2016). The management of AD must consider the clinical and pathogenic variabilities of the disease and also target flare prevention. Diagnostic and treatment guidelines have been developed in different countries and by different societies (e.g. Ring et al., 2012a/b; Rubel et al., 2013; Werfel et al., 2016).

The most important basic therapeutic measure is regularly applied hydrating topical treatment and prevention of irritation and/or exsiccation (e.g. by overhygiene, excessive washing procedures etc.). Other specific and/or unspecific provocation factors should also be avoided if known. Anti-inflammatory treatment of visible skin lesions is based on topical glucocorticosteroids and topical calcineurin inhibitors. Tacrolimus and mid-potent steroids are proven for "proactive therapy", which is long-term intermittent (e.g. once weekly) anti-inflammatory local therapy on the frequently relapsing skin areas (Wollenberg A et al., 2016). Systemic anti-inflammatory or immunosuppressive treatment is indicated for severe and or refractory cases. Biologicals targeting key mechanisms of the atopic immune response are promising emerging treatment options and have been licensed very recently (Hanifin, 2016). Microbial colonization and superinfection may cause disease exacerbation and justify additional antimicrobial treatment in such instances. Adjuvant therapy includes UV irradiation, preferably UVA1 or narrow-band UVB 311 nm. Dietary recommendations should be patient specific and elimination diets should only be advised in case of proven food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Psychosomatic counselling is recommended to address stress-induced exacerbations. "Eczema school" educational programmes have been proven to be helpful for children and adults (Werfel et al., 2014).

1.2 Itch

Itch has been defined by the German physician Samuel Hafenreffer in 1660 as "*unpleasant sensation, that elicits the desire to scratch*" (Hafenreffer, 1660; Carlsson and Wallengren, 2010). It is one of the leading symptoms of AD without which the diagnosis cannot be made. It´s severity can range from mild to extremely severe depending on the physiological state of the skin, the degree of skin inflammation, the size of the area involved, the duration and also the patient´s perception. Itch can influence a patient´s quality of life dramatically up to mutilating scratching and even suicide. Very frequently itch causes severe sleep disturbances with following physical and psychological exhaustion.

Reception of itch is by free nerve endings in the epidermis, papillary dermis and around skin appendages that are activated by various endogenous and exogenous pruritogens through respective receptors. Itch is then mediated by unmyelinated C-fiber afferents and thinly myelinated Ad fiber afferents originating from cell bodies in the dorsal root ganglion. The skin-nerve interface is altered in atopic skin, with increased innervation density and expression of several inflammatory neuropeptides (eg, substance P, calcitonin gene–related peptide, and vasoactive intestinal peptide) in lesional atopic skin. Numerous exogenous stimuli (eg, irritants and relevant allergens) and endogenous factors (such as histamine, cytokines, neuropeptides, and other inflammatory molecules) activate the above mentioned receptors (Mollanazar et al., 2016).

Particularly histamine is one of the major itch mediators that has been well evaluated. Direct application of histamine to human skin induces itching and a subsequent axonal reflective vasodilation clinically visible as flare. Two of four known histamine receptors, namely H1R and H4R have been identified as potential pruritoceptors. Topical and oral antihistamines (drugs with antihistamine action) are routinely recommended by physicians to help control atopic itch. Despite this widespread practice, histamine's role in triggering itch in AD is still limited and evidence supporting the use of histamine 1 (H1) or histamine 2 (H2) receptor antagonists in AD management is sparse. Emerging evidence suggests that the H4 receptor may play an important role in mediating histamine-induced inflammation and itch in AD; however, H4 antagonists are currently not commercially available. In addition, histamine mediated itch represents just one kind of itch relevant in

AD and there are nonhistaminergic pathways that are equally important (Mollanazar et al., 2016). Recent neuroimaging studies have focused on brain imaging of histamine-induced itch in humans. It was demonstrated in functional neuroimaging studies that acute histamine-induced itch captivates the anterior cingulate cortex, insular and primary somatosensory cortex, premotor and supplementary motor areas, prefrontal cortex, and thalamus in healthy persons (Napadow et al., 2015).

AD patients experience an even broader excitation of the brain. When itching skin lesions are scratched, a brain region known as the "reward system" is much more reactive than when non itching skin is scratched. Therefore it was concluded that activation of the "reward system" may be one reason for the sometimes overly excessive and repetitive scratching behavior of AD patients. In addition, central sensitization, perception and interpretation of pruritus in AD patients are strongly influenced by cognitive and affective processes. Interestingly in that context, Napadow and coworkers could recently show, that nocebo saline applied to AD patients could mimic both the sensory and the neural effects of real allergens. They argued that this provides an insight to the brain mechanisms supporting nocebo-induced itch in AD and thereby aides to the understanding of the role of expectations and other psychological factors in modulating itch perception in chronic itch patients (Napadow et al., 2015). This may be the basis of the itch dampening effect of centrally CNS-modulating drugs (reviewed in Kido-Nakahara et al., 2017).

The repertoire of pruritogens is expanded in AD such that normally nonpruritogenic and/or painful stimuli (such as acetylcholine and bradykinin) can cause itch rather than pain. Inflammatory cytokines such as interleukin (IL)-31 are elevated in atopic skin and can directly activate peripheral receptors to induce itch signaling. Pathogenic bacteria and yeast that often colonize the skin of eczema patients may also directly activate peripheral nerves and thereby exacerbate itch. In addition, patients with atopic eczema can experience so called alloknesis, which is abnormal itch sensations elicited by normally nonitchy (e.g. thermal, or mechaninc, e.g. by wool clothing) stimuli. A wide range of other "exacerbators" of itch in AD are well known such as perspiration, psychological factors (stress) or scratching (Murota and Katayama, 2017).

The central projections of the above mentioned afferent nerve fibers send itch signals to second order spinal neurons in the dorsal horn of the spinal cord, which in turn project to the ventrocaudal part of the nucleus medialis dorsalis in the thalamus via the contralateral spinothalamic tract and then onto higher cortical areas. The sensation of itch is perceived after activation of the somatosensory cortex and a subsequent scratching reflex is

generated in the motor cortex and associated motor cortex. The intensity and quality of itch signals can be influenced at various points along these peripheral, spinal, and/or cortical pathways by other ascending inputs from the periphery (e.g., other incoming pain or tactile or temperature-evoked sensations) and also by descending neural circuits (e.g., influence of mood and attention). Understanding these modulatory circuits is of particular interest and relevance in atopic itch because neurophysiologic and psychomimetric testing demonstrates that patients with AD exhibit reduced thresholds for itch and above mentioned alloknesis (the ability of a nonpruritic stimulus to evoke itch) in involved and uninvolved skin (reviewed in Elmariah, 2017; Mollanazar et al., 2016; Kido-Nakahara et al., 2017; Katayama et al., 2017).

Exacerbations of AD often start as increased itch without visible skin lesions - which has led to the label: *"…the itch that rashes…."* - followed by erythema, papules and infiltration. As stated above, systemic antihistamines targeting H1R are used in acute AD flares against itch. In general, antihistamines are safe to use, also for a long period of time and the major advantage seems to be relief of the symptoms of co-morbidities such as allergic asthma, rhino-conjunctivitis, urticarial dermographism and urticaria (Werfel et al., 2014). Topical antihistamines have no effect on itch beyond that of their cooling vehicles (mostly as a gel) and are in contrast often times clinically not helpful since they exsiccate the skin via this galenic mechanism and even aggrevate itch that way. In summary there are limited data for the antipruritic effect of antihistamines (H1-antagonists) in AD and the effect of both first and second generation antihistamines on pruritus, in patients suffering from AD. The first generation of sedative antihistamines, such as hydroxyzine, clemastine fumarate and dimetinden maleate, may allow a better sleep pattern in acute situations with exacerbations of eczema. Long-term use in children is not recommended. Ongoing studies concentrate on the blockade of alternative histamine receptors such as H4R, which may be more important in AD.

Antipruritic therapy in AD is multidimensional treating the symptom itself, the contributing factors such as dry skin, inflammation and the related scratch lesions. Therefore, several general measures are recommended. Short-term relief of pruritus can be achieved by topical creams or ointments containing urea, menthol, or camphor as well as wet, cooling or fat-moist wrappings, wrappings with black tea. Therefore even the use of these so called basic therpay measures needs to be controlled in clinical studies on itch and AD. The anti-inflammatory effect of topical corticosteroids in AD is well established and it has been shown that corticosteroids have a rapid antipruritic effect and can also be used in so called "proactive therapy" (Wollenberg et al., 2016). Most likely the anti-inflammatory

effect of glucocorticosteroids is the mechanism that helps suppress the itch. The same applies for systemic glucocorticosteroids, for which no specific studies on an anti-itch effect in AD are available.

Biological treatments using anti–IL-31 receptor A or anti–IL-4 receptor alpha appear to be beneficial in reducing atopic itch (Hanifin, 2016). Combined therapy with conventional topical remedies and these biologics may provide new treatment strategies for atopic patients.

In addition, all patients should be educated on how best to repair and reinforce the skin barrier in efforts to limit access to infection, irritants, or allergens, all of which stimulate or aggravate itch. Use of topical anesthetics or systemic neuromodulators can dampen itch signaling and may limit neural sensitization when used sufficiently early and used consistently. Finally, addressing physical and emotional stress is integral to an effective therapeutic regimen (reviewed in Mollanazar et al., 2016; Ring et al, 2012a/b; Zeidler et al., 2016).

1.3 Atopic dermatitis and itch in traditional chinese medicine

As with many other chronic and difficult to treat diseases or symptoms patients seek desperately help in alternative or complementary medicine strategies such as traditional chinese medicine (TCM) and others (Augustin et al., 2012a).

A recent AD treatment guideline quantified this growing interest in complementary alternative treatment (CAT or complementary alternative medicine, CAM) as treatment for AD. According to Ring et al., (2012a) France (49%) and Germany (46%) have the highest usage of CAM in Europe. The growing interest in CAM in the public was also seen in the United States, where an increase in the usage of CAM from 33.8% to 42.1% from 1990 and 1997 was observed. In Switzerland 37% of 202 inpatients with atopic disorders said to have used CAM previously; most frequently homoeopathy (48%), diet (35%) and herbalism (28%), autologous blood injection (28%), phytotherapy (20%) and acupuncture (18%). From 444 inpatients with AD in Norway 51% reported the previous use of CAM, most frequently homoeopathy (34%), herbalism (19%), food supplements (18%), diet change (18%) and acupuncture (11%). In a German population-based telephone survey 26.5% of adults with allergies claimed that they had used CAM, most commonly homoeopathy (35.3%), autologous blood injection (28.1%), acupuncture (16.6%) and bioresonance (10.0%) (reviewed in Ring et al., 2012b).

Although CATs are becoming increasingly used in the management of chronic skin diseases, such as AD, few high-quality studies addressed their efficacy. A recent comprehensive meta-analysis of RCTs of CATs demonstrated efficacy of acupuncture and acupressure, hypnosis, massage, biofeedback, balneotherapy, herbal preparations, and oral evening primrose oil (Elmariah, 2017).

Another very recent (2017) systematic review by Shi and coworkers looked at traditional Chinese medicines and related therapies such as acupuncture and moxibustion and did not find statistical differences in clinical effectiveness, SCORAD amelioration, and SSRI (Symptom Score Reducing Index) amelioration for these AD treatments compared with the respective control groups. They claimed, however to have found EASI (Eczema Area and Severity Index) amelioration by traditional Chinese medicines and related treatments for AD as being superior to control groups and treatments, respectively.

They concluded that although they were able to find Eczema Area and Severity Index (EASI) amelioration in the meta-analysis they presented, the clinical meaning of these findings would be restricted by the low number of included articles. In summary they did not find a superiority of traditional Chinese medicine and related treatments in AD therapy (Shi et al., 2017).

Two years earlier Viera et al. published a systematic review on complementary and alternative medicine for AD and basically found what they called some "level I" evidence to support the use of acupuncture and acupressure, stress-reducing techniques such as hypnosis, massage, and biofeedback, balneotherapy, herbal preparations (with many important caveats), certain botanical oils, oral evening primrose oil, vitamin D supplementation, and topical vitamin B12. They saw despite the heterogeneity among many of the studies they looked at, their mostly small sizes, and their relatively low quality enough evidence to support the use of selected complementary and alternative therapies for AD. They concluded that they hoped with more RCTs and comparative efficacy studies alternative treatments could become mainstream in time (Vieira et al., 2016).

1.4 Acupuncture for the treatment of itch

Carlsson and Wallengren (2010) speculated that sensory cutaneous innervation, which is often dense in neuropathic pruritus, prurigo nodularis and in uremic pruritus is the main target of acupuncture in pruritic skin. They cited in their comprehensive review several studies that demonstrated efficacy of acupuncture for neuropathic and uremic itch such as a retrospective study that showed symptomatic relief of neuropathic pruritus in 12 of 16 patients and a study of six patients with intractable pruritus secondary to chronic renal failure ameliorated by electrical needle stimulation at an acupoint on the elbow (LI11), whereas control treatment with superficial electrical stimulation was ineffective. Another study randomized 40 patients with refractory uraemic pruritus into two groups and applied acupuncture unilaterally on acupoint LI11 in one group three times weekly for 1 month. In the control group, acupuncture was applied at a non-acupoint 2 cm lateral from the elbow. Subjects responded to a pruritus score questionnaire given before and at the end of the 1-month treatment and at a 3-month follow-up and pruritus scores were reduced by about 50% after acupuncture and at the 3-month follow-up while they were unchanged in the control group.

Ma and colleagues recently (2015) reviewed systemically the use of acupuncture as a primary treatment modality for dermatologic conditions. They claimed to have identified 24 studies, 16 of which were RCTs. Acupuncture was used to treat atopic dermatitis, urticaria, pruritus, acne, chloasma, neurodermatitis, dermatitis herpetiformis, hyperhidrosis, human papillomavirus warts, breast inflammation, and facial elasticity. In 17 of 24 studies, acupuncture showed statistically significant improvements in outcome measurements compared with placebo acupuncture, alternative treatment options, and/ or no intervention. They concluded that acupuncture can improve outcome measures in the treatment of dermatitis, chloasma, pruritus, urticaria, hyperhidrosis, and facial elasticity. For future studies they asked for clear standardizing of the control intervention, exemplified with placebo acupuncture as the control for the evaluation of the validity of acupuncture points and meridians, blinding of participants to treatment modalites and blinding of acupuncturists to the disease being treated to exclude psychological and procedural bias in an area already prone to subjectivity (Ma et al., 2015).

Tan and coworkers aimed to evaluate the efficacy of acupuncture against placebo/sham acupuncture in the management of AD in systematic literature review in 2015. They included only studies comparing the effects of acupuncture with those of placebo/sham acupuncture on severity of disease or symptoms/signs of AD and did not find any studies that were eligible to be included in their systematic review (Tan et al., 2015).

1.5 Acupuncture for the treatment of atopic itch

Salameh et al. published in 2008 a clinical study of 20 patients with mild-to-severe AD that were given a combined treatment of acupuncture and Chinese herbal medicine. The patients received acupuncture treatments twice a week and a Chinese herbal formula three times daily for a total of twelve weeks. After 12 weeks of treatment, an improvement in EASI (Eczema Area and Severity Index) was noted in all patients and 78.8% of patients experienced a reduction in DLQI (Dermatology Quality of Life Index) and VAS (visual activity score) for itch. They did not observe adverse effects.

Yu et al. published in 2015 a systematic literature review and meta-analysis to assess the efficacy of acupuncture therapy against itch. They included RCTs that compared acupuncture therapy and placebo acupuncture or no treatment group and claimed to have found three articles of randomized controlled trials (RCTs) from a total of 2530 articles. In their opinion they were able to show in their meta-analysis that acupuncture therapy was effective to alleviate itch compared with placebo acupuncture and no treatment groups. In conclusion they cautiously suggested that acupuncture therapy is effective for ameliorating itch intensity in itch-related diseases (Yu et al., 2015).

The latest version of the German guidelines for AD lists acupuncture as procedure that was not considered to be included because there was not enough evidence for it´s efficacy (Werfel et al., 2016b).

1.6. Rationale for this review in the context of what is known - PICOS

The basic efficacy of acupuncture for the treatment of several forms of itch - meaning itch in several disease entities - seems proven by the existing literature as outlined above. With respect to the very complex mechanisms of itch in patients with AD that in addition can be influenced by various internal and external factors, the question of this systematic literature review is whether there is robust data on the efficacy of acupuncture for the treatment of atopic itch in a clinical context - meaning in ameliorating itch in daily patients´ lives.

In short **PICOS** means in the context of this review therefore:

Participants - AD patients with (atopic) itch

Interventions - acupuncture as monotherapy

Comparisons - control interventions or no treatment

Outcomes - amelioration of atopic itch (over time)

Study design - randomized controlled trial (RCT)

2. MATERIALS AND METHODS

2.1. Search Strategy / Protocol

The systematic literature search was performed according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines (Moher et al., 2009). Three databases (Pubmed, Web of Science and SCOPUS) were searched in August 2017 from their inception up to August 2017. The search string for all three databases was: ((acupoint* OR acupuncture OR electroacupuncture OR moxibustion OR moxa) AND (pruritus OR itch) AND atopi* AND (skin OR derm*)). The reference chapters / bibliographies of standard textbooks and the articles searched (regardless if included or excluded) were also checked for additional literature.

2.2. Study Selection Criteria

The study / article selection was performed according to the following inclusion criteria: (1) full-text randomized controlled trials, (2) related to the treatment of itch in atopic dermatitis patients, (3) criteria for the diagnosis of atopic dermatitis are given (e.g. SCORAD, EASI), (4) acupuncture as only treatment modality (monotherapy), (5) acupoints are given, (6) quantified measure of outcome (e.g. VAS for improvement of itch), (7) at least abstract in English available. Exclusion criteria for articles / studies were: (1) animal studies, (2) diagnoses other than clearly defined atopic dermatitis (e.g. urticaria, contact dermatitis etc.), (3) combination treatments (e.g. with herbs), (4) case reports, comments, reviews, editorials etc.

2.3. Data Extraction and Management

Data of selected articles were extracted by the author and independently reviewed by a second investigator. Both checked in depth inclusion and exclusion criteria by full text analysis of the papers. The literature characteristics comprised the following items: (1) author and publication year; (2) study design; (3) number of individuals in treatment and control groups; (4) participants' age; (5) and gender; (6) diagnostic criteria for AD (where applicable); (7) allergen used (where applicable); (8) Treatment(s): Acupoint(s) / Duration / Frequency / Comedications (where applicable); (9) Control Intervention(s); (10) Outcome measure(s); (11) results; and (12) side effects and are listed in **Tables 1-3**.
Any discrepancies were discussed and solved as necessary.

3 RESULTS

3.1. Literature search results

A schematic description of the search results is given as a flow diagram in **Figure 1**.

In detail, the initial search yielded 104 articles, 26 of which were excluded as they were duplicates and another 67 after carefully reading titles and abstracts.

11 studies qualified for detailed full text review.

3 of these were excluded because they

(1) investigated needeling effects in non-acupunture points on the buttock (Carlsson et al., 2006),

(2) examined nocebo-induced itch in atopic dermatitis patients by functional magnet resonance imaging but did not apply acupuncture (Napadow et al., 2015) and

(3) described a temperature modulated histamine-itch model in lesional and non-lesional skin in atopic dermatitis patients to evaluate itch perception by functional magnet resonance imaging and psychophysical test but also did not apply acupuncture (Pfab et al., 2010).

The remaining 8 studies are discussed in detail in the discussion section and detailed in **Tables 1-3**.

Shortly, three of them had to be excluded because they describe one single acupuncture session to treat histamine induced itch in healthy volunteers: Belgrade et al., 1984; Lundeberg et al., 1987; and Pfab et al., 2005.

Another three studies had to be excluded because they investigated one single acupuncture treatment to treat allergen induced itch in patients with atopic dermatitis: Pfab et al., 2010; Pfab et al., 2012; and Napadow et al., 2014.

Finally, only 2 studies described the treatment of atopic itch by repeated treatments of acupuncture points over several sessions over some time in clinical settings.

One of them, however, by acupressure (Lee et al., 2012), the other one by acupuncture (Pfab et al., 2011). The latter was however not sufficiently controlled and therefore excluded as well as the first one because it was on self-applied acupressure (and not on acupuncture).

In summary we did not find any studies that were eligible to be included in this systematic review.

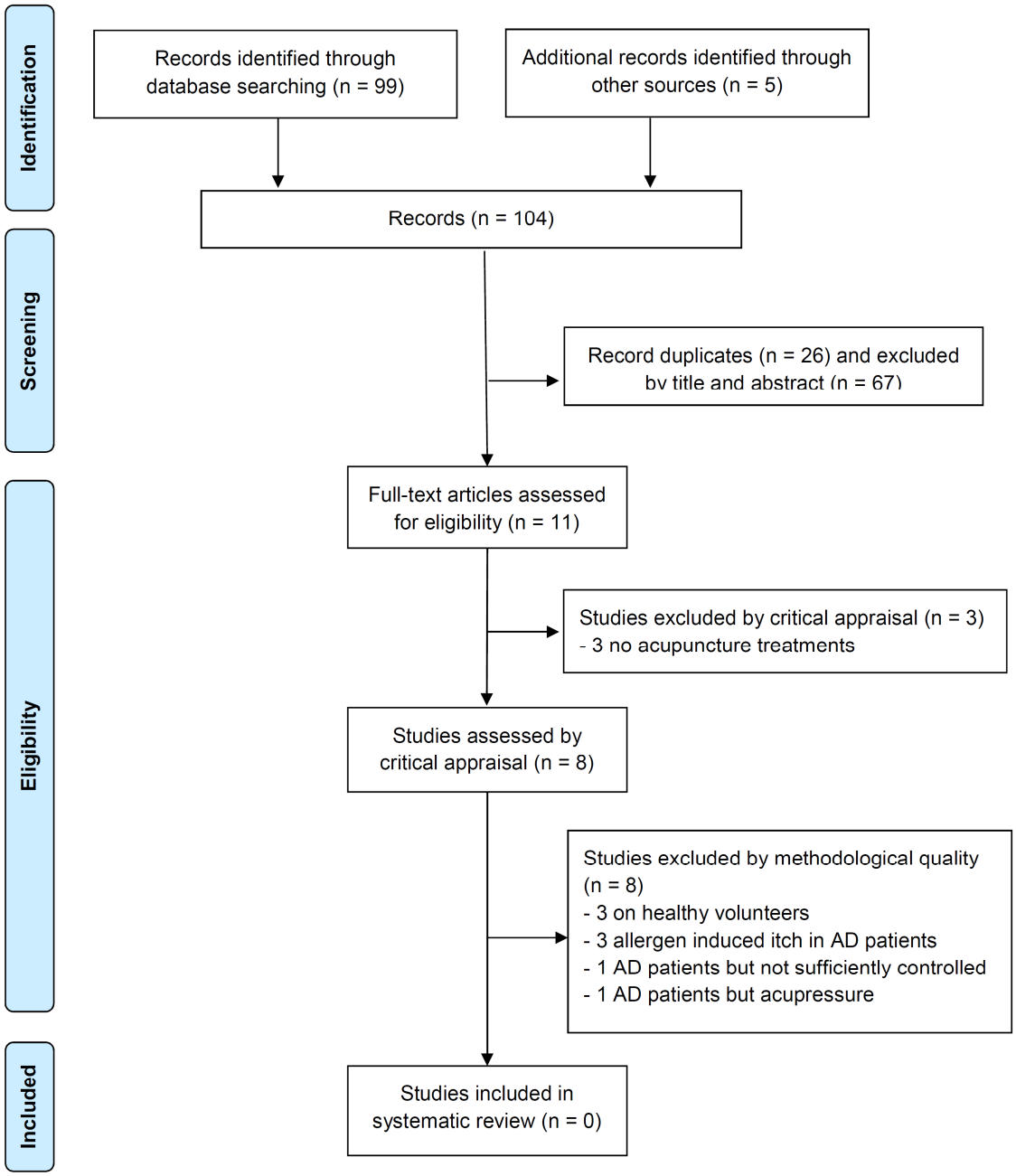

Figure 1 - Flow chart Literature search

4. DISCUSSION

4.1. Summary of main evidence

As stated in the Results section no studies were eligible to be included in this systematic review. The main reasons are described in the Results section above and visualized in brief in **Figure 1**.

It seems nevertheless reasonable to discuss eight of the eleven full-text-evaluated studies in more detail since they may give input as to where further research seems to be most valuable. These 8 papers are therefore detailed in **Tables 1-3** with regard to (1) author and publication year; (2) study design; (3) number of individuals in treatment and control groups; (4) participants' age; (5) and gender; (6) diagnostic criteria for AD (where applicable); (7) allergen used (where applicable); (8) Treatment(s): Acupoint(s) / Duration / Frequency / Comedications (where applicable); (9) Control Intervention(s); (10) Outcome measure(s); and (11) results. Side effects were not reported in any of the studies and are therefore not listed seperately.

4.1.1 Treatment of histamine induced itch

The oldest study identified dates back to 1984: Belgarde and coworkers asked whether acupuncture would be able to modify the onset, duration and flare size of histamine-induced itch in 25 healthy volunteers. All participants were treated with acupuncture, pseudoacupuncture or no intervention 15 min prior to an intradermal injection of histamine on the left forearm. They used needle acupuncture at LI 11 (on the left elbow) and electroacupuncture on the right lower leg (SP6; 5–7 cm proximal to the medial malleolus and SP10; 1–2 cm above the medial upper border of the patella). Placebo-acupuncture treatment consisted of needeling closely to but not on classical acupuncture points. Acupuncture reduced duration and intensity of itch at a time point and histamine induced flare size. The timing of onset of itch and maximal itch intensity were not significantly modified. Needling at acupuncture points resulted in smaller flares and lower intensity of itch than placebo-acupuncture.

A second study on histamine-induced itch in healthy volunteers was published three years later by Lundeberg et al. (1987): they asked if histamine-induced itch could be prevented by or reduced using pseudo-acupuncture (needles inserted superficially at real

acupuncture points), needle acupuncture and/or electroacupuncture (2 and 80 Hz) in 10 volunteers. Acupuncture points utilized were (LU3 and LU4 situated on the upper radial part of m. biceps brachii) - very close to the area where histamine was injected intradermally; proximal to the pruritic area (LU1 and LU2 situated in front of the shoulder joint) in the same conduit and extrasegmentally on the lower leg (H6 and H5, both situated on the medial aspect of the lower leg about 15–22 cm above the medial malleolus) in another conduit (meridian). Pseudo-acupuncture consisted of very superficially needeling the same points. Acupuncture and electro-acupuncture but not pseudo-acupuncture at the site of the histamine injection or close to it reduced the maximal intensity. The duration of itch was not changed significantly.

The third study on histamine-induced itch in healthy volunteers was published by Pfab and coworkers in 2005: they treated LI 11 and compard with placebo-acupuncture at a non-acupoint in the same dermatome (C6) and no intervention 15 minutes before a histamine prick induced itch. Acupuncture at LI11 reduced itch intensity compared to pseudo-acupuncture and no acupuncture and lead to a reduced flare size compared to no acupuncture but not compared to pseudoacupuncture.

A detailed data extraction of these three studies is given in **Table 1** below.

Table 1: Characteristics of studies excluded but analyzed in detail: **histamine induced itch in healthy volunteers treated with acupuncture**

Author Year	Study design	#Treated/ Controls	Age (mean) Treat/Contr	Sex T/C F/M	Treatment: Acupoint(s) /Duation / Frequency	Control intervention(s)	Outcome measure(s)	Result(s)
Belgrade 1984	RCT w. CO	25	21-33	12/13	EACU LI11; SP10; SP6 / 15 min once	PLEACU (non-acupoint) and NI	VAS cumulative and maximum itch and itch duration, flare size	Cumulative itch intensity, duration and flare size significantly lower in EACU vs. PLEACU (p<0,02/0,006/0,04)) and no NI (p<0,001/0,001/0,003); no influence on maximum itch or time to onset of itch
Lundeberg 1987	Controlled-CO	10	18-35	3/7	ACU and EACU (2 and 80Hz): LU3+4, LU1+2 5 or 20 min once, before and after histamine	PSACU: LU3+4 superficial needle, NI, extrasegmental ACU H 5+6	VAS maximum itch and, duration, and flare size	ACU(p<0,05) and 2/80 Hz EACU (p<0,05/0,01) significantly reduced VAS for maximum itch intensity when applied intrasegmentally. No significant effects were obtained when stimulation was applied extrasegmentally. Itch duration was not influenced.
Pfab 2005	RCT w. CO	10	NG	NG	ACU LI11 / 15 min / once	PLACU (non acupoint), NI	VAS max and mean Itch intens wheal/flare size	Mean VAS for itch int lower in ACU (p<0,001) vs. PLACU and NI, wheal size lower in ACU (p<0,03) vs NI

Abbreviations: RCT: randomized controlled trial, CO: cross over study design; T: treated; C: controls; F: female; M: male; NG: not given; ACU: acupuncture; EACU: electroacupuncture; PSACU: pseudoacupuncture (not penetrating); PLACU: placebo-acupuncture at non-acupoint(s); NI: no intervention; VAS: visual activity score; Acupoints: LI: large intestine, SP: spleen, LU: lung, H: liver conduit (meridian)

4.1.2 Treatment of allergen induced itch

Three other studies found in this search examined allergen prick induced itch in atopic patients with known type-I allergy to the respective allergens.

Two studies by the same group around Pfab and coworkers were published 2010 and 2012, respectively. They found that acupuncture significantly reduced allergen-induced itch intensity when compared with placebo and no treatment tested in 30 individuals (Pfab et al., 2010), and that electroacupuncture was more effective than the orally applied antihistamine cetirizine (Pfab et al., 2012), when used abortively rather than preventatively. In the latter patient- and examiner-blinded, randomized, placebo-controlled crossover trial comparing electroacupuncture to the oral antihistamine cetirizine in 20 adults with AD, abortive verum acupuncture significantly reduced allergen induced itch, when compared to both placebo and no intervention controls (Pfab et al., 2012). Despite the lack of clearly listed diagnostic criteria for AD in these two studies, both stated that participating subjects had to have a type I hypersensitivity to (at least) an aeroallergen, which is commonly seen in AD. The studies also mentioned that participants had to have a score of > 18 or >20, respectively on the SCORAD, a validated outcome measure instrument for AD. One of these studies also mentioned having recruited subjects from an outpatient clinic and had "AD diagnosed". Both studies were crossover studies (one with three arms and the other one with seven). The studies involved itch provocation by exposure to a known allergen and the evaluation of a single acupuncture session on the itch evoked as measured by preventive (when acupuncture was conducted before itch provocation) and direct (or "abortive" - when acupuncture was applied after itch provocation) effects. The outcome measures evaluated were itch intensity measured by VAS, the Eppendorf Itch Questionnaire (EIQ), and sizes of weal and flare.

Both studies therefore aimed at amelioration of allergen-induced and histamine-mediated itch in AD by acupuncture, rather than the management of AD as a disease. Both studies concluded that acupuncture significantly reduced type I hypersensitivity itch reactions, and may therefore be useful in the management of itch, urticaria or eczema in atopic patients.

Thirdly, Napadow and coworkers published 2014 a very sophisticated functional magnetic resonance imaging (fMRI) study investigating the underlying brain circuitry supporting allergen-induced itch reduction in AD patients receiving acupuncture, oral antihistamine, or placebo treatments. This study included 14 individuals and showed the greatest itch reduction following acupuncture therapy. In addition, acupuncture was associated with a greater reduction in putamen activity, which is an area implicated in the urge to scratch. Following these authors, acupuncture appears to be an effective adjunct antipruritic treatment strategy in the setting of atopic itch.

A detailed data extraction of these three studies is given in **Table 2** below.

Table 2: Characteristics of studies excluded but analyzed in detail: **allergen induced itch in atopic subjects treated with acupuncture**

Author Year	Study design	#Treated/ Controls	Age (mean) Treat/Contr	Sex T/C F/M	Dx crit AD	Allergens used	Acupoint(s) / Duration / Frequency	Control intervention	Outcome measure	Result(s)
Pfab 2010	RCT w. CO	30	28,6 18 - 50	14/16	SCORAD > 18	grass 13 / Dp 17)	ACU LI11 + SP10 / 10 min / once / before and after allergen	PLACU; NI	VAS mean and max itch; wheal and flare size; Perfusion; EIQ	VAS mean itch intensity significantly lower in ACU vs. NI (p<0,009) and PLACU (p<0,022)after and significantly lower in ACU (p<0,001) and PLACU (p<0,002) vs NI before histamine; mean wheal size sign. smaller in ACU vs. NI (p<0,015); mean flare size sign. smaller ACU vs. PLACU (p<0,02) after allergen induction; flare size significantly lower in ACU vs. NI and PLACU before allergen; PLACU showed significant preventative but not direct effect on itch intensity.
Pfab 2012 Kirchner 2013	RCT w. CO	20	23,3+/- 1,7 (18 -50)	14/6	SCORAD > 20	allergens (Dp 9; Df 3; grass 4; birch 1; cat 2; dog 1)	EACU LI11 + HT3+ ST34+SP10 / 20 min / once / before and after allergen	NI, PLPSEACU, Oral Ceterizine, PLCetirizine	VAS itch intensity; WF-Size EIQ AttnScore Blinding	EACU significantly lower mean itch intensity vs. all other arms (p<0,1); no difference between EACU and cetirizine but both better than their placebos
Napadow 2014	CO	14	18-60; 25,4 +/-9,1;	NG	SCORAD > 18	allergens (grass 8; Dp 3; Df 3)	EACU LI11+HT3 / 15 min once before allergen	PLPSEACU, levocetirizine PL-levocetirizine	VAS itch intensity	VAS itch intensity significantly (p<0,005) lower compared to PLEACU, levocetirizine and PL-levocetirizine

Abbreviations: RCT: randomized controlled trial, CO: cross over study design; T: treated; C: controls; F: female; M: male; NG: not given; Dx Crit AD: diagnostic criteria for the diagnosis of AD; SCORAD: Severity Scoring of Atopic Dermatitis; grass: grasspollen; Dp Dermatophagoides pteronyssimus (European house dust mite); Df Dermatophagoides farinae (American house dust mite); ACU: acupuncture; EACU: electroacupuncture; PLPSEACU: placebo-pseudo-electroacupuncture (at non acupoint and non penetrating); PLACU: placebo-acupuncture (at non-acupoint(s); PL-levocetirizine: placebo levocetirizine; NI: no intervention; VAS: visual activity score; WF-size: wheal/flare size; Attn score: attention score; Acupoints: LI: large intestine, SP: spleen, HT: heart conduit (meridian)

4.1.3 Treatment of atopic itch in a clinical setting

Finally two studies targeting atopic itch by repeated treatments of acupuncture points over several sessions over some time in clinical settings were identified. One of them, however, by acupressure (Lee et al., 2012), the other one by acupuncture (Pfab et al., 2011). The latter was however not sufficiently controlled and therefore excluded as well as the first one because it was on self-applied acupressure.

Pfab et al. published in 2011 a single-blind pilot study of 5 patients and 5 control subjects with a history of AD for > 10 years, a disease severity by SCORAD > 20, and allergic rhinitis with sensitization to timothy grass and European house dust mite. The study compared twice-weekly acupuncture treatments for 10 sessions (33 days) with no intervention, and evaluated disease severity using SCORAD, and itch intensity using VAS and basophil (CD68) activation as an experimental side study. The authors found significant reductions in VAS, itch intensity and basophil activation. However the SCORAD of both arms did not differ significantly after the treatment period. However, class I-II topical corticosteroid therapy was allowed and not controlled for (which was one main reason for exclusion from the systematic part of the review - not giving the individual acupuncture points for each patient being the other one).The authors concluded that acupuncture maybe able to modify IgE-mediated allergic disease (Pfab et al., 2011).

Lee et al. chose self applied acupressure as treatment for 15 patients with moderate-to-severe AD in an investigator-blinded trial. Their study showed that self applied acupressure with a 1.2 mm small titanium bead to massage acupoint LI11 on the arm for 3 minutes 3 times per week for 1 month significantly improved pruritus ($p < 0.04$), lichenification ($p < 0.03$) and Investigator Global Assessment (IGA) ($p < 0.03$) scores. The overall Eczema Area and Severity Index (EASI) scores of the patients remained however unchanged. The control patients had no intervention in addition to their basic emollients and OTC (over the counter treatment) remedies that were also allowed but not rigorously controlled for in the treatment or the groups.

A detailed data extraction of these three studies is given in **Table 3** below.

Table 3: Characteristics of studies excluded but analyzed in detail: **treatment of atopic itch in a clinical setting**

Author Year	Study design	# Treated/ Controls	Age (mean) Treat/Contr	Sex T/C F/M	Dx crit. AD	Treatment: Mode of treatment / Acupoint(s) / Duation / Frequency / Comedication(s) allowed	Control Intervention	Outcome measure(s)	Result(s)
Pfab 2011	RCT	5/5	25,2+/-4,5	2/8	SCORAD	ACU LI11+LI4+ST36+SP10 plus individual acupoints for each patient / 20 min x 2/ week x 10 sessions (33 days) -- topical class I and II corticosteroids allowed	NI - topical class I and II corticosteroids allowed	SCORAD VAS itch CD63 expression activity	VAS itch intensity significantly lower on day 15 (p<0,024) and day 33 (p<0,022) in ACU; SCORAD not significantly changed; CD63 expression significantly different in ACU vs. NI
Lee 2012	RCT w. CO	8/7	28,5 y (34/36) (19 - 79)	4/4 1/6	VAS EASI IGA	Acupressure LI11/ 3 min/ 3x/week for 4 weeks - OCT meds or lotions	OCT meds or lotions	VAS IGA EASI	Acupressure improved itch intensity (p<0,04) and lichenification in EASI (p<0,03)

Abbreviations: RCT: randomized controlled trial, CO: cross over study design; T: treated; C: controls; F: female; M: male; Dx Crit AD: diagnostic criteria for the diagnosis of AD; SCORAD: Severity Scoring of Atopic Dermatitis; ACU: acupuncture; NI: no intervention; VAS: visual activity score; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; OCT: over the counter drugs; Acupoints: LI: large intestine, ST: stomach; SP: spleen conduit (meridian)

4.2. Acupunture points mostly used in the studies discussed in detail

Four of the eleven named acupuncture points used as treatment in the eight studies discussed in detail above: LU1, LU2, LU3, LU4; HT3; LI 4, LI11; SP10, SP6; ST34, ST36 will be explained in some detail because at least some of them have been dubbed "classical acupuncture points" for cutaneous pruritus (Pfab et al., 2005; Augustin, 2012b).

As far as LU1, LU2, LU3, LU4 are concerned were these most likely chosen because they were either very close to the area of induction of itch ("local points") for LU3 and LU 4 or on the same conduit (for LU1 and LU2) in the experiments on histamine induced itch by Lundeberg and coworkers, 1987.

The by far most frequently used acupuncture point in all studies was:

LI11 / large intestine 11/ IC 11/ Quchi / *stagnum curvum* **/** cools xue on the extima

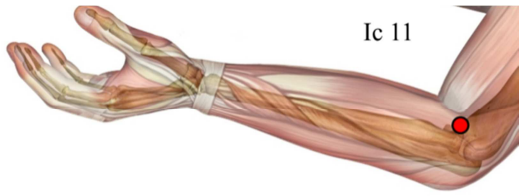

Figure 2 - Acupuncture point LI11

Position: within the crease situated radially above the elbow joint.

Effects of stimulation: Expelling ventus, opening up the extima, checking calor, draining humor, harmonizing constructive energy and the xue.

Symptoms and Indications: …dryness of the skin; exanthema and ulcerations, itching all over the body…. (Porkert & Hempen 1995b; Xinnong 1987; Greten, 2017a).

Situated on the same conduit and therefore logically also applicable is:

LI4 / large intestine 4/ IC 4 / Hegu / *valles coniunctae* / dispels ventus and distributes defensive qi (also a so- called c,v, h-point)

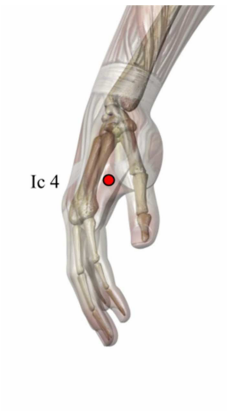

Figure 3 - Acupuncture point LI4

Position: At the radial side, approximately in the center oft he 2nd metacarpal, in a concavity.

Effects of stimulation: Dispelling ventus-heteropathies, releasing the extima, pressing down pain, unclogging reticular conduits.

Symptoms and Indications: External ventus…., Internal ventus….exanthemas… (Porkert & Hempen 1995b; Xinnong 1987; Greten, 2017a).

Nota bene: Greten (2017a) mentions that LI4 in some sources is named the "*aspirine-point*" referring to a particular potency against pain - as stated above in the text itch and pain share some modes of reception and transmission and therefore this dual effect seems logical.

SP10 / spleen 10 / L10 / Xuehai / *mare xue*

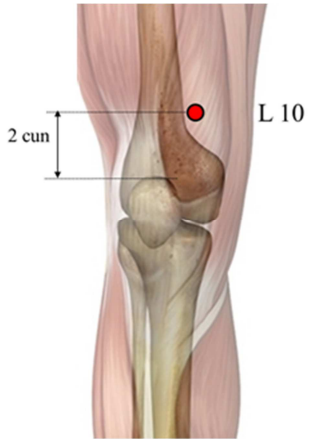

Figure 4 - Acupuncture point SP10

Position: 2 PI vertically over the upper, medial margin oft he patella.

Effects of stimulation: Regulating the xue, correcting disorders of menstruation.

Symptoms and Indications: …itch on different parts oft he body. (Porkert & Hempen 1995b; Xinnong 1987; Greten, 2017a).

Nota bene: Greten (2017b) mentions an extrapoint called **nidulus bestiolorum** and located 1 PC above SP10 that particularly treats itch. This point is also mentioned by Xennong (1987) in the same context and named **Baichongwo** *("hundred insect burrow"),* and in other sources called EX-LE3.

ST36 / stomach 36 / S 36 / Zusanli / *vicus tertius pedis*/ “the Soldier’s Point”

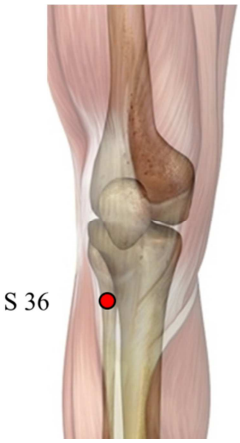

Figure 5 - Acupuncture point ST36

Position: 3 PI below the foramen S35, hence at the lower margin of the patella, and at one finger´s width (1 PC) from the anterior margin of the tibia near the *tuberositas tibiae*.

Effects of stimulation: Stabilizing and regulating the lienal and the stomach orb, harmonizing the qi and the xue.

Symptoms and Indications: …acute and chronic disorders affecting those people whose assimilative and integrative capacities are overtaxed by civilization: ….asthma….allergies…. (Porkert & Hempen 1995b; Xinnong 1987; Greten, 2017a).

4.3. Acupunture point selection and combination

Importantly, Pfab and Coworkers (2011) used in the only study that investigated the effect of acupuncture on atopic dermatitis and itch **individual acupuncture points** - selected by an "experienced acupuncturist" - but not given in detail in the publication - together with a "standard set" of points which were: LI11, LI4, ST36 and SP10 (Pfab et al. 2011).

Similarly the Heidelberg School recommends to always individualize acupuncture treatments according to the TCM diagnosis based on several different diagnostic criteria (Greten, 2016 and 2017a/b). Nevertheless certain clinical signs and symptoms used to describe AD or itch in Western medicine can be related to TCM heteropathies according to the Heidelberg model as well and are exemplified below in **Table 4**:

Symptom	**Causes (TCM)**	**Acupuncture points**
Dry, scaling, pale skin	lack of fluids lack of xue (yin)	LU 5, KI 7, SP 6, SP 10 (P 5, R 7, L 6, L 10)
Red skin	calor, hepaticity	ST 44, LI 11 (S 44, IC 11)
Itching	ventus, hepaticity	H 3, LI 11, LU 5 **(**H 3, IC 11, P 5) (bleeding), nidus bestiolorum (EX-LE 3)

Table 4 - Symptoms, causes and acupuncture points in dermatology (translated and modified after: Greten, 2017b)

Particularly LI11 and SP10 occur in most of the studies, textbooks and models.

4.4. Contols: no intervention vs. pseudoacupuncture vs. placebo-acupuncture

In the studies described various methods and modes of interventions for the control groups were utilized: no intervention, placebo-acupuncture (needles penetrating and at non-acupoint(s), pseudo-acupuncture (needles not penetrating but at acupoint(s), placebo-pseudo-acupuncture (at non acupoint(s) and non penetrating), in some studies also as electroacupuncture. Evidence exists however, that placebo procedures as described can as well have treatment effects superior to no intervention or even active treatments (Lundeberg et al. 2011). On the other hand very sophisticated but also complex double-blind-placebo-controlled study schemes have been performed and published (Karner et al., 2013) or planned (Seca et al., 2016).

4.5. Limitations

The main limitation for the primary goal of this review, namely to identify high quality studies to evaluate the clinical value of acupuncture alone in the treatment of itch in patients with atopic eczema is the paucicity of studies on the topic in general, RCTs in particular and the absence of any study meeting all inclusion criteria.

One could argue that this systematic literature review searched only three and Western databases and only articles with at least an English abstract and therefore may have overlooked important studies. This seems, however, rather unlikely since other systematic reviewers that included many more databases did not find anymore relevant studies in the relatively recent past. In addition it is very likely that Eastern medicine researchers would have published their results from high quality RCTs on the topic such that they would have been found by this or the above mentioned systemic reviews.

Limitations concerning the extended discussion of interesting studies that failed inclusion but nevertheless seemed worthwhile to be explored into depth are the low number of studies (2), the low patient numbers enrolled (15 and 10, respectively (Lee et al, 2012; Pfab et al. 2010)), and the lack of adequate control for concomitant basic therapies (such as moisturizers), that alone can have dramatic effects on itch. Finally the acupuncture points were individualized in the latter study and are therefore not comparable.

4.6. Suggestions for further research

RCTs on the clinical value of acupuncture alone - as monotherapy - as only therapeutic intervention at a given time - in the treatment of itch in patients with atopic eczema would be needed. These would have to be rigorously controlled for several concomitant factors such as basic therapy with moisturizers, active concomitant therapy with e.g. local corticosteroids, allergen exposure (e.g. seasonal allergies) and many others. Furthermore a double-blind placebo controlled setting for the acupuncture vs. placebo-acupuncture would indeed be possible, as exemplified in acupuncture studies in the past (Karner et al., 2013) but very laborious and therefore probably hard to establish.

The often complex personalities of AD patients that seemingly also influence itch reception and perception on various levels may prevent control of studies as well.

Therefore it may be virtually impossible to design or even more difficult to carry out these studies - which in turn may explain, why such studies have not been done to date.

5. CONCLUSION

In conclusion, this systematic literature review did not find high quality data to judge the effect of acupuncture as single treatment (monotherapy) for atopic itch in a clinical setting and therefore no evidence-based recommendations can be made based on this review.

This is in contrast with several other systemic reviews that have been published in recent years, some of which claimed to have found such studies and therefore included them into their reviews (Ma et al. 2015; Yu et al. 2015) and very recently (Shi et al. 2017).

Others reviewers were more cautious and therefore in line with the conclusion here in that they stated that the data available are too sparse and too inhomogeneous (Viera et al. 2016) or came to the same result as the review presented here and excluded the studies completely (Tan et al. 2015).

Several studies demonstrated however effectiveness of acupuncture in ameliorating histamine induced itch in healthy volunteers and atopic individuals as well.
There are also several studies on the effectiveness of allergen induced itch in atopic subjects.
Finally two studies showed ameliorating effects of acupuncture and acupressure on atopic itch in clinical practice, however not in a RCT and only with very small patient numbers.

Therefore rigorously designed and controlled RCTs to assess the efficacy of acupuncture in the management of atopic itch in clinical practice would be needed to clarify its usefullness as monotherapy. It may however for several reasons not be realistic that such studies will ever be performed. First, because patients, particularly those suffering from severe itch may not accept acupuncture as monotherapy. Secondly and related to the latter it would be very difficult to control for concomitant basic therapies such as moisturizers etc. over longer periods of time.

Notably no side effects were reported through all studies and also in all reviews cited in this work, although many of these papers stated that they explicitely investigated / searched for them. This may indicate that acupuncture is a safe intervention in AD patients.

Therefore the conclusion of this review is that acupuncture seems to be one possible treatment option to ameliorate atopic itch and thereby also be beneficial in supporting the treatment of atopic eczema but not necessarily as monotherapy.

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