SEVC SOUTHERN EUROPEAN VETERINARY CONFERENCE
SEVILLE, 23-25 October 2025

THE ENDOCANNABINOID SYSTEM AND SKIN: IS THERE A ROLE AND HOW CAN WE TREAT?

Joseph J Wakshlag
Cornell University/Ellevet Sciences
Department of Clinical Sciences
Ithaca, NY
United States of America

The endocannabinoid system:

Cannabinoids from hemp have gained popularity in the United States and other countries due to the ability to influence the endocannabinoid system. In short, the endocannabinoid system revolves around a naturally produced fatty acid within synapses and tissues as two major molecules that undergo heavy recycling at cell membranes. The two most prominent of these molecules is Anandamide (Arachydonyl ethanolamide) and 2-arachidonyl glycerol (2-AG) that can influence a variety of receptor systems. Cannabinoids from hemp appear to influence the same receptor systems as the endogenous ligands. The major cannabinoids formed in hemp are based on strains that have synthase activities towards major cannabinoids with the biggest three found predominantly being cannabigerolic acid (CBGA), cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA). (1) As you can see the plant makes acidic forms of these cannabinoids which when extracted under high heat causes decarboxylation to the forms we know as cannabidiol (CBD), delta 9 - tetrahydrocannabinol (THC) and cannabigerol (CBG). (2) Most of the legal hemp cultivars across countries will be rich in CBDA or CBGA with very little THCA that will eventually become CBD, THC and CBG in products with other minor cannabinoids if it is a full spectrum or broad spectrum product. Most countries allow at least 0.2% THC or slightly greater in products that are saleable. Most products focus on CBD as the major cannabinoid and is where most of the research has been done, with other cannabinoids having promise as therapeutics as well.

Its not cannabinoid 1 and 2 receptors!

Much of the literature focuses on the cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptor as a major interaction point for cannabinoids, but this is not the case for CBD or CBDA. The relevant receptors systems identified as CBD or CBDA targets begin with the transient receptor potential ion channels (TRP). This family of ion channels are surely affected by CBD due to the high affinity at concentrations well below 1 uM. These receptors are important in the peripheral and central nervous system for nociception of the pain response and the binding of CBD to these receptors act in an agonistic and desensitization response leading to mitigation of pain.(1)

Groups of receptors associated with ion channel gating as well as intracellular signaling that are poorly studied including the g protein orphan receptors (GPR), glycine, peroxisomal proliferation gamma (PPAR-g) and adenine receptor system. The GPR55 and glycine receptors appear to be influenced by CBD and CBDA at relevant concentrations and are involved in the neuronal signaling and depolarization potential, whereby GPR55 may promote depolarization if activated by endogenous cannabinoids and CBD appears to be an antagonist of this receptor. Conversely, the glycine receptor when activated allows for repolarization due to influx of chloride causing hyperpolarization – both mechanisms lead to less depolarization potential thereby dampening transmission of nociceptive pain primarily in the central nervous system. The PPAR-gamma receptor is an intracellular receptor that influences transcription and translation of genes that are usually involved in cytokine production in immune cells leading to mild dampening of the inflammatory response globally. More specifically to seizures, CBD and CBDA appear to interact at the adenosine receptor/equilibrate nucleotide transporter leading to alterations in

glutamatergic signaling. Lastly a more popular receptor system affected by CBD and CBDA is the 5HT1A receptor and lesser so the 5HT2A receptor, both serotonin receptors that appear to be influenced by CBD as an agonist to promote a serotonergic stimulus and homeostasis around serotonin signaling for a feeling of wellness.(1)

When trying to understand the mechanisms by which CBD or CBDA are having their actions at a cellular level there are two major focus' including 1) pharmacologically relevant concentrations and 2) receptor interactions. Over the past 10 years is it relatively clear that current safe dosing of 1-10 mg/kg in dogs, and 1-5 mg/kg in cats lead to significant levels in the serum, which can have potential pharmacological interactions at receptors. (3,4) This large range suggests that dose may be relevant to clinical effect hence serum cannabinoid testing may be worthwhile – although there are no labs currently running these diagnostics in veterinary medicine. A majority of this work has been done in dogs with even less known about achievable serum concentrations in cats, with only a single 6 month chronic dosing of CBD at 4 mg/kg once a day showing safety in cats and in dogs there are three relevant long term dosing studies ranging from 4 mg/kg once a day to 100 mg/kg suggesting safety as doses of up to 10 mg/kg safely long term.(4)

Why CBD/CBDA?

CBDA has similar activities as CBD, however in some receptor systems CBDA appears to have greater activity. In general, CBD appears to have greater affinity and activity for the TRP system. However, CBDA has greater potency and ability to interact at the 5HT1A receptor, which appears to be involved not only in the feeling of wellness like most serotonergic systems, but appears to have better anti-nausea and vomiting influences than CBD. Additionally, CBDA and most of the acidic forms of cannabinoids appear to have potential as native COX-1 and COX-2 inhibitors. More importantly, CBDA appears to stimulate the PPAR system leading to overall decreased COX enzyme production in cells as a part of its anti-inflammatory effect.(2)

Atopic Dermatitis (and inflammation):

Initial studies on the receptors discussed above have shown that the CB1 and particularly the CB2 receptor appear to be upregulated in the skin of atopic dogs, not only in the keratinocytes, but also the adnexal and immune cells of the skin. Similarly, there is an increase in the GPR55, TRPV1, TRPA and 5HT receptors that appears to mirror the upregulation in the various cell types in the skin of atopic dogs. These immunohistologic finding have led to the hypothesis that these receptors may be potential targets for intervention.(5,6)

Further clinical evidence is now pointing to the potential utility of CBD use in the pruritic response associated with atopic dermatitis.(7) A recent publication in Veterinary Dermatology in a randomized placebo-controlled trial has shown a significantly diminished pruritic response through validated owner pruritus scores compared to placebo over a 4 week period when utilizing a CBD/CBDA rich hemp at 2 mg/kg twice daily in conjunction with other interventions in dogs with atopic dermatitis. This is the first demonstration in veterinary and human medicine that orally consumed cannabinoids have utility in control pruritus. (8) The use of hemp CBD has been confirmed further in a recently published open label pilot study as well as a healthy dog shelter cohort where accelerometry data was collected to examine activity, which was not altered, yet kenneled dog pruritic activity was shown to be quelled with similar dosing as the randomized controlled clinical trial.(9,10) What should be noted is that although pruritic activity was diminished with the use of CBD/CBDA the actual CADESI scoring of dogs was not observed to be significantly different suggesting a neurological response rather than an inflammatory response.

Although there is ample preclinical evidence that the inflammatory milieu related to macrophage and lymphocyte activation and release of inflammatory cytokines can be influenced by CBD/CBDA, the actual clinical literature is sparse.(11) Many in vitro or ex vivo studies of cannabinoids like CBD can dampen pro-inflammatory responses in experimental models; the reality is that much of this examination has been done through intraperitoneal injections and supraphysiological doses that may not be realistic with oral delivery. Currently, we are not observing that physiological concentrations (0.1-1 uM) of CBD or CBDA heavily influence things such as neutrophil migration or macrophage/lymphocyte production of pro or anti-inflammatory cytokines.(12) In concert with the lack of immunological alteration in the study of Loewinger et al, 2022 for atopic dermatitis; a study by Morris and colleagues, who examined similar dosing (2.5 mg/kg every 12 hours) and followed generalized humoral responses to KLH antigen, showed CBD did not negatively or positively influence humoral immunity.(13)

Other open label studies in dog with atopic dermatitis should also be recognized showing the potential for CBD in treating atopic dermatitis. A small cohort of 8 dogs with refractory atopic dermatitis were treated in an open label format with the higher dose being approximately 0.25 mg/kg of CBD in an oil format. The results suggest an improvement in clinical signs, however these dogs were being treated with other pharmaceuticals and it cannot be deduced on whether this was truly effective due to lack of a placebo group.(9) Interestingly, a larger study examining activity and itch in normal dogs being given 5 mg/kg as a high dose of CBD in a treat format did show that activity was not diminished in this shelter cohort, but that itching activity was diminished based on activity collars.(10) These data are pointing towards a neurological effect that leads to anti-pruritic activity more than an anti-inflammatory effect of cannabinoids.

Other nutraceutical use also points towards the endocannabinoid system as a target with an open labeled study examining the nutraceutical palmitoyl ethanolamine (PEA) supplementation. PEA is a natural compound that may have activity at the CB1 and CB2 receptors that are upregulated in the immune cells, keratinocytes and adnexal structures. A large open label study using 10 mg/kg of this nutraceutical suggested improvements in the VAS pruritic score and the CADLI scoring system for atopic dermatitis over 8 weeks in mild, moderate and severe cases of atopic dermatitis. Considering the large nature of the study with 160 dogs it does suggest potential efficacy even though not placebo blinded. Again, these dogs were under dermatologists care on other treatments that could not be altered during the protocol.(14) Lastly, a study performed by Marsella and colleagues using a endocannabinoid reuptake inhibitor of the enzymes involved in degredation of natural endocannabinoids in a colony of atopic dogs when used as 1% topical showed improvements in skin lesions and pruritic activity in the colony further suggesting that the endocannabinoid system is a target for pruritus and possibly dermal inflammation. (15)

Topicals and local use:

While in the human arena there has been more topical utilization of cannabinoid products than oral products suggesting promise for local application of cannabinoids. In dogs it has been shown that cannabinoids can get to meaningful serum concentrations when applied transdermally with one study using 20 mg/kg transdermal SID and 4 mg/kg applied BID.(16) Interestingly the acidic from of CBDA was shown to achieve 4-5 fold greater concentrations than CBD as the 4 mg/kg dose BID was an equal mix of CBD and CBDA. (17) The fact that serum concentrations can be measured suggests that there could be clinical application as a potential local anti-inflammatory. From personal experience, the author has not observed local ani-inflammatory activity per se when applied aurally as a means for transdermal and in fact when using a whole plant extract there may be other phenols and polyphenols that can cause skin reactions in sensitive dogs making isolates the preferred cannabinoids at this juncture for research.

However, with proper formulation and application based on Marcella and colleague study this is an area in need of further research.

As CBD and CBG have antibacterial properties born out in preclinical models as preliminary pilot study was performed using CBD and CBG isolates in a spray to mediate experimentally induced local staph dermatitis which is a starting point.(18) This pilot study used 42 mg application twice a day after lesion induction and staph application and when compared to the placebo there appeared to be no improvement of clinical lesion, neutrophil counts or staphylococcal count differences from placebo treated dogs other than a statistically significant lesion reduction two days quicker on the 42 mg equal mix of CBD/CBG when using a placebo ethanol glycerol based spray. Another pilot study was performed using 42 mg/ml in a hydrogel-based cream versus control hydrogel cream applied BID after lesion and staphylococcus induction. Again, in this study there was no improvement of lesion store, neutrophils or staphylococcus found between the placebo and treatment groups. This is disappointing however the clinical resolution of these induced lesions in healthy beagle dogs does not mimic the typical staphylococcal infection, but it was evident that the CBD/CBG or CBG alone treatments did not influence cocci enumeration in the lesion which was the primary objective.

The future:

Currently the use of oral CBD rich hemp appears to be a possible entity to help curtail the pruritic response in the allergic and atopic dog and with the use of PEA as a supplement it is pointing towards involvement of the endocannabinoid system in the atopic dog. The potential for topical treatment is similarly intriguing and there are a number of cannabinoids that could be tested that may be better than CBD that may have increased ability to penetrate skin, however the evidence is currently lacking for efficacy of topicals in dogs, yet it has not been thoroughly investigated either.

Selected References:

1.) Cristino L, Bisogno T, Di Marzo V.Cannabinoids and the expanded endocannabinoid system in neurological disorders.Nat Rev Neurol. 2020 Jan;16(1):9-29. doi: 10.1038/s41582-019-0284-z.
2.) Ukai M, McGrath S, Wakshlag J. The clinical use of cannabidiol and cannabidiolic acid-rich hemp in veterinary medicine and lessons from human medicine.J Am Vet Med Assoc. 2023 Mar 23;261(5):623-631. doi: 10.2460/javma.23.02.0064.
3.) Deabold KA, Schwark WS, Wolf L, Wakshlag JJ.Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats. Animals (Basel). 2019 Oct 19;9(10):832. doi: 10.3390/ani9100832
4.) Di Salvo A, Conti MB, Della Rocca G. Pharmacokinetics, efficacy, and safety of cannabidiol in dogs: an update of current knowledge. Front Vet Sci. 2023 Jun 30;10:1204526. doi: 10.3389/fvets.2023.1204526
5.) Chiocchetti R, Salamanca G, De Silva M, Gobbo F, Aspidi F, Cunha RZ, Galiazzo G, Tagliavia C, Sarli G, Morini M.Cannabinoid receptors in the inflammatory cells of canine atopic dermatitis. Front Vet Sci. 2022 Sep 15;9:987132. doi: 10.3389/fvets.2022.987132.
6.) Chiocchetti R, De Silva M, Aspidi F, Cunha RZ, Gobbo F, Tagliavia C, Sarli G, Morini M. Distribution of Cannabinoid Receptors in Keratinocytes of Healthy Dogs and Dogs With Atopic Dermatitis. Front Vet Sci. 2022 Jul 8;9:915896. doi: 10.3389/fvets.2022.915896.
7.) Bizarro AF, Schmidt VM, Fernandes B, Pinto M, Pereira H, Marto J, Lourenço AM.The Potential of Cannabidiol for Treating Canine Atopic Dermatitis. Vet Sci. 2025 Feb 12;12(2):159. doi: 10.3390/vetsci12020159
8.) Loewinger M, Wakshlag JJ, Bowden D, Peters-Kennedy J, Rosenberg A. The effect of a mixed cannabidiol and cannabidiolic acid based oil on client-owned dogs with atopic dermatitis. Vet Dermatol. 2022;33:329-e77

9.) Mogi C, Yoshida M, Kawano K, Fukuyama T, Arai T .Effects of cannabidiol without delta-9-tetrahydrocannabinol on canine atopic dermatitis: A retrospective assessment of 8 cases. Can Vet J. 2022 Apr;63(4):423-426.
10.) Morris EM, Kitts-Morgan SE, Spangler DM, Gebert J, Vanzant ES, McLeod KR, Harmon DL. Feeding Cannabidiol (CBD)-Containing Treats Did Not Affect Canine Daily Voluntary Activity. Front Vet Sci. 2021 Apr 29;8:645667. doi: 10.3389/fvets.2021.645667
11.) Dixon S, Deb A, Archer T, Kaplan BLF.Potential to use cannabinoids as adjunct therapy for dexamethasone: An in vitro study with canine peripheral blood mononuclear cells. Vet Immunol Immunopathol. 2024 Mar;269:110727. doi: 10.1016/j.vetimm.2024.110727.
12.) Jani T, Santoro D, Shmalberg J.Investigation of the in vitro effects of cannabidiol, cannabidiolic acid, and the terpene beta-caryophyllene on lymphocytes harvested from atopic and healthy dogs: A preliminary study. Res Vet Sci. 2025 Jan;182:105483. doi: 10.1016/j.rvsc.2024.105483.
13.) Morris EM, Kitts-Morgan SE, Spangler DM, McLeod KR, Suckow MA, Harmon DL.Feeding treats containing cannabidiol (CBD) did not alter canine immune response to immunization with a novel antigen. Res Vet Sci. 2022 Mar;143:13-19. doi: 10.1016/j.rvsc.2021.12.012.
14.) Noli C, Della Valle MF, Miolo A, Medori C, Schievano C; Skinalia Clinical Research Group. Efficacy of ultra-micronized palmitoylethanolamide in canine atopic dermatitis: an open-label multi-centre study. Vet Dermatol. 2015 Dec;26(6):432-40, e101. doi: 10.1111/vde.12250.
15.) Marsella R, Ahrens K, Sanford R, Trujillo A, Massre D, Soeberdt M, Abels C.Double blinded, vehicle controlled, crossover study on the efficacy of a topical endocannabinoid membrane transporter inhibitor in atopic Beagles. Arch Dermatol Res. 2019 Dec;311(10):795-800. doi: 10.1007/s00403-019-01963-4.
16.) Bartner LR, McGrath S, Rao S, Hyatt LK, Wittenburg LA.Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs.Can J Vet Res. 2018 Jul;82(3):178-183
17.) Hannon MB, Deabold KA, Talsma BN, Lyubimov A, Iqbal A, Zakharov A, Gamble LJ, Wakshlag JJ. Serum cannabidiol, tetrahydrocannabinol (THC), and their native acid derivatives after transdermal application of a low-THC Cannabis sativa extract in beagles. Vet Pharmacol Ther. 2020 Sep;43(5):508-511. doi: 10.1111/jvp.12896.
18.) Luz-Veiga M, Amorim M, Pinto-Ribeiro I, Oliveira ALS, Silva S, Pimentel LL, Rodríguez-Alcalá LM, Madureira R, Pintado M, Azevedo-Silva J, Fernandes J. Cannabidiol and Cannabigerol Exert Antimicrobial Activity without Compromising Skin Microbiota. Int J Mol Sci. 2023 Jan 25;24(3):2389. doi: 10.3390/ijms24032389.