Stirring the Pot: Cannabinoids and AD

Cannabinoids are a diverse group of compounds that may hold significant therapeutic capabilities applicable to many areas of medicine, including dermatology.

BY MICHAEL SHALABY, HELENA YARDLEY, PhD, AND PETER A. LIO, MD

Atopic dermatitis (AD) is one of the most prevalent skin diseases, affecting up to 20 percent of the population in the developed world and with a predilection for children.[1] AD has a significant disease burden, both taxing economically and decreasing the quality of life for patients.[2,3] Although the pathophysiology of AD has been increasingly understood, functional treatments have historically lagged behind discoveries regarding the disease's basic scientific underpinnings.[4] Recently, several new AD therapies have been launched, and the pipeline for new therapies is more robust than ever before.

While these pharmaceutical advancements are truly exciting for both patients and clinicians, there is perhaps a greater drive in AD than in other conditions for alternative, "natural," and unconventional treatments to circumvent some of the common side effects of long-term use. One intriguing area of the intersection between scientific discovery and natural approaches lies within the science of cannabinoids. Topical cannabinoids for itch and pain are already being marketed on the Internet but are not yet available as prescription medications from physicians without a special license; and even then, the regulatory systems limit access to only certain states.

Infamous as the main chemical agent in marijuana, delta (9)-tetrahydrocannabinol (THC), has led to a lingering stigma around cannabis because of its psychoactive properties. Perhaps as a consequence of this stigmatization and hazy legal status, research in this area has been largely overlooked until recently. Cannabinoids are a remarkable and diverse group of compounds that hold significant therapeutic capabilities applicable to many areas of medicine, including dermatology.[5,6] Since the first human cannabinoid receptors were discovered in the twentieth century, a myriad of noteworthy applications for these promising derivatives of the Cannabis plant have been discovered. Of particular interest in dermatology are their application for inflammation, the immune system, and skin homeostasis.[7]

CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

Marijuana, derived from the plant *Cannabis sativa* is one of the oldest and most widely used drugs in the world.[8] Of the more than 60 agents in marijuana and five major cannabinoids, including cannabidiol (CBD), cannabichromene (CBC), cannabigerol (CBG), delta (9)-tetrahydrocannabinol (THC), and cannabinol (CBN), only THC has intoxicating effects, and this one constituent has perpetuated the stigma and contributed to its illicit status in most states in the US. This status has also created considerable hurdles to research on the use of cannabinoids as approved medicines. However, the relatively recent discovery of cannabinoid receptors and their ligands throughout the human body has led to more open discussion on their role in physiological conditions and in various pathologies. Applications for cannabis have been explored in many conditions including anorexia, chronic pain, nausea, spasticity, atherosclerosis, autoimmune disorders, inflammatory bowel disease, multiple sclerosis, and tumorigenesis.[9] Cannabinoids have sought a place in dermatological disorders as well, including use in acne, eczematous disorders, lichen simplex, melanoma and nonmelanoma skin cancer, melasma, prurigo, pruritus, psoriasis, scleroderma and systemic sclerosis, and seborrheic dermatitis.[10]

The endocannabinoid system consists of cannabinoid receptors (CBRs), their lipid ligands, and regulatory enzymes. Endocannabinoids, such as arachidonoyl ethanolamide (anandamide, AEA), 2-arachidonoyl glycerol (2-AG) and palmitoylethanolamide (PEA), are synthesized endogenously.[11,12] Phytocannabinoids, such as THC and CBD are naturally produced by plants, while synthetic cannabinoids are designed in laboratories.[13] CBRs have been found in keratinocytes and on peripheral nerve fibers, and this distribution may play an important role in skin disease therapy.[14] Early research demonstrated that cannabinoids act upon CBRs, but newer studies have demonstrated their wide array of associations with other channels and receptors, such

APPLICATIONS EXPLORED FOR CANNABIS[9]	
Anorexia	Dermatological disorders
Chronic pain	Acne Eczematous disorders Lichen simplex Melanoma and nonmelanoma skin cancer Melasma Prurigo Pruritus Psoriasis Scleroderma and systemic sclerosis Seborrheic dermatitis
Nausea	
Spasticity	
Atherosclerosis	
Autoimmune disorders	
Inflammatory bowel disease	
Multiple sclerosis	
Tumorigenesis	

as TRPV1, GPR55, PPAR-γ, PPAR-α, as well as their direct effects on keratinocytes independent of CBRs, opening up even more potential targets in dermatological disease treatments.[15,16]

ATOPIC DERMATITIS

AD is a disease that has become increasingly prevalent in the modern world. While it has been well-established that mutations in FLG, the gene that codes for the structural protein filaggrin disrupt the skin barrier in AD,[17] and that Th2 cytokines drive inflammation,[18] the story does not end there. New chemokines have been implicated in inflammatory pathways of AD. For example, thymic stromal lymphopoietin (TSLP) is a protein that is highly expressed by epithelial cells of patients with AD.[19] TSLP incites the Th2 response via chemokines such as IL-4, -5, -13 and TNF-α. These chemokines, in turn, up-regulate TSLP, spawning a vicious cycle.[20] Chemokine ligand 8 (CCL8) is another prominent inflammatory mediator which instigates a Th2-type reaction. These and other mediators promote inflammation, skin barrier dysfunction, and pruritus in AD.

CANNABINOIDS IN PAIN, PRURITUS, AND ATOPIC DERMATITIS

Pruritus is signaled by a complex interaction of mediators both in the skin and the central nervous system that leads to the "itchy" sensation. It can be so profound that it can disrupt sleep quality with frequent awakenings and reduced sleep quality, which result in increased tiredness throughout the day[21] and decreased levels of cognitive performance.[22]

Many features of AD contribute to pruritus, including dry skin, histamine release, and sensory nerve fiber hypertrophy. Dry skin exacerbates pruritus by causing the release of pruritogenic mediators from keratinocytes.[23] Th2 lymphocytes of patients with AD have up-regulated histamine receptors.[24] Sensory nerve fiber hypertrophy is induced by growth factors released by irritated keratinocytes.[25]

Cannabinoids, however, are potently antipruritic and work against each of these defined mechanisms and others. CBR agonists, by stimulating CB1 and CB2 receptors on sensory nerve fibers in the skin, reduce pruritus by inhibiting the release of calcitonin gene-related peptide (CGRP), a ligand known contribute to flare-reactions in AD.[26,27] Synthetic cannabinoids have also been shown to reduce pruritus via anti-histaminergic properties.[28] Topical PEA reduces itch by desensitizing the TRPV1 channel, an important initiator of pruritus and an integrator of other sensory phenomena such as pain and heat.[29] Further supporting this understanding is the fact that inhibitors of the enzymes that degrade endocannabinoids have also been shown to mitigate pruritus.[30] Topical cannabinoids have even helped relieve uremic pruritus, though the mechanism is unclear.[31]

Cannabinoids also exhibit anti-inflammatory properties, another important characteristic relevant to AD. Applicable to the pathophysiology of AD, Gaffal et al demonstrated that topical THC suppresses allergic contact dermatitis in mice by activating CB1 receptors.[32] Notably, THC was also shown to be able to bypass CBRs entirely and directly stimulate keratinocytes to decrease inflammation.

Confusingly, however, some studies have shown that the absence of cannabinoid receptors leads to a heightened inflammatory response, suggesting a more complex role of the endocannabinoid system in modulating cutaneous inflammation. Furthermore, the absence of CB1 receptors delays skin permeability barrier recovery after exposure to irritants and also results in decreased levels of filaggrin, loricrin, and involucrin.[33,34,35]

While most authors seem to acknowledge the benefit of overall increased endocannabinoid tone on inflammation, pruritus, and pain, there is some debate over whether cannabinoids mitigate inflammation or actually worsen it. For example, Ueda et al. determined that a CB2 antagonist decreased inflammation in mice.[36] In a similar study, a CB2 agonist exacerbated inflammation in mice.[37] In an equally puzzling finding, CB2 receptor-deficient mice have shown speedier recovery from skin irritants.[38] Thus, there may be more complex modulatory roles beyond simply being anti-inflammatory, and these nuances require more research in order to be understood.

Despite the complexities of the underlying mechanisms, there are tantalizing reports of direct improvement of AD via topical cannabinoids and CBR agonists. Nam et al. showed that CB1 receptor agonists ameliorate AD in mouse models, possibly via mast cell down-regulation.[39] In another rodent study, CB1 receptor activity improved AD by reducing levels of TSLP and CCL8.[35] Kim et al. devised a compound structurally similar to anandamide, which enhanced

epidermal barrier function and suppressed Th2-biased cytokine expression in mice as well by binding CB1 receptors.[40]

Human trials have also shown promising outcomes for AD. In a trial for pediatric and adult patients, a PEA-containing cream significantly reduced mean time to the next flare.[41] Similarly, in a pilot study, a topical cannabinoid emulsion resulted in clinical resolution and prevented relapse of mild atopic dermatitis in 80 percent of patients.[42] In another trial, a PEA-containing cream improved severity of itch and loss of sleep by an average of 60 percent among subjects.[43] Twenty percent of subjects discontinued their topical immunomodulators, 38 percent ceased using their oral antihistamines, and 33.6 percent no longer felt the need to maintain their topical steroid regimen by the end of the study.

WHAT LIES AHEAD

Cannabinoids represent an exciting prospect for the future of AD therapy. They exhibit measurable antipruritic, antinociceptive, and anti-inflammatory properties, and their use in AD has already been demonstrated. While the studies are relatively few and the responses somewhat modest, the significant disease burden of AD warrants exploration of any promising therapeutic approach. More studies are required of cannabinoids, and their widely illegal status continues to make this even more challenging. With hope, more clinical data will help open doors for this compelling group of compounds. ■

Conflicts of interest statement: Helena Yardley, PhD is an employee of Franklin BioScience, the manufacturer of Altus products. Peter Lio, M.D. is on the advisory board of Franklin BioScience.

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