

IN-DEPTH REVIEWS

Caffeine in the Treatment of Atopic Dermatitis and Psoriasis: A Review

Mais Alashqar, MD¹, Norman Goldstein, MD²

¹Alfaisal University, Riyadh, Saudi Arabia

²Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT

Atopic dermatitis (AD) and psoriasis are inflammatory skin diseases. AD is characterized by immune dysregulation and barrier impairment, while psoriasis is by immune dysfunction and resultant keratinocyte hyperproliferation. Caffeine has shown positive effects on the symptoms of both diseases, but it is not conclusive through which pathways. The aim of this study was to provide a detailed discussion of available work on this topic, as well as known modes of action of caffeine that are relevant to these two conditions. After an extensive review of the literature, we found that both diseases have decreased intracellular cyclic adenosine monophosphate (cAMP) levels in cutaneous leukocytes, so it is very likely that being a methylxanthine, and hence a phosphodiesterase (PDE) inhibitor, caffeine raises intracellular cAMP levels, which suppresses inflammatory pathways and potentiates anti-inflammatory ones. Moreover, caffeine is known to be an ATR (ataxia-telangiectasia mutated) kinase and an ATM (ATM- and Rad3-Related) kinase inhibitor, which promotes prompt apoptosis of damaged cells. It was also found to have anti-necrotic effects in reactive oxygen species (ROS)-damaged cells. These pro-apoptotic and anti-necrotic properties may also be reducing the inflammation. Finally, caffeine's metabolites have shown antioxidizing effects against ROS, which certainly would reduce inflammation caused by lipid peroxidation, DNA damage and organelle destruction. We find that caffeine acts in a number of ways to improve symptoms of inflammation and that it may be an effective adjunct to therapy in AD and psoriasis.

INTRODUCTION

Atopic dermatitis (AD) and psoriasis are inflammatory, T-cell mediated disorders of the skin. AD presents as erythematous, pruritic papules, exacerbated by xerosis. Its chronic lesions become lichenified, hyperpigmented, and are often excoriated. [1] It usually starts in childhood, but may have an adult onset as well. [2] It was believed that the majority of children affected would outgrow this condition, but recent work in

JAMA Dermatology has shown that for most it will be a life-long disorder. [3] Up to 20% of children in the World are affected by AD, and up to 3% of adults, so this disease is one of significant global burden. [4]

Psoriasis presents as well-demarcated micaceous plaques or papules, usually with silver scales. Sometimes it presents with pustules, and many psoriasis patients also have nail and/or joint involvement. Stress and infections usually worsen the symptoms. In a 2014 study, the prevalence of psoriasis in

adults was reported as 3.2% in the United States.[5]

Topical caffeine has been shown to help both diseases, in a number of trials. Below we review available work on the topic and currently known modes of action of caffeine in inflammatory skin disorders.

MODELS OF PATHOGENESIS

These diseases are, at their core, idiopathic, but many theories exist to explain the laboratory and clinical findings associated with them.

Atopic Dermatitis:

Atopic patients were known to have hypersensitivity to β -adrenergic blockade, which spiked an interest in the possible role of cAMP level abnormalities and β -adrenergic dysregulation in AD. [6] There is a statistically significant decrease in cAMP levels of cutaneous and peripheral blood leukocytes in atopic dermatitis. [6] This decrease may be due to the increased activity of PDE in these cells, as was reported in many studies. [7-11] Normal PDE levels in local and peripheral leukocytes have also been declared. [12, 24]

Despite the mixed results, PDE inhibitors, which raise the intracellular cAMP, remain effective in the treatment of AD. [14-18] One such example is E6005. It is a topical, potent PDE4 inhibitor that has proven to alleviate the pruritic component of AD, by multiple mechanisms: suppressing the proteinase-activated receptor 2 (PAR2) effect (a known possible component of the pruritic pathway [19]) and by raising cAMP levels, which reduces LTB₄ production in keratinocytes (also a possible component of the pruritic

pathway [20]). [21-23] Forskolin, also a cAMP elevator, has shown to have anti-pruritic properties. [22] Rolipram, Ro 20-1724, and nitraquazone have all been shown to improve AD as well, in a study from 1993. [24] In 2016, two double-blind studies confirmed the efficacy and safety of the use of crisaborole ointment, another PDE4 inhibitor, in the treatment of AD. [14,25]

Higher cAMP levels have been shown to inhibit pro-inflammatory pathways, induce anti-inflammatory pathways, and affect gene expression (through modulation of cAMP response element-binding proteins (CREB)) in leukocytes, keratinocytes, and cutaneous fibroblasts. [6,26] This includes reduced levels of IFN- β , IFN- γ , TNF- α , interleukin 12, inducible nitric oxide (NO) synthase, leukotriene B₄, macrophage inflammatory proteins 1 α and 1 β , and Nuclear Factor-kappaB; while increased production of interleukin 10. [6,26-28]

Theories that attempt to explain AD are many, but there is definitely a component of immune dysregulation and one of poor skin barrier function; yet which ignites the other remains controversial. [1]

The *outside-inside hypothesis* suggests that genetic abnormalities cause a barrier dysfunction, and secondarily dermatitis. For example, FLG gene mutations, affecting the filaggrin protein, impair the integrity of the corneal layer and tight junction mutations affect that of the granular layer of the skin in AD. [1] Both of these mutations can increase the skin's permeability to allergens, irritants, and infectious agents, that would ignite inflammation.[1]

The *inside-outside hypothesis*, however, suggests the genetic abnormalities cause immune dysregulation first. AD leukocytes

have intrinsically higher levels of cAMP phosphodiesterase, and consequently lower intracellular cAMP and higher IgE production, which suppresses the Th1 immune responses, and promotes a Th2-oriented response, with resultant cytokines and ROS-damage weakening the barrier. [1]

Alternatively, the *outside-inside-outside hypothesis* suggests that the immune dysfunction and the impaired barrier act simultaneously to form a vicious cycle, both exacerbating one another. An impaired barrier would allow allergens to easily penetrate, and activate the inflammatory process, which being abnormal and exaggerated, would further damage the barricade. [1]

Regardless of the sequence, each component in the inflammatory pathway and the barrier dysfunction involved is a potential target for novel therapy.

Psoriasis:

Psoriasis is a multifactorial disease that remains largely idiopathic. It is known to be autoimmune and inflammatory, with both genetic and environmental triggers and aggravators. [1,29] In fact 71% of children affected have a family history of psoriasis, as reported by Morris et al. [30]

A vicious cycle exists in predisposed individuals, where an abnormal and inflated immune response to an allergen occurs, with cytokines released actually causing both inflammation, as well as keratinocyte hyperproliferation; hence the distinctive raised plaques and mica-like scales of psoriasis. [29] The cell cycle of the keratinocytes is also expedited. [31] These keratinocytes produce cytokines, themselves, that attract more

leukocytes to the lesion, further propagating the cycle.[29]

In psoriasis, as with AD, the findings include decreased cAMP levels. [32,33] Some studies have countered this, and researchers offered that previously recorded cAMP levels were altered by the biopsying technique, or by the lack of β -adrenergic response and ischemic effect in psoriatic lesions. [34-36] The overwhelming mass of research, however, has recognized the beneficial effects of PDE inhibitors for the treatment of psoriasis. The fact that they raise intracellular cAMP levels supports the initial notion that cAMP levels are decreased in leukocytes of psoriatic lesions. [19]

For example, Apremilast and benzoxaboroles (particularly crisaborole) are both PDE4 inhibitors, and they have shown great results, diminishing psoriatic lesions and reducing inflammatory cytokine production. [6,38-40,44]

PHARMACOLOGY

Caffeine has been shown to provide relief to AD patients. [45,46] In 1976, Kaplan et al conducted a preliminary trial on 20 patients, where they compared the effectiveness of 10% caffeine (in a hydrophilic base) with a placebo, on the following scales: erythema, pruritus, scaling, oozing, lichenification, and overall subjective evaluation. [45] They found a statistically significant improvement in the overall subjective evaluation, so pursued a follow-up study using a caffeine concentration of 30% on 40 AD patients (28 were included in the analysis). [45,46] In the second research, published the year after, Kaplan et al reported a statistically significant improvement in all scales tested in the caffeine group, while the placebo group showed improvement only in pruritus. [46] In

1978, another study on 83 AD patients was published comparing three formulations (all in hydrophilic bases): 0.5% hydrocortisone ointment, caffeine 30% and hydrocortisone 0.5% ointment, and betamethasone valerate 0.1% cream. They noted improvement in all study groups on all scales; however, the caffeine-hydrocortisone group and the betamethasone group were significantly superior to the hydrocortisone group on the scales of excoriation, lichenification, and global impression. Moreover, the caffeine-hydrocortisone and the betamethasone groups did not differ statistically significantly on any scale. [47]

The main side effect of the caffeine preparation was an immediate pruritic or burning sensation, which occurred in 4 out of an original 90 participants selected for the study. This may have been due to the “grittiness” of the caffeine blend, as described by the authors. [47]

Corticosteroids, on the other hand, may cause side effects such as pigment changes, perioral dermatitis, delayed wound healing, and others, making the use of caffeine to enhance the effect of lower concentrations of corticosteroids an attractive option. [47,48] In another trial, Vali et al tested caffeine 10% (in a plastibase of liquid paraffin and polyethylene) on the plaque psoriasis of 39 patients, versus a placebo. A statistically significant difference was observed, but only after 8 weeks of treatment. One side effect was noted, which was mild pruritus. [49]

Caffeine as a PDE Inhibitor:

Caffeine is a methylxanthine, so is an inhibitor of the PDE enzymes, and hence increases intracellular cAMP levels. As discussed earlier, this has an anti-inflammatory effect, as it counteracts the

noted decrease in cAMP levels in AD and psoriasis. In fact, Kaplan et al and Vali et al both associate their findings to this sequence. [45-47,49]

Caffeine as an ATR Kinase Inhibitor:

Generally, when a cell in the body undergoes DNA damage, checkpoint activations are induced and are followed by cell cycle arrest, and then apoptosis or DNA repair. [50,51] The repair process, also known as the DNA damage response (DDR), is a network of interlinked pathways, controlled by the ATM (ataxia-telangiectasia mutated) and ATR (ATM- and Rad3-Related) kinases. While ATM is mainly concerned with double-stranded DNA breaks (DSBs), ATR is activated by many forms of DNA damage, including DSBs.[50,52]

The function of this process is to restore the DNA; however, sometimes the repair is imperfect, and although allows the cell to survive, it causes abnormalities in the cell cycle, potentially leading to malignancy. [50,53] Inhibition of these pathways induces unhazardous cell apoptosis instead. [63, 68] Many studies have recognized the value of inhibiting ATR and ATM in 1) preventing cancers and 2) in improving therapeutic outcomes. Work by Charrier et al describes the use of aminopyrazines to inhibit ATR, and so allow DNA-damaging chemotherapy to work more effectively, by preventing the cancerous cells from repairing their DNA after this tackle. [64] Pires et al and Fokas et al used the ATR inhibitors VE-821 and VE-822 to successfully improve outcomes of radiotherapy. [55,56]

Caffeine is also a known DNA repair inhibitor, as described by Lehmann and Rauth. [52, 57] Later work describes that gaps formed during DNA replication in the daughter strands were

not repaired if caffeine was present in the medium. [57-60] In fact, caffeine has been used to enhance the cytotoxic effect of radio- and chemotherapy in many trials. Gaudin et al showed that caffeine could re-sensitize Cytoxan-resistant plasmacytomas to the effects of X-rays, nitrogen mustard, and Cytoxan. [61] Rauth et al used it to enhance cytotoxicity to mitomycin c.[62] Sarkaria et al identified caffeine as both an ATR *and* an ATM inhibitor and noted its ability to increase radiosensitivity of cultured cells. [63]

Zajdela et al conducted two independent experiments on healthy mice ears, where they coated one ear with 0.1% caffeine solution before irradiating both ears with UV light, to find that 89% of uncoated ears developed cutaneous tumors, while only 47%-54% of coated ears did. [64] Upon ROS-induced damage, caffeine was found to reduce necrosis of skin fibroblasts. [65] Moreover, that study reported *no* statistically significant increase in the number of apoptotic fibroblasts, indicating that the anti-necrotic effect may have been through another unidentified pathway.

What is of interest to us here is that caffeine seems to possess both pro-apoptotic and anti-necrotic properties, which serve to inhibit inflammation caused by external factors. Necrosis causes a sudden release of self-antigens and cell components into the surrounding milieu, which promotes harmful consequent inflammation.[66] At the same time, cells that *are* damaged beyond repair should be removed instantaneously by apoptosis. Additionally, the inhibition of ATR and ATM has been shown to upregulate IL10 gene expression, and IL-10 is a prominent anti-inflammatory cytokine.[67] These properties may play a role in caffeine's anti-inflammatory effect on psoriasis and AD.

Caffeine as an Antioxidant:

Oxidants are chemical compounds with the ability to damage other particles by acquiring one or more of their electrons; thereby creating a self-propagating, destructive succession of free radicles.

In the setting of a cell, such a sequence occurs commonly, from toxins or UV radiation for example, ionizing compounds. Not only does this cause DNA damage, but also inflammation by lipid peroxidation and other destructive processes. Thankfully, antioxidants are abundant in the body, like glutathione. It is then a balance between the oxidants and the anti-oxidants.

In 2007, a study reported that daily oral caffeine intake reduced the risk of non-melanoma skin cancer by 30%.[68,69] Later reports confirmed this relationship for melanoma as well. [70]

An in vitro study by Chu et al found that *crude* caffeine had antioxidant activity and cyclooxygenase-2 inhibition. Interestingly they did not find the same effects in pure caffeine.[71]

Other in vitro investigations also record the ability of caffeine to neutralize singlet oxygen and oxygen radicles and to decrease subsequent lipid peroxidation. [72,73]

More recent work has actually identified the caffeine metabolites: 1-methylxanthine, 1-methyl uric acid, and 1,7-dimethyl uric acid as the real facilitators of this antioxidant activity. [74,75] These results support those of the study by Silverberg et al, where the topical caffeine exerted a protective effect against ROS-damage, but *not* through an antioxidantizing effect (there was a time delay in action), presumably because it had not gone

through the systemic circulation and was not turned into its metabolites by hepatic microsomes. [65,76]

Patients with AD are particularly vulnerable to oxidative stress, as their immune dysfunction and barrier impairment cause chronic inflammation. [1] In this already sensitive environment, any additional oxidative DNA or organelle damage would directly defect the physical barrier further, as well as induce more pro-inflammatory cytokines. [77] Those, in turn, would produce more ROS and would exacerbate the pruritus and physical damage, and the vicious cycle continues.[77] Tsukahara et al present that children with acute AD exacerbations had abnormally elevated markers of oxidative stress, oxidative DNA damage, and lipid peroxidation, compared to their healthy counterparts.[78]

ROS are very likely contributors in the development of psoriasis, as well, as redox-sensitive transduction systems are known to be implicated in its pathogenesis. [79-82] Additionally, administering antioxidants has proven useful in the treatment of psoriasis.[83,84]

This suggests a possible role of caffeine and its metabolites in the treatment of AD and psoriasis, through an ROS-related mechanism.

PENETRATION

Caffeine is usually used as the model for hydrophilic compounds in penetration studies; hence, much data establishes caffeine's skin penetration from work both in vivo and in vitro. Absorption of this highly water-soluble compound is unaffected by skin thickness, and was even shown to penetrate through hair follicles at higher

speeds than through the inter-follicular epidermis.[85,86] Delivering this compound in hydrophilic-lipophilic nanoemulsions, solid lipid nanoparticles, and the addition of chemical penetration enhancers all further heighten its permeation.[87-89]

It is expected that damage of the stratum corneum, which usually protects the skin, would cause an increase in permeability. Work by Rubio et al shows that as skin barrier impairment increases, the rate of caffeine absorption increases *exponentially*. [90] This is not true for all compounds, as they also found that the increase in the case of salicylic acid is only linear.[90] With barrier dysfunction underpinning the pathogenesis of AD, these results further promote caffeine as a potential part of the therapy.[1]

DISCUSSION

Because we do not fully understand neither the pathogenesises of these diseases, nor the thorough pharmacology of this compound, we are only left to hypothesize on its possible modes of action in each case; but what we do know is that it is useful. We know that it is effective in inhibiting DNA repair and inducing sound apoptosis of UV-damaged cells. We know that it can reduce injurious necrosis of ROS-damaged cells. We know that it can help reduce inflammation by raising intracellular cAMP levels of cutaneous and peripheral leukocytes. Finally, we know that its metabolites can neutralize oxidants in the body. All of these effects, combined, may act to reduce inflammation caused by internal and external sources, which is particularly valuable in inflammatory cutaneous disorders like psoriasis and atopic dermatitis. In fact, because the vast majority of skin diseases have at least some degree of inflammation, we may see caffeine supplementing the

therapy of others in the future. More research is needed to fully elucidate its potential, but so far results are promising.

Caffeine is a cheaper, safer alternative that could complement the long-term therapy of AD and psoriasis patients.

Conflict of Interest Disclosures: None.

Funding: None.

Corresponding Author:

Mais Alashqar, MD
Alfaisal University
Riyadh, Saudi Arabia
maisalashqar@gmail.com

References:

1. Rudikoff, D., Cohen, S. R., & Scheinfeld, N. (2014). Atopic dermatitis and eczematous disorders. Boca Raton: CRC Press, Taylor & Francis Group.
2. Leung, D. Y., & Bieber, T. (2003). Atopic dermatitis. *The Lancet*, 361(9352), 151-160. doi:10.1016/s0140-6736(03)12193-9
3. Margolis, J. S., Abuabara, K., Bilker, W., Hoffstad, O., & Margolis, D. J. (2014). Persistence of mild to moderate atopic dermatitis. *JAMA Dermatology*, 150(6), 593-600.
4. Nutten, S. (2015). Atopic dermatitis: global epidemiology and risk factors. *Annals of Nutrition and Metabolism*, 66(Suppl. 1), 8-16.
5. Rachakonda, T. D., Schupp, C. W., & Armstrong, A. W. (2014). Psoriasis prevalence among adults in the United States. *Journal of the American Academy of Dermatology*, 70(3), 512-516.
6. Sawai, T., Ikai, K., & Uehara, M. (1995). Elevated cyclic adenosine monophosphate phosphodiesterase activity in peripheral blood mononuclear leucocytes from children with atopic dermatitis. *British Journal of Dermatology*, 132(1), 22-24.
7. Salpietro, D. C., Naccari, F., Polimeni, I., & Pellegrino, C. (1998). Reduced plasma c-AMP levels in children with atopic dermatitis. *Pediatric Allergy and Immunology : Official Publication of the European Society of Pediatric Allergy and Immunology*, 9(3), 130-132. doi:10.1111/j.1399-3038.1998.tb00358.x
8. Hanifin, J. M., Chan, S. C., Cheng, J. B., Tofte, S. J., Henderson, W. R., Kirby, D. S., & Weiner, E. S. (1996). Type 4 Phosphodiesterase Inhibitors Have Clinical and In Vitro Anti-inflammatory Effects in Atopic Dermatitis. *Journal of Investigative Dermatology*, 107(1), 51-56. doi:10.1111/1523-1747.ep12297888
9. Butler, J. M., Chan, S. C., Stevens, S., & Hanifin, J. M. (1983). Increased leukocyte histamine release with elevated cyclic AMP-phosphodiesterase activity in atopic dermatitis. *Journal of Allergy and Clinical Immunology*, 71(5), 490-497.
10. Grewe, S. R., Chan, S. C., & Hanifin, J. M. (1982). Elevated leukocyte cyclic AMP—phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP—agonist hyporesponsiveness. *Journal of Allergy and Clinical Immunology*, 70(6), 452-457.
11. Chan, S. C., Reifsnnyder, D., Beavo, J. A., & Hanifin, J. M. (1993). Immunochemical characterization of the distinct monocyte cyclic AMP-phosphodiesterase from patients with atopic dermatitis. *Journal of allergy and clinical immunology*, 91(6), 1179-1188.
12. Levy, J., Zhou, D. M., & Zippin, J. H. (2016). Cyclic Adenosine Monophosphate Signaling in Inflammatory Skin Disease. *Journal of Clinical and Experimental Dermatology Research*, 7(326), 2.
13. Hanifin, J. M., & Chan, S. C. (1995). Monocyte phosphodiesterase abnormalities and

dysregulation of lymphocyte function in atopic dermatitis. *Journal of investigative dermatology*, 105(1), S84-S88.

14. Paller, A. S., Tom, W. L., Lebwohl, M. G., Blumenthal, R. L., Boguniewicz, M., Call, R. S., ... & Spellman, M. C. (2016). Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology*, 75(3), 494-503.

15. Ahluwalia, J., Udkoff, J., Waldman, A., Borok, J., & Eichenfield, L. F. (2017). Phosphodiesterase 4 Inhibitor Therapies for Atopic Dermatitis: Progress and Outlook. *Drugs*. doi:10.1007/s40265-017-0784-3

16. Felding, J., Sørensen, M. D., Poulsen, T. D., Larsen, J., Andersson, C., Refer, P., ... & Hegardt, P. (2014). Discovery and early clinical development of 2-{6-[2-(3,5-dichloro-4-pyridyl)acetyl]-2,3-dimethoxyphenoxy}-N-propylacetamide (LEO 29102), a soft-drug inhibitor of phosphodiesterase 4 for topical treatment of atopic dermatitis. *Journal of Medicinal Chemistry*, 57(14), 5893-5903.

17. Hanifin, J. M., Chan, S. C., Cheng, J. B., Tofte, S. J., Henderson, W. R., Kirby, D. S., & Weiner, E. S. (1996). Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *Journal of Investigative Dermatology*, 107(1), 51-56.

18. Samrao, A., Berry, T. M., Goreski, R., & Simpson, E. L. (2012). A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Archives of dermatology*, 148(8), 890-897.

19. Frateschi, S., Camerer, E., Crisante, G., Rieser, S., Membrez, M., Charles, R. P., ... & Rotman, S. (2011). PAR2 absence completely rescues inflammation and ichthyosis caused by altered

CAP1/Prss8 expression in mouse skin. *Nature communications*, 2, 161.

20. Tsuji, F., Aono, H., Tsuboi, T., Murakami, T., Enomoto, H., Mizutani, K., & Inagaki, N. (2010). Role of leukotriene B4 in 5-lipoxygenase metabolite-and allergy-induced itch-associated responses in mice. *Biological and Pharmaceutical Bulletin*, 33(6), 1050-1053.

21. Andoh, T., & Kuraishi, Y. (2014). Antipruritic mechanisms of topical E6005, a phosphodiesterase 4 inhibitor: Inhibition of responses to proteinase-activated receptor 2 stimulation mediated by increase in intracellular cyclic AMP. *Journal of Dermatological Science*, 76(3), 206-213. doi:10.1016/j.jdermsci.2014.10.005

22. Wakita, H., Ohkuro, M., Ishii, N., Hishinuma, I., & Shirato, M. (2015). A putative antipruritic mechanism of the phosphodiesterase-4 inhibitor E6005 by attenuating capsaicin-induced depolarization of C-fibre nerves. *Experimental Dermatology*, 24(3), 215-216. doi:10.1111/exd.12606

23. Andoh, T., Yoshida, T., & Kuraishi, Y. (2014). Topical E6005, a novel phosphodiesterase 4 inhibitor, attenuates spontaneous itch-related responses in mice with chronic atopy-like dermatitis. *Experimental Dermatology*, 23(5), 359-361. doi:10.1111/exd.12377

24. Serezani, C. H., Ballinger, M. N., Aronoff, D. M., & Peters-Golden, M. (2008). Cyclic AMP: master regulator of innate immune cell function. *American journal of respiratory cell and molecular biology*, 39(2), 127-132.

25. Dina Coronado, B. S., & Zane, L. T. (2016). Crisaborole topical ointment, 2%: a nonsteroidal, topical, anti-inflammatory phosphodiesterase 4 inhibitor in clinical development for the treatment of atopic dermatitis. *J Drugs Dermatol*, 15(4), 390-396.

26. Grewe, S. R., Chan, S. C., & Hanifin, J. M. (1982). Elevated leukocyte cyclic AMP—phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP—agonist hyporesponsiveness. *Journal of Allergy and Clinical Immunology*, 70(6), 452-457.
27. Qi, X. F., Kim, D. H., Yoon, Y. S., Li, J. H., Song, S. B., Jin, D., ... & Lee, K. J. (2009). The adenylyl cyclase-cAMP system suppresses TARC/CCL17 and MDC/CCL22 production through p38 MAPK and NF- κ B in HaCaT keratinocytes. *Molecular immunology*, 46(10), 1925-1934.
28. Hanifin, J. M., & Chan, S. C. (1995). Monocyte phosphodiesterase abnormalities and dysregulation of lymphocyte function in atopic dermatitis. *Journal of investigative dermatology*, 105(1), S84-S88.
29. Menter, A., Ryan, C., & Menter, A. (2017). *Psoriasis*. Boca Raton, FL: CRC Press, Taylor & Francis Group.
30. Morris, A., Rogers, M., Fischer, G., & Williams, K. (2001). Childhood psoriasis: a clinical review of 1262 cases. *Pediatric dermatology*, 18(3), 188-198.
31. Grewal, I. S. (2009). *Emerging protein biotherapeutics*. Boca Raton: CRC Press.
32. Voorhees, J. J., Duell, E. A., Bass, L. J., Powell, J. A., & Harrell, E. R. (1972). Decreased cyclic AMP in the epidermis of lesions of psoriasis. *Archives of Dermatology*, 105(5), 695-701.
33. Voorhees, J. J., Stawiski, M., Duell, E. A., Haddox, M. K., & Goldberg, N. D. (1973). Increased cyclic GMP and decreased cyclic AMP levels in the hyperplastic, abnormally differentiated epidermis of psoriasis. *Life Sciences*, 13(6), 639-653. doi:10.1016/0024-3205(73)90281-6
34. Adachi, K., Iizuka, H., Halprin, K. M., & Levine, V. (1980). Epidermal cyclic AMP is not decreased in psoriasis lesions. *The Journal of investigative dermatology*, 74(2), 74-76.
35. Herlin, T., & Kragballe, K. (1981). Enhanced monocyte and neutrophil cytotoxicity and normal cyclic nucleotide levels in severe psoriasis. *British Journal of Dermatology*, 105(4), 405-414.
36. Iizuka, H., & Ohkawara, A. (1986). "Ischemic" rise of epidermal cyclic AMP is a beta-adrenergic adenylate cyclase-dependent process. *Journal of investigative dermatology*, 86(3), 271-274.
37. Wittmann, M., & Helliwell, P. S. (2013). Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. *Dermatology and therapy*, 3(1), 1-15.
38. Gooderham, M., & Papp, K. (2015). Selective Phosphodiesterase Inhibitors for Psoriasis: Focus on Apremilast. *BioDrugs*, 29(5), 327-339. doi:10.1007/s40259-015-0144-3
39. Dong, C., Virtucio, C., Zemska, O., Baltazar, G., Zhou, Y., Baia, D., . . . Jarnagin, K. (2016). Treatment of Skin Inflammation with Benzoxaborole Phosphodiesterase Inhibitors: Selectivity, Cellular Activity, and Effect on Cytokines Associated with Skin Inflammation and Skin Architecture Changes. *Journal of Pharmacology and Experimental Therapeutics*, 358(3), 413-422. doi:10.1124/jpet.116.232819
40. Tenor, H., Hatzelmann, A., Church, M. K., Schudt, C., & Shute, J. K. (1996). Effects of theophylline and rolipram on leukotriene C4 (LTC4) synthesis and chemotaxis of human eosinophils from normal and atopic subjects. *British journal of pharmacology*, 118(7), 1727-1735.
41. Samrao, A., Berry, T. M., Goreshi, R., & Simpson, E. L. (2012). A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Archives of dermatology*, 148(8), 890-897.

42. Schafer, P. H., Parton, A., Gandhi, A. K., Capone, L., Adams, M., Wu, L., ... & Baillie, G. S. (2010). Apremilast, a cAMP phosphodiesterase - 4 inhibitor, demonstrates anti - inflammatory activity in vitro and in a model of psoriasis. *British journal of pharmacology*, 159(4), 842-855.
43. Nazarian, R., & Weinberg, J. M. (2009). AN-2728, a PDE4 inhibitor for the potential topical treatment of psoriasis and atopic dermatitis. *Current opinion in investigational drugs (London, England: 2000)*, 10(11), 1236-1242.
44. Rafael, A., & Torres, T. (2016). Topical therapy for psoriasis: a promising future. Focus on JAK and phosphodiesterase-4 inhibitors. *European Journal of Dermatology*, 26(1), 3-8.
45. Kaplan, R. J., Daman, L., Shereff, R., Rosenberg, E. W., & Robinson, H. (1976). Treatment of atopic dermatitis with topically applied caffeine. *Archives of dermatology*, 112(6), 880-881.
46. Kaplan, R. J., Daman, L., Rosenberg, E. W., & Feigenbaum, S. (1977). Treatment of atopic dermatitis with topically applied caffeine—a follow-up report. *Archives of dermatology*, 113(1), 107-107.
47. Kaplan, R. J., Daman, L., Rosenberg, E. W., & Feigenbaum, S. (1978). Topical use of caffeine with hydrocortisone in the treatment of atopic dermatitis. *Archives of dermatology*, 114(1), 60-62.
48. Furue, M., Terao, H., Rikihisa, W., Urabe, K., Kinukawa, N., Nose, Y., & Koga, T. (2003). Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. *British Journal of Dermatology*, 148(1), 128-133.
49. Vali, A., Asilian, A., Khalesi, E., Khoddami, L., Shahtalebi, M., & Mohammady, M. (2005). Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *Journal of dermatological treatment*, 16(4), 234-237.
50. Maréchal, A., & Zou, L. (2013). DNA damage sensing by the ATM and ATR kinases. *Cold Spring Harbor perspectives in biology*, 5(9), a012716.
51. Tibbetts, R. S., Brumbaugh, K. M., Williams, J. M., Sarkaria, J. N., Cliby, W. A., Shieh, S. Y., ... & Abraham, R. T. (1999). A role for ATR in the DNA damage-induced phosphorylation of p53. *Genes & development*, 13(2), 152-157.
52. Lehmann, A. R. (1972). Effect of caffeine on DNA synthesis in mammalian cells. *Biophysical journal*, 12(10), 1316-1325.
53. Khanna, K. K., & Jackson, S. P. (2001). DNA double-strand breaks: signaling, repair and the cancer connection. *Nature genetics*, 27(3), 247.
54. Charrier, J. D., Durrant, S. J., Golec, J. M., Kay, D. P., Knechtel, R. M., MacCormick, S., ... & Rutherford, A. P. (2011). Discovery of potent and selective inhibitors of ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase as potential anticancer agents. *Journal of medicinal chemistry*, 54(7), 2320-2330.
55. Pires, I. M., Olcina, M. M., Anbalagan, S., Pollard, J. R., Reaper, P. M., Charlton, P. A., ... & Hammond, E. M. (2012). Targeting radiation-resistant hypoxic tumour cells through ATR inhibition. *British journal of cancer*, 107(2), 291.
56. Fokas, E., Prevo, R., Pollard, J. R., Reaper, P. M., Charlton, P. A., Cornelissen, B., ... & Muschel, R. J. (2012). Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. *Cell death & disease*, 3(12), e441.
57. Rauth, A. M. (1967). Evidence for dark-reactivation of ultraviolet light damage in mouse L cells. *Radiation research*, 31(1), 121-138.
58. Domon, M., & Rauth, A. M. (1969). Ultraviolet-light irradiation of mouse L cells: Effects on cells

- in the DNA synthesis phase. *Radiation research*, 40(2), 414-429.
59. M. Domon, B. Barton, A. Porte & A.M. Rauth (1970) The Interaction of Caffeine with Ultra-violet-light-irradiated DNA, *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine*, 17:4, 395-399, DOI: 10.1080/09553007014550481
60. Roberts, J. J., Sturrock, J. E., & Ward, K. N. (1974). The enhancement by caffeine of alkylation-induced cell death, mutations and chromosomal aberrations in Chinese hamster cells, as a result of inhibition of post-replication DNA repair. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 26(2), 129-143.
61. Gaudin, D., & Yielding, K. L. (1969). Response of a "Resistant" Plasmacytoma to Alkylating Agents and X-Ray in Combination with the "Excision Repair Inhibitors Caffeine and Chloroquine*. *Proceedings of the Society for Experimental Biology and Medicine*, 131(4), 1413-1416.
62. Rauth, A. M., Barton, B., & Lee, C. P. Y. (1970). Effects of caffeine on L-cells exposed to mitomycin C. *Cancer research*, 30(11), 2724-2729.
63. Sarkaria, J. N., Busby, E. C., Tibbetts, R. S., Roos, P., Taya, Y., Karnitz, L. M., & Abraham, R. T. (1999). Inhibition of ATM and ATR kinase activities by the radiosensitizing agent, caffeine. *Cancer research*, 59(17), 4375-4382.
64. Zajdela, F., & Latarjet, R. (1973). Inhibitory effect of caffeine on the induction of cutaneous cancers by ultraviolet rays in the mouse. *Comptes rendus hebdomadaires des séances de l'Académie des sciences. Série D: Sciences naturelles*, 277(12), 1073-1076.
65. Silverberg, J. I., Patel, M., Brody, N., & Jagdeo, J. (2012). Caffeine protects human skin fibroblasts from acute reactive oxygen species-induced necrosis. *Journal of drugs in dermatology: JDD*, 11(11), 1342-1346.
66. Rock, K. L., & Kono, H. (2008). The inflammatory response to cell death. *Annual Review of Pathology*, 3, 99-126. <http://doi.org/10.1146/annurev.pathmechdis.3.121806.151456>
67. Muralidharan, S., & Mandrekar, P. (2013). Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation. *Journal of leukocyte biology*, 94(6), 1167-1184.
68. Abel, E. L., Hendrix, S. O., McNeeley, S. G., Johnson, K. C., Rosenberg, C. A., Mossavar-Rahmani, Y., ... & Kruger, M. (2007). Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. *European Journal of Cancer Prevention*, 16(5), 446-452.
69. Song, F., Qureshi, A. A., & Han, J. (2012). Increased caffeine intake is associated with reduced risk of basal cell carcinoma of the skin. *Cancer research*, 72(13), 3282-3289.
70. Loftfield, E., Freedman, N. D., Graubard, B. I., Hollenbeck, A. R., Shebl, F. M., Mayne, S. T., & Sinha, R. (2015). Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study. *Journal of the National Cancer Institute*, 107(2), dju421.
71. Chu, Y. F., Chen, Y., Brown, P. H., Lyle, B. J., Black, R. M., Cheng, I. H., ... & Prior, R. L. (2012). Bioactivities of crude caffeine: Antioxidant activity, cyclooxygenase-2 inhibition, and enhanced glucose uptake. *Food Chemistry*, 131(2), 564-568.
72. Devasagayam, T. P. A., Kamat, J. P., Mohan, H., & Kesavan, P. C. (1996). Caffeine as an antioxidant: inhibition of lipid peroxidation induced by reactive oxygen species. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, 1282(1), 63-70.

73. Shi, X., Dalal, N. S., & Jain, A. C. (1991). Antioxidant behaviour of caffeine: efficient scavenging of hydroxyl radicals. *Food and chemical toxicology*, 29(1), 1-6.
74. Lee, C. (2000). Antioxidant ability of caffeine and its metabolites based on the study of oxygen radical absorbing capacity and inhibition of LDL peroxidation. *Clinica Chimica Acta*, 295(1), 141-154.
75. Scurachio, R. S., Mattiucci, F., Santos, W. G., Skibsted, L. H., & Cardoso, D. R. (2016). Caffeine metabolites not caffeine protect against riboflavin photosensitized oxidative damage related to skin and eye health. *Journal of Photochemistry and Photobiology B: Biology*, 163, 277-283.
76. Berthou, F. R. A. N. C. O. I. S., Flinois, J. P., Ratanasavanh, D., Beaune, P. H. I. L. L. I. P. E., Riche, C. H. R. I. S. T. I. A. N., & Guillouzo, A. N. D. R. E. (1991). Evidence for the involvement of several cytochromes P-450 in the first steps of caffeine metabolism by human liver microsomes. *Drug metabolism and disposition*, 19(3), 561-567.
77. Ji, H., & Li, X. (2016). Oxidative stress in atopic dermatitis. *Oxidative Medicine and Cellular Longevity*, 2016, 1-8. doi:10.1155/2016/2721469
78. Tsukahara, H., Shibata, R., Ohshima, Y., Todoroki, Y., Sato, S., Ohta, N., ... & Mayumi, M. (2003). Oxidative stress and altered antioxidant defenses in children with acute exacerbation of atopic dermatitis. *Life sciences*, 72(22), 2509-2516.
79. Zhou, Q., Mrowietz, U., & Rostami-Yazdi, M. (2009). Oxidative stress in the pathogenesis of psoriasis. *Free Radical Biology and Medicine*, 47(7), 891-905.
80. Gabr, S. A., & Al-Ghadir, A. H. (2012). Role of cellular oxidative stress and cytochrome c in the pathogenesis of psoriasis. *Archives of dermatological research*, 304(6), 451-457.
81. Yildirim, M., Inaloz, H. S., Baysal, V., & Delibas, N. (2003). The role of oxidants and antioxidants in psoriasis. *Journal of the European Academy of Dermatology and Venereology*, 17(1), 34-36.
82. Api, H., & Atik, U. (2003). Oxidant/antioxidant status in patients with psoriasis. *Yonsei medical journal*, 44(6), 987-990.
83. Lin, X., & Huang, T. (2016). Oxidative stress in psoriasis and potential therapeutic use of antioxidants. *Free radical research*, 50(6), 585-595.
84. Kharaeva, Z., Gostova, E., De Luca, C., Raskovic, D., & Korkina, L. (2009). Clinical and biochemical effects of coenzyme Q 10, vitamin E, and selenium supplementation to psoriasis patients. *Nutrition*, 25(3), 295-302.
85. Othberg, N., Patzelt, A., Rasulev, U., Hagemester, T., Linscheid, M., Sinkgraven, R., ... & Lademann, J. (2008). The role of hair follicles in the percutaneous absorption of caffeine. *British journal of clinical pharmacology*, 65(4), 488-492.
86. Wilkinson, S. C., Maas, W. J., Nielsen, J. B., Greaves, L. C., van de Sandt, J. J., & Williams, F. M. (2006). Interactions of skin thickness and physicochemical properties of test compounds in percutaneous penetration studies. *International archives of occupational and environmental health*, 79(5), 405-413.
87. Abd, E., Namjoshi, S., Mohammed, Y. H., Roberts, M. S., & Grice, J. E. (2015). Synergistic skin penetration enhancer and nanoemulsion formulations promote the human epidermal permeation of caffeine and naproxen. *Journal of pharmaceutical sciences*.
88. Jagannath, S. S., Manohar, S. D., & Bhanudas, S. R. (2013). Chemical penetration enhancers—a

review. World Journal of Pharmacy and Pharmaceutical Sciences, 3(2), 1068-80.

89. Abd, E., Roberts, M. S., & Grice, J. E. (2016). A comparison of the penetration and permeation of caffeine into and through human epidermis after application in various vesicle formulations. Skin pharmacology and physiology, 29(1), 24-30.

90. Rubio, L., Alonso, C., López, O., Rodríguez, G., Coderch, L., Notario, J., ... & Parra, J. L. (2011). Barrier function of intact and impaired skin: percutaneous penetration of caffeine and salicylic acid. International journal of dermatology, 50(7), 881-889.