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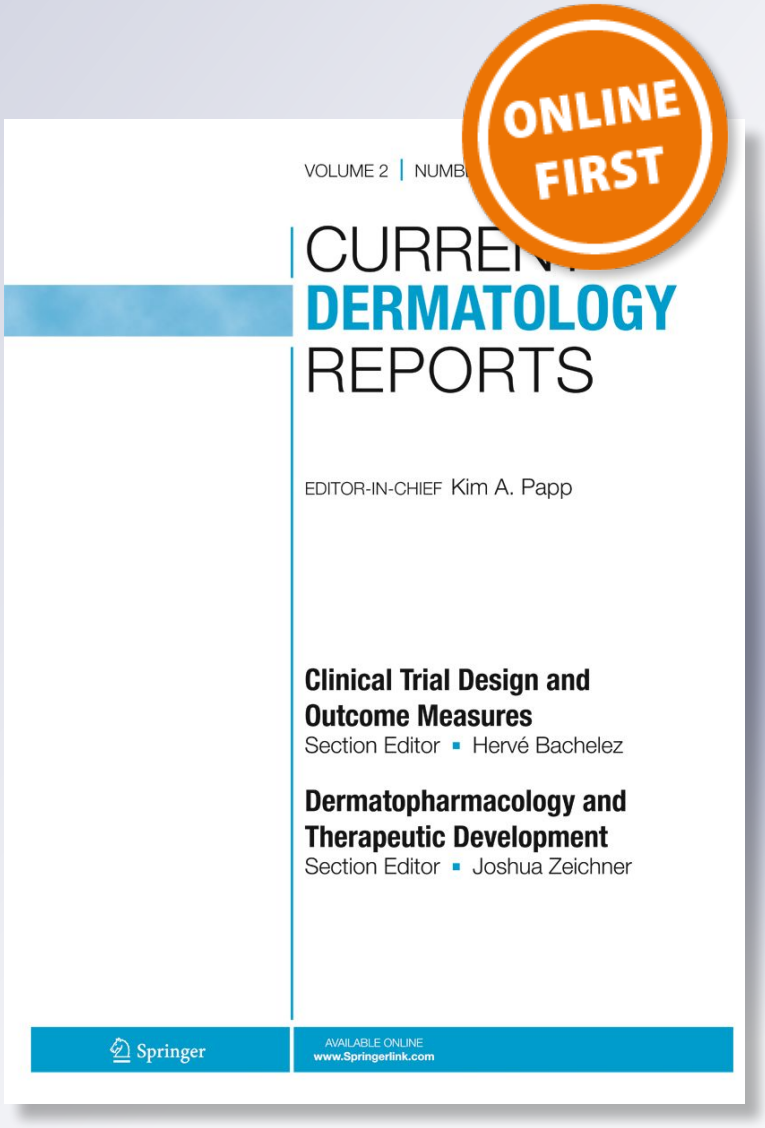
Current Dermatology Reports

e-ISSN 2162-4933

Curr Derm Rep
DOI 10.1007/s13671-017-0200-y



Springer

Curr Derm Rep
https://doi.org/10.1007/s13671-017-0200-y

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Botanical Complementary and Alternative Medicine for Pruritus: a Systematic Review

Jonathan G. Bonchak[1] · **Shalini Thareja**[2] · **Suephy C. Chen**[1] · **Cassandra L. Quave**[1,3]

Abstract
Purpose of Review Complementary and alternative medicine (CAM) is widely used by patients who suffer from chronic pruritus, but there is little data on the efficacy or antipruritic mechanism of these interventions. This review assesses the current understanding of the clinical efficacy and purported mechanisms of CAM therapy for pruritic skin disease, and serves as a basis for further investigation into the pharmacological basis of plant-based CAM for pruritus and patient motivations in the adoption of these types of therapies.
Recent Findings To assess the current state of the literature, we queried multiple databases for reports of botanical CAM therapies for pruritic skin conditions. Numerous in vitro and animal studies show positive results, but antipruritic effects in human trials are varied. Many of these topical and systemic therapies have demonstrated measurable impact on inflammatory pathways, including some that are known to be crucial in transmission of itch signaling.
Summary CAM is a frequently utilized but somewhat poorly understood intervention for chronic pruritus, though our understanding of the impact of these therapies on pruritus has improved in recent years. Further studies into the mechanism and efficacy of CAM-based therapies for chronic pruritus, and patient attitudes towards these practices, are warranted.

Keywords Pruritus · Itch · CAM · Complementary · Alternative · Botanical

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This article is part of the Topical Collection on *Itch*

✉ Jonathan G. Bonchak
jonathan.bonchak@emory.edu

[1] Department of Dermatology, Emory University School of Medicine, 1525 Clifton Rd, Suite 100, Atlanta, GA 30329, USA

[2] Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

[3] Center for the Study of Human Health, Emory University, Atlanta, GA, USA

Introduction

Complementary and alternative medicine (CAM) encompasses a diverse array of treatment modalities with varied efficacy practiced by many patients. CAM therapies can be divided into alternative medical systems (Traditional Chinese medicine, Ayurvedic medicine, etc.), biologically based therapies (e.g., herbal supplements), diet-based therapies, manipulative and body-based therapies, and mind-body therapies. Motivations for pursuing CAM include desire for personal control, holistic beliefs and spirituality, and dissatisfaction with conventional medicine [1, 2]. Patients typically initially consult family, friends, and close associates for CAM recommendations, and they often use internet resources to ensure the CAM intervention fits within their own value system [3].

The use of CAM in the USA is widespread and frequently practiced without consultation with a physician. Analysis of National Health Interview Survey data revealed that not only do 38% of adults [4••] and 12% of children [5] use CAM therapies, but the annual expenditures for CAM services and products in 2012 alone reached $30.2 billion in out-of-pocket expenses [6]. This figure includes $1.9 billion spent specifically on children age 4 to 17 years old. “Natural products,” such as dietary supplements, are among the most common CAM approaches used [7].

Published online: 19 October 2017

According to national data, 84% of people with skin disease reported use of CAM in 2009 [8]. In this survey, herbal therapies were the second most commonly used CAM (32%) behind vitamins and minerals. The most frequently reported dermatological indication for initiation of CAM is xerosis (29%) followed by pruritus (14%), far ahead of the next three commonest indications: wrinkles, (7%), skin cancer (5%), and toenail fungus (5%) [9•]. Despite its widespread adoption, physicians are often unaware their patients are using CAM. In one study of 1584 adults, 57% admitted to CAM use without notifying their physician [10].

Pruritus is common and has significant impact on quality of life. The estimated lifetime prevalence of chronic pruritus in European adults is 26% [11] and the point prevalence in various studies ranges from 8 [12, 13] to 27% [13–15]..Shive et al. found from the 1999 to 2009 National Ambulatory Medical Care Survey (NAMCS) that 1% of all outpatient visits, approximately 7 million per year, included a code for itch, of which one-third were considered chronic [16]. Carr et al. utilized the Veteran's Affairs national care database to randomly select 6000 veterans who had at least one encounter with the VA hospital system. Of the 1075 who agreed to participate, 403 (37%) reported pruritus lasting for at least 6 weeks [17]..

Quality of life (QoL) impact has been investigated in small specific populations. Yosipovitch et al. found that pruritus affected sleep in 58% of chronic idiopathic urticaria patients and 61% of uremic patients surveyed. They also found a significant percentage of depression in both the patients with urticaria (14%) and the uremic patients (8%) [18]. Kini et al. emphasized this impact by employing time trade-off utilities, a health economic measure of QoL and found that surveyed chronic pruritus patients were willing to trade 13 years of life, on average, to have the remainder of their lives without itch [19]. Halvorsen et al. found that adolescents with chronic pruritus were three times as likely to have suicidal ideation compared to adolescents without itch, which is comparable to results in similar studies on chronic pain [20].

CAM represents an often-used but somewhat poorly characterized treatment modality for chronic pruritus. The aims of our review are two-fold: (1) to identify reports of botanical CAM interventions for pruritus in the literature and (2) to investigate reports on potential mechanisms of action and clinical efficacy. This serves as a basis for further investigation into the role of CAM in management of pruritus, patient attitudes, and motivations in the adoption of CAM for itch, and the pharmacological basis of these plant-based therapies.

Methods

A search of the literature was performed in PubMed, Scopus, and Medline. In PubMed, a combination of Boolean operators, mesh terms, and title and abstract tags were utilized to optimize comprehensiveness of results. Search terms used to limit results to pruritic conditions include "itch," "pruri*" (to include pruritus, pruritic, prurigo), "atopic," "eczema," and "psoriasis." Terms used to invoke plant-based ethnobotanical therapies include "CAM," "complementary," "integrative," "plant," and "botanical".

All resulting abstracts were analyzed for relevance to this study. Reports that did not specifically address the botanical therapy's antipruritic effect in terms of either efficacy or purported mechanism were not included. Clinical trials, case reports and case series, and animal studies investigating individual botanical therapies for itch were tabulated in an Excel database. These studies were organized by family, species, and common plant name; type of pruritus in report; study type; and description of the bioactivity or efficacy of plant. Botanical and fungal nomenclature follows Angiosperm Phylogeny Group IV [21] and Mycobank [22] recommendations, respectively.

Results

The combination of search terms for inclusion in this review yielded 48 reports of 12 plant and 1 fungal species with antipruritic activity. Both systemic and topical routes of administration were described. Pruritus of multiple etiologies and dermatologic conditions were studied, including uremic pruritus, histaminergic pruritus, atopic dermatitis, and psoriasis. The results consist of 12 clinical trials, 13 case series or reports, and 20 animal studies. The following plant-based therapies for itch were chosen for discussion based on availability of reports regarding either their clinical efficacy or anti-inflammatory mechanism.

CAM Efficacy and Mechanisms

Here, we review data concerning the bioactivity, clinical efficacy, and mechanism of action for 8 phytotherapeutics with reported antipruritic activity. Detailed anti-inflammatory and antipruritic pathways for these particular plants have been elucidated (Tables 1 and 2), though there are numerous ethnobotanical reports of plants with possible antipruritic activity whose mechanism has not yet been investigated.

Oats

Colloidal oatmeal is a common home remedy utilized for centuries for pruritic skin conditions such as eczema, contact dermatitis, and varicella zoster. It is derived from the finely ground grains of *Avena sativa* L., Poaceae. It can be purchased in moisturizers, as bath therapy, or prepared at home from oats.

Table 1 Various plant and fungal species reported for the treatment of pruritus

Family	Species	Common name	Type of pruritus	Study type	Reports
Asphodelaceae	*Aloe vera* (L.) Burm. f.	Aloe vera	PSO	CT	[23–29]
Asteraceae	Various (e.g., *Matricaria recutita* L., *Chamaemelum nobile* (L.) All.)	Chamomile	HP	A	[30–35]
Cannabaceae	*Cannabis sativa* L.	Cannabis	HP UP LSC PN ACD Cholestasis	A, CS, CT	[36••, 37–46]
Convolvulaceae	*Cuscuta campestris* Yunck.	Dodder	AD	CT, ER	
Fabaceae	*Glycyrrhiza glabra* L.	Licorice	AD	CT	
Lamiaceae	Various *Mentha* spp.	Menthol	Lichen amyloid, EB, Pruritus gravidarum, TRP pruritus	A, S, CS, CT	[47–50]
Lamiaceae	*Scutellaria baicalensis* Georgi	Chinese skullcap	PSO	A	
Lauraceae	*Cinnamomum camphora* (L.) J. Presl	Camphor tree	EB Starch-induced	S, CS	[51–54]
Pleurotaceae	*Pleurotus ostreatus* (Jacq.) P. Kumm.	Oyster mushroom	AD	CT	
Poaceae	*Avena sativa* L.	Oat	AD Burns ACD	A, CS	[55–59]
Solanaceae	various *Capsicum* spp.	Peppers	UP PN PRP Pruritus ani	CS, CT	
Zingiberaceae	*Curcuma longa* L.	Turmeric	PSO UP Mustard-induced	CT	[60–64]

Type of pruritus: *PSO* psoriasis, *HP* histaminergic pruritus, *AD* atopic dermatitis, *UP* uremic pruritus, *LSC* lichen simplex chronicus, *PN* prurigo nodularis, *ACD* allergic contact dermatitis, *EB* epidermolysis bullosa, *PRP* pityriasis rubra pilaris. Study type: *CT* clinical trial, *A* animal study, *CS* case series/report, *ER* ethnobotanical report, *S* survey study

Table 2 Summary of known bioactive components, mechanisms of action, and pruritic condition treated by botanicals

Botanical	Bioactive component	Purported mechanism	Pruritic condition treated	Route of admin.
Colloidal oatmeal	Avenanthramides	Natural emollient ↓NF-kB ↓IL-8	Burn wounds [56] Tyrosine-kinase inhibitor-induced itch [57, 58] Atopic dermatitis [59]	Topical
Aloe vera	Aloin Aloesin	↓NF-kB translocation ↓IL-1B, ↓IL-6 ↓COX-2, ↓Thromboxanes	Psoriasis [28, 29]	Topical
Camphor	Camphor	Activates TRPV1 and TRPA1	Epidermolysis bullosa [53] Hydroxyethyl starch-induced pruritus [54]	Topical
Cannabis	Various cannabinoids	Activates CB1, CB2 Activates TRPV1	Histaminergic itch [43] Uremic pruritus [44] Lichen simplex chronicus [45] Prurigo nodularis [45] Cholestatic pruritus [46]	Systemic, topical
Chile peppers	Capsaicin	Activates TRPV1	Pruritus ani [65] Uremic pruritus [66, 67] Prurigo nodularis [68] Pityriasis rubra pilaris [69]	Topical
Chamomile	Bisabolol Apigenin	↓AP-1, NF-kB, TNF-α ↓IL-6, IL-4 ↓IgE	None reported	
Mint	Menthol	Activates TRPM8, TRPA1	Lichen amyloidosis [50] Epidermolysis bullosa [53] Pruritus gravidarum [70]	Topical
Turmeric	Curcumin	↓AP-1, NF-kB, protein kinase C ↓IL-22, IL-8 ↓hs-CRP	Psoriasis [71] Uremic pruritus [61] Sulfur mustard-induced pruritus [62]	Systemic

Colloidal oatmeal forms a protective barrier against irritants and has hydrocolloids that prevent transepidermal water loss (TEWL). Attenuation of TEWL is important particularly in atopic dermatitis as it reflects integrity of the epidermal barrier, a key pathogenic factor in the disease. Antipruritic effects of oats are also derived, in part, from its emollient properties. Further, they contain avenanthramides, alkaloids that confer anti-inflammatory properties in vitro by attenuating NF-kB signaling and reducing IL-8 production in keratinocytes [55]. Studies suggest that colloidal oatmeal reduces itch associated with burn wounds [56], tyrosine-kinase inhibitors [57, 58], and atopic dermatitis [59].

Aloe Vera

Aloe vera (*Aloe vera* (L.) Burm. f., Asphodelaceae) is a popular medicinal plant that has been used for centuries and is best known for its healing and soothing effects when the inner leaf gel is applied to skin. More than 200 bioactive components are contained within the plant. The best known include the anthraquinones aloin and aloresin, and the polysaccharides aloeride and acemannan [23].

Aloe vera is one of the most commonly used herbal remedies amongst dermatology patients [24]. Dietary aloe appears to decrease expression of IL-1B and IL-6, and decreases translocation of NF-kB from the cytosol in mice [25]. In vitro studies suggest inhibition of Cox-2 and thromboxanes by aloesin [26]. Finberg et al. showed that a topical *Aloe ferox* and *Aloe vera* extract decreases IgE levels in a mouse model of atopic dermatitis [27]. Human trials are lacking, especially considering the popularity of aloe vera. Studies comparing aloe vera extract to placebo or to triamcinolone cream in psoriasis show mixed results [28, 29].

Camphor

Camphor is a terpene derived from the wood of the Camphor tree (*Cinnamomum camphora* (L.) J. Presl, Lauraceae), an evergreen native to East Asia. Though its most common ethnobotanical use is as an inhalant, providing relief as an antitussive and decongestant, it has analgesic and antipruritic effects when applied topically.

Camphor affects itch sensation by activating and desensitizing the transient receptor potential channel (TRP) V1 and A1 [51, 52]. This family of thermosensitive receptor channels is integral in pruritogenesis. Substances with antipruritic activity that produce a heating or cooling effect on the skin seem to work at these receptors. Despite its common use as a CAM agent, few studies exist analyzing camphor's clinical efficacy for dermatologic conditions. Patients report that vaporizing rub, which contains menthol, camphor, and eucalyptus, is an effective antipruritic in epidermolysis bullosa [53]. Camphor with menthol successfully treated hydroxyethyl starch-induced pruritus in one patient [54].

Cannabis

Members of the *Cannabis* genus have been used for centuries in India, China, and Africa for a host of maladies. They have long been used topically for the remedy of pruritus and eczema in traditional Indian medicine [72], and was used in the nineteenth and early twentieth century in Western Europe and America for similar indications [73, 74]. Because they impact numerous cutaneous processes, the role of cannabinoids in cutaneous disease has garnered increased attention in recent years [36••].

Cannabis spp. contain several bioactive components known as cannabinoids. The best known are tetrahydrocannabinol (THC) and the non-psychoactive cannabinoids cannabidiol and cannabinol. These compounds affect the itch pathway by acting at cannabinoid receptors (CB1 and CB2) and by activating various TRPs [37]. Numerous studies in mice suggest that cannabinoid agonists alter itch perception [38–41]. Endogenous cannabinoids have been shown to downregulate mast cell activation [42]. In humans, topical cannabinoid agonists have been shown to attenuate histaminergic itch [43], uremic pruritus [44], and pruritus due to lichen simplex chronicus and prurigo nodularis [45]. Cholestatic pruritus has been successfully treated with systemic cannabinoids in the form of dronabinol [46].

Chile Peppers

Native to the Americas, *Capsicum* spp. of the Solanaceae family bear peppers that are the source of capsaicin, an alkaloid that gives hot peppers their spicy kick and also possesses numerous medicinal properties. Capsaicin produces a hot sensation when applied to the skin which confers its antipruritic effects, activating TRPV1 which is key in the various itch pathways including histaminergic pruritus [75]. Trials have shown that neuropathic itch can be remedied with a transdermal capsaicin patch [76, 77]. Idiopathic, intractable pruritus ani has been relieved with topical capsaicin [78]. Other conditions successfully treated with capsacin include uremic/hemodialysis pruritus [66, 67], prurigo nodularis [68], and pityriasis rubra pilaris [69]. Capsaicin failed to ameliorate serotonergic itch in healthy volunteers [79].

Chamomile

Chamomile is one of the most long-used medicinal herbs known. A popular form of chamomile sold in the marketplace is German Chamomile (*Matricaria recutita* L., Asteraceae). The flower contains dozens of bioactive terpenoids and flavonoids which confer the plant's anti-inflammatory properties [80]. Bisabolol and apigenin are the best known of these compounds. The former has been shown to inhibit activation of various inflammatory markers including AP-1, NF-kB, TNF-alpha, and IL-6 in murine models [30, 31]. Apigenin mitigates NF-kB and IL-4 expressions and decreases IgE levels in mice. Multiple studies have shown that chamomile decreases histaminergic pruritus [32–34] and inhibit anaphylaxis [32] in type I hypersensitivity allergy models in mice. In these experiments, rodents exhibited significantly less scratching behavior in response to compound 48/80-induced mast cell degranulation, and the effect was more pronounced when chamomile was given together with a first-generation antihistamine. In a mouse model of atopic dermatitis, application of German chamomile led to decreased scratching behavior, attenuated lymphocyte infiltration on histology, and reduced serum IgE levels [35].

Mint

Peppermint (*Mentha x piperita* L., Lamiaceae) has been used medicinally in Japan for millennia. Its most interesting active component is menthol, a cyclic terpene alcohol which gives plants in the *Mentha* genus their characteristic smell [47]. It boasts a variety of CAM applications. Applied to the skin, it creates a cooling sensation and activates the thermosensitive TRPM8 and TRPA1, which results in inhibited itch signal transmission [48, 49, 75]. It has been reported as effective in relieving pruritus in conditions such as lichen amyloidosis and epidermolysis bullosa [50, 53]. Despite its widespread use, the literature is relatively scant regarding its pharmacological utility in humans.

Turmeric

Turmeric (*Curcuma longa* L., Zingiberaceae) is an herbaceous plant native to South Asia from which the well-known culinary spice turmeric is derived. It has been an element of Indian spiritual and medicinal practice for thousands of years, and is still used in the Ayurvedic and Chinese systems of medicine today. Touted for antimicrobial and anti-inflammatory properties within these traditional systems, turmeric is used topically to treat a host of dermatologic ailments including scabies, ulcers, pruritus, and fungal infections [81–84].

There is evidence that curcumin, a bioactive constituent of turmeric, is beneficial in a variety of pruritic dermatological diseases. In psoriasis, oral curcumin together with topical corticosteroids achieved greater reduction of disease burden than topical corticosteroids alone. This correlated with greater reductions of IL-22 in that same group [60]. Patients with uremic pruritus report decreased itch and have lower high-sensitivity C-reactive protein (hs-CRP) levels when given turmeric orally [61]. Curcumin also improves itch and decreases hs-CRP and IL-8 levels in veterans with chronic pruritus due to sulfur mustard exposure [62, 63]. Though the relationship between curcumin and the itch pathway remains unclear, it has been shown to decrease expression of thymic stromal

lymphopoietin [64] which is an important pruritogenic cytokine in atopic diseases [85].

Conclusion

Patients have long utilized CAM for chronic pruritus. Numerous plants have purported antipruritic effects, but relatively few studies exist investigating the mechanism by which they work. Considering the prevalence of CAM usage for chronic pruritus, further studies are warranted to better characterize patients' use of CAM therapies for chronic pruritus and their motivations for doing so. Further, as the physiological basis for antipruritic activity of plant-based CAM therapies is better understood, clinicians can leverage botanical treatments as adjuvant therapy and glean insight from their use to develop novel treatments for itch.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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