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Review Article

Therapeutic Use of Caffeine in Dermatology: A Literature Review

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Abstract

Introduction: Caffeine is a naturally occurring methylxanthine alkaloid, with numerous molecular properties that make its application to the field of dermatology promising. **Purpose:** This review aims to describe the dermatological implications and applications of caffeine. **Methods:** PubMed was searched for literature related to caffeine use in dermatology using the search terms "caffeine and dermatology." **Results:** Caffeine may stimulate the hair growth in androgenetic alopecia and may prevent the risks of incident rosacea and both nonmelanoma and melanoma skin cancers. Numerous limitations exist for caffeine's application in dermatology, including few well-designed, clinically based trials in the treatment of hair loss, blurring of caffeine's potential therapeutic effects through combination with other active ingredients, potential for recall bias in prospective questionnaire-based studies, and lack of reporting on absolute effects in data analysis. **Conclusion:** Caffeine's numerous effects at the cellular level have potential application in the treatment of disorders related to the skin and hair. Caffeine may be beneficial in the treatment of hair loss and prevention of rosacea and skin cancer, but numerous limitations restrict the practical application of these findings.

Keywords: Androgenetic alopecia, basal cell carcinoma, caffeine, hair loss, melanoma, rosacea, squamous cell carcinoma

Introduction

Caffeine is a naturally occurring stimulant with numerous beneficial molecular properties implicated in dermatology. As the most widely consumed psychoactive stimulant, an estimated 85% of U.S. adults regularly consume caffeine.[1,2] Caffeine is a 1,3,7-trimethylxanthine [Figure 1]. Its physiologic effects are mediated by rapid absorption by the gastrointestinal tract when consumed most commonly in caffeinated beverages.[3] Caffeine has several molecular actions, including an ability to act as a phosphodiesterase inhibitor, ryanodine, and adenosine receptor agonist, in addition to numerous cytoprotective properties through its antioxidant role and ability to inhibit carcinogenesis.[3-8]

The high availability and widespread daily consumption of caffeine have led to numerous studies investigating its effects on health outcomes, including cardiovascular disease and risk, cancers, neurological, metabolic, and liver conditions.[9] In dermatology, the implications of caffeine are far-reaching, as its role serving as an antioxidant, phosphodiesterase inhibitor, and cosmetic and nutraceutical ingredient come with the potential for immense application in the field [Table 1]. This review aims to describe the dermatological implications and applications of caffeine in the treatment of disorders related to skin and hair.

Methods

A thorough PubMed search using the search terms "caffeine and dermatology" was conducted on June 25, 2019, yielding 96 results. Article titles and abstracts were scanned to identify the relevant literature. Thirty-two articles describing the molecular implications and clinical applications of caffeine use in dermatology were chosen.

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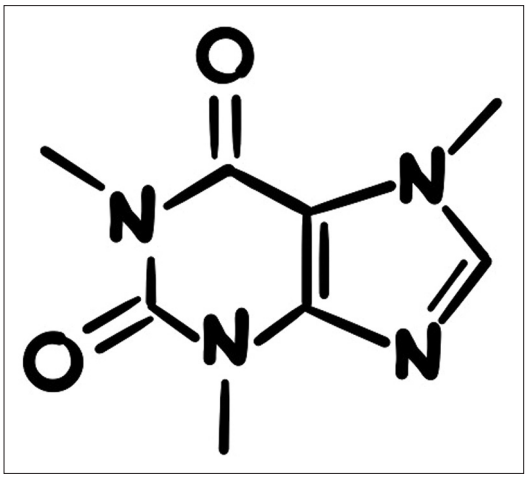

Figure 1: The molecular structure of caffeine, a 1,3,7-methylxanthine alkaloid with numerous molecular properties

Cutaneous-Related Molecular Effects of Caffeine

Caffeine has numerous molecular effects on human skin that may be important in dermatology [Table 2]. The basis of these molecular effects may stem from the antioxidant activity and phosphodiesterase inhibition. Caffeine improves transepidermal barrier function, prevents free radical-mediated damage, and inhibits lipid peroxidation and cell necrosis.[4-6] Caffeine protects mouse and human keratinocytes *in vivo* and *in vitro*, respectively, following ultraviolet (UV) radiation exposure, inducing apoptosis in unrepaired UV-damaged cells.[7,8] Whether these effects would occur at achievable blood caffeine levels in humans is not clear.

While caffeine has beneficial properties through reducing reactive oxygen species-mediated damage, caffeine was antagonistic to the promotion of wound healing in human skin.[10] Caffeine has an inhibitory effect on the proliferation and migration of keratinocytes in the setting of wound healing, which delayed healing and wound epithelization. This finding may be related to an unsustainable, hypermetabolic state induced by caffeine that imposes negative effects on the skin and hair.[11]

Hair Disorders

Of the dermatological implications of caffeine, one of the most widely reported has been caffeine's impact in hair growth. Androgenetic alopecia (AGA) is a frequently diagnosed hair disorder and suspected to be the result of both genetic predisposition and androgen-mediated anagen phase shortening with follicular miniaturization.[12,13] Demonstrating this mechanism, *ex vivo* hair follicles obtained from the scalp biopsies of patients with AGA were inhibited by the application of 5 μg/ml testosterone.[11] This effect was mitigated by concomitant treatment of 0.0001% and 0.005% concentrated caffeine. Hair follicles treated with caffeine alone experienced pronounced growth in culture compared to hair follicles in a control medium during an extended cultivation window, as measured by hair shaft elongation measurements and confirmed with Ki-67 immunohistochemistry ($P < 0.001$).

To investigate these findings further, microdissected hair follicles obtained from the scalps of both male and female participants were treated with either testosterone alone or a testosterone and caffeine combination (composed of 0.005%–0.0005% concentration of caffeine).[14] In the latter group, caffeine promoted the growth of human hair follicles through enhancing hair shaft elongation for males and females ($P < 0.05$), increasing the length of anagen phase in male hair follicles ($P < 0.05$), and stimulating keratinocyte proliferation in males and females ($P < 0.05$).

Although these findings demonstrate the positive effect of caffeine on hair growth, over-treating hair follicles with caffeine (concentrations >0.01%) cause a decrease in hair growth.[11] This is believed to be secondary to a hypermetabolic state induced by excess caffeine. This occurrence is crucial in determining the proper strength of future topical caffeine applications. The rapid penetration of hair follicles by caffeine may also be implicated in this determination. An essential component of effective AGA treatment involves follicular penetration of the drug, and caffeine is rapidly absorbed by hair follicles within 20 min of application.[15]

Topical caffeine was studied in three clinical trials assessing its efficacy in hair disorders. In a double-blind, placebo-controlled parallel trial of females diagnosed with AGA, participants treated with phyto-caffeine-containing shampoo had fewer hairs extracted on hair pull test following 6 months of treatment and reported a higher subjective satisfaction compared to placebo therapy ($P < 0.001$ for both).[16] In another randomized, open-label study investigating the effect of caffeine-based 0.2% topical liquid compared to minoxidil 5% solution in 205 male participants with AGA, mean improvement in the proportion of anagen hairs from baseline (determined using frontal and occipital trichograms) was 10.6 for 0.2% topical caffeine and 11.7% for 5% minoxidil after 6 months of treatment ($P = 0.574$).[17] Caffeine-based topical liquid was noninferior to minoxidil in treating men with AGA. The 0.2% caffeine liquid reduced scalp itchiness following 6 months of treatment ($P = 0.003$). This effect was not seen in the 5% minoxidil treatment group ($P = 0.211$).

Rosacea

Rosacea is a chronic inflammatory disorder that is suggested to be exacerbated by numerous triggers, including caffeine and hot beverages.[18,19] However, reports of caffeine as an exacerbating factor have been contradictory, with the findings of a positive association between caffeine consumption and rosacea but also no association between the two.[20,21] While heat is a risk factor for incident rosacea, the distinction between caffeine and hot caffeinated beverages (such as coffee) in studies examining these triggers of rosacea has not been clear.[19,22]

Table 1: Clinical applications of caffeine use in dermatology

Author (s), year	Study design	Number of participants	Condition studied	Key findings
Oh *et al*., 2019[28]	Retrospective review of prospective cohort	63257	NMSC	Caffeinated coffee and black tea consumption were associated with a reduced risk of NMSC The consumption of three or more cups of caffeinated coffee per day showed a lower risk of both BCC (HR, 0.54, 95% CI, 0.31-0.93) and SCC (0.33, 95% CI, 0.13-0.84) in comparison to those who consumed caffeinated coffee only once weekly The inverse relationship between caffeine consumption and NMSC was seen in daily consumers of caffeinated black tea as well (HR, 0.70, 95% CI, 0.52-0.94).
Li *et al*., 2018[22]	Retrospective review of prospective cohort	4945	Rosacea	Inverse relationship between increased caffeine intake from coffee and the risk of incident rosacea
Loftfield *et al*., 2015[29]	Prospective design	2904	Melanoma	Consuming ≥4 cups of caffeinated coffee per day was inversely associated with malignant melanoma There was no inverse association between decaffeinated coffee consumption and melanoma risk
Wu *et al*., 2015[30]	Retrospective review of prospective cohort	2254	Melanoma	Higher caffeine intake was associated with lower risk of melanoma Results most pronounced in women and body sites with a higher potential for sun exposure
Ferrucci *et al*., 2014[26]	Case-control study	767	NMSC	Regular consumption of caffeinated coffee with hot tea was inversely associated with early-onset BCC Participants with the highest caffeine consumption experienced the largest risk reduction for BCC after establishing the estimated lifetime caffeine intake (43% reduced risk, OR 0.57, 95% CI, 0.34-0.95)
Ferzli *et al*., 2013[23]	Prospective analysis	16	Facial redness	Caffeine, in combination with resveratrol and green tea polyphenol extracts, reduced facial redness after 6 weeks of twice-daily application
Song *et al*., 2012[27]	Prospective analysis	25480	NMSC	Caffeine intake from dietary sources (caffeinated coffee, tea, soda, and chocolate) was inversely associated with BCC risk Individuals who drank more than three cups of caffeinated coffee per day had a lower risk of BCC compared to individuals who drank less than one cup of caffeinated coffee per month (RR 0.83, 95% CI, 0.77-0.87) Decaffeinated coffee consumption showed no association with risk of BCC
Abram *et al*., 2010[20]	Retrospective review of prospective cohort	172	Rosacea	No significant relationship exists between caffeine intake and risk of incident rosacea
Vali *et al*., 2005[39]	Randomized, double-blinded, placebo-controlled, split-comparison	39	Psoriasis vulgaris	Caffeine resulted in a reduction of PASI scores compared to baseline compared to placebo-treated group

PASI: Psoriatic Area and Severity Index, NMSC: Nonmelanoma skin cancer, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, CI: Confidence interval, RR: Relative risk, HR: Hazard ratio, OR: Odds ratio

In a study evaluating the specific associations between caffeine intake, coffee consumption, and risk of incident rosacea, 4945 incident cases of rosacea in women were identified.[22] An inverse association between the highest quintile of caffeine intake and the risk of rosacea was seen, and this relationship was diminished with progression toward the lowest quintile of caffeine intake among the cohort (HR for the highest quintile of caffeine intake versus the lower, 0.76, 95% confidence interval [CI], 0.69–0.84, $P < 0.001$ for trend). There was also an inverse relationship seen with an increase in caffeinated coffee consumption and the risk of rosacea within the cohort ($P < 0.001$ for trend), and this was not seen in decaffeinated coffee consumers ($P = 0.39$ for trend). However, relationships with caffeinated tea and soda consumption and decreased risk of rosacea were not seen ($P = 0.30$ for trend, $P = 0.08$ for trend, respectively).[22]

The inverse relationship between caffeine consumption and risk of rosacea was suspected to be from caffeine's ability to act as a vasoconstrictor, which averts vasodilation that leads to the symptoms of rosacea. Additional proposed mechanisms of caffeine's action include caffeine's antioxidant and immunosuppressive properties that lead to a reduction of inflammation, as well as caffeine-induced hormonal modulation. The suggestion that caffeine's antioxidant property leads to a reduction of incident rosacea is bolstered by reporting on the effect of topically-applied caffeine in combination with other antioxidants, such as resveratrol and green tea polyphenols that resulted in a reduction of facial redness after

Table 2: Summary of the beneficial cutaneous-related molecular effects of caffeine

Author/study	Findings
Gherardini *et al*., 2019[48]	Caffeine provides protection toward UV radiation-mediated HF toxicity and dystrophy
	Caffeine upregulates catagen-promoting growth factor
Fischer *et al*., 2014[14]	Caffeine enhances hair shaft elongation, prolongs anagen-phase duration, and stimulates hair matrix keratinocyte proliferation
	Caffeine counteracts testosterone-enhanced TGF-β2 protein expression in male HFs
	Caffeine enhances IGF-1 protein expression
	Stimulates cell proliferation, inhibits apoptosis (in undamaged keratinocytes) and necrosis of outer root shaft keratinocytes
Silverberg *et al*., 2012[6]	Protects again acute reactive oxygen species-mediated cell necrosis in skin fibroblasts
Han *et al*., 2011[7]	Exerts pro-apoptotic effects in UVB-damaged, unrepaired keratinocytes
	Inhibited two critical oncogenic pathways (COX-2 and AKT phosphorylation) in skin tumorigenesis
Brandner *et al*., 2006[4]	Reduced transepidermal water loss in male skin, enhancing barrier function
Fischer *et al*., 2007[11]	Stimulates hair follicle growth
	Counteracts suppression of *ex vivo* hair follicle growth induced by testosterone
Huang *et al*., 1997[8]	Inhibition of UVB-induced carcinogenesis in mice

UV: Ultraviolet, HF: Hair follicle, TGF-β2: Transcription growth factor-beta 2, IGF-1: Insulin-like growth factor-1, COX-2: Cyclooxygenase-2, AKT: Akt: Protein kinase B

6 weeks of therapy.[23] This further supports a possible use of caffeine for the reduction of facial redness in rosacea.

Skin Cancer

The impact of caffeine on carcinogenesis has been widely studied and was originally investigated in mice.[8] Caffeine prevented UVB-induced carcinogenesis when given orally to mice, and these effects were lost with the removal of caffeine from green or black tea. When applied to human cells, caffeine induced apoptosis in keratinocytes that were inflicted with UVB damage and stymied two critical oncogenic pathways in skin tumorigenesis after UVB exposure.[7]

These early promising findings led to not only large-scale studies conducted to evaluate any association with caffeine consumption and the risk of nonmelanoma and melanoma skin cancer but also more specific studies to identify the genetic markers influencing the relationship of caffeine and UV-induced carcinogenesis. A specific DNA repair gene (NEIL3) involved in the base excision DNA repair pathway was identified as a key player in caffeine-mediated skin tumor inhibition, further shedding light on caffeine's role in skin cancer prevention.[24]

Nonmelanoma skin cancer

In a cross-sectional analysis of Caucasian women, those who consumed caffeinated coffee had a 10.8% lower prevalence of self-reported nonmelanoma skin cancer (NMSC), and consumption of six or more cups of caffeinated coffee resulted in a 30% reduction in self-reported NMSC after adjusting for various lifestyle and demographic variables (odds ratio [OR] 0.70, CI: 0.56–0.89, $P < 0.001$).[25] There was no similar reduction in risk of self-reported NMSC in Caucasian women who consumed only decaffeinated coffee.

Caffeine reduced the risk of basal cell carcinoma (BCC) in both a retrospective (OR 0.60, 95% CI, 0.38–0.96) and prospective study (relative risk [RR] 0.84, 95% CI, 0.80–0.87).[26,27] The retrospective study used age-matched controls and consumption of both caffeinated coffee and caffeinated tea was inversely associated with the risk of early-onset BCC.[26] According to the prospective study, the highest quintile of women who were daily caffeine consumers (median of 604 mg consumed per day, or about six and a half eight-ounce cups of coffee) had the lowest risk of BCC compared to the lowest quintile of women who were daily caffeine consumers (median of 31 mg consumed per day), with a RR of 0.82 (95% CI, 0.77–0.86).[27] However, the calculated multivariate absolute risk reduction was 0.00291, the equivalent of number needed to treat (NNT) of 344 patients (i.e., 344 patients would have to consume close to 604 mg of caffeine per day for one additional patient to not develop BCC).

An analysis of the Singapore Chinese Health Study prospective cohort supported the relationship between the consumption of caffeinated beverages (caffeinated coffee and black tea) and reduced risk of NMSC.[28] Overall, participants in this cohort who consumed 400 mg/day of caffeine (approximately four cups of coffee) had the lowest risk of NMSC (hazard ratio [HR], 0.59, 95% CI, 0.34–1.04).[28]

Melanoma skin cancer

Reporting of the effects of caffeine on melanoma skin cancer is not as prevalent as NMSC, yet similar relationships showing a lower risk of melanoma with caffeine intake have been shown. A large US cohort study of nonhispanic Caucasians reported an age-adjusted RR of reduction for melanoma by 20% with ≥4 cups of caffeinated coffee consumption per day (HR 0.75, 95% CI, 0.64–0.89, *P*-trend 0.01) compared to no caffeinated coffee consumption per day.[29] There was no association with decaffeinated coffee (*P*-trend = 0.55). The absolute risk reduction is 0.000217 resulting in 4600 people needing to consume ≥4 cups of coffee per day for one additional patient not to have melanoma. The authors suggested these findings warranted further investigation, but lifestyle modifications with modest protective effects may reduce disease burden and morbidity in melanoma.

In an analysis of the Nurses' Health Study II, a decreased risk of melanoma was noted with increasing caffeine intake and caffeinated coffee consumption after adjusting for additional risk factors that may lead to increased risk of developing melanoma.[30] Higher total caffeine intake (>393 mg/day, about four cups of coffee) was associated with a lower risk of melanoma when compared to lower total caffeine intake (<60 mg/day) (HR 0.94,

95% CI, 0.75–1.2). The inverse association between caffeinated coffee consumption and melanoma was most pronounced in sun-exposed locations (HR 0.71, 95% CI, 0.59–0.86, *P*-trend 0.001) and insignificant in melanoma of the trunk (HR 0.90, 95% CI 0.70–1.2, *P*-trend 0.60). This difference in association based on the location exemplifies caffeine's ability to inhibit UV-induced carcinogenesis and initiate apoptosis in damaged human keratinocytes in prior reporting.[30] A meta-analysis of nine observational studies supports the inverse relationship between caffeinated coffee consumption and risk of melanoma; pooled RR for melanoma among caffeinated coffee consumers was 0.75 (95% CI 0.63–0.89, $P = 0.001$).[31] In both studies, the lack of association with decaffeinated coffee consumption and risk of melanoma further supports the role of caffeine in carcinogenesis-inhibition and steers away from theories that other compounds in coffee are responsible for a lower rate of carcinogenesis.[30,31]

Risks and Toxicity

Risks associated with moderate caffeine consumption are minimal, but high levels of consumption or an acute increase in intake may lead to adverse cardiovascular effects and death.[32,33] The range of postmortem blood caffeine concentrations in caffeine-related deaths was 33–567 mg/L in one study, with a median value of 180 mg/L.[34] However, the average caffeine blood level after a 130 mg oral caffeine dose (about 10 ounces of caffeinated coffee) was 4 mg/L in multiple participants, far less than the toxic doses reported from ingestion of caffeine powder or tablets.[35] Caffeine does not increase the risk of atrial fibrillation, rather a lower incidence of atrial fibrillation occurs with high doses of daily caffeine consumption (>436 mg/day).[36] In normotensive populations, caffeine does not cause an increased risk of hypertension.[37] Patients diagnosed with hypertension are more sensitive to the effects of caffeine consumption and may experience acute increases in blood pressure compared to normotensive patients consuming caffeine.[37] The consumption of 400 mg of caffeine (equivalent of about four and a half 8 oz coffee cups) per day was not associated with adverse cardiovascular effects, behavioral effects, reproductive and developmental effects, or adverse effects on the bone in a systematic review of 381 articles.[38]

Discussion

Caffeine has numerous beneficial molecular properties that contribute to its widespread application in the field of dermatology, such as its ability to act as an antioxidant, phosphodiesterase inhibitor, and anti-carcinogen. Not only it is possibly effective in the treatment and prevention of skin cancer and rosacea, as well as the treatment of AGA, but also it is associated with few reports of side effects (mild itching).[39] While the adverse effects of ingested caffeine are well described, side effects of topical caffeine application require more extensive investigation. The application of topical caffeine in AGA and possibly other hair loss disorders is promising since oral finasteride and topical minoxidil are the only approved medications.[40] The additional uses for caffeine in dermatology include applications in psoriasis vulgaris and the cosmetic treatment of cellulite, but data are limited.[39,41,42]

There are several limitations to the studies mentioned in this review regarding the applications of caffeine in dermatology. In the evaluation of caffeine's efficacy for the treatment of hair loss, while numerous molecular-based studies have been performed showing caffeine's potential utility, few clinically-based, double-blinded, placebo-controlled studies directly examining the results of topical caffeine use have been conducted. The largest of the three studies involves a multi-faceted approach to the treatment of AGA in men involving minoxidil, finasteride, and a proprietary injectable blend of caffeine along with over ten other active compounds.[43] Although hair regrowth was experienced by the cohort, the entanglement of caffeine with multiple other active drugs and compounds prevents conclusions on caffeine's efficacy in hair growth.

In terms of the inverse relationship between rosacea and caffeine intake, as well as the inverse relationship between caffeine intake and skin cancer, conclusions were based on findings from questionnaires administered to large prospective database cohorts. This methodology raises the risk of recall bias from the participants.

Limitations applying to the findings of a reduced risk of incident rosacea seen with increasing caffeine consumption are two-fold. Polyphenols, which are also present in coffee along with caffeine, are beneficial in the treatment of rosacea.[44] The lack of association seen with heated, decaffeinated coffee consumption and the risk of rosacea may be from the counteracting effects of polyphenols.[22] There also was a lack of distinction made between the subtypes of rosacea.

The inverse relationship between caffeine consumption and SCC was only discussed in one study. As SCC risk is associated with UV radiation exposure, one would suspect more evidence on caffeine's ability to inhibit UV-induced carcinogenesis, specifically in SCC. Many of the studies describing the relationship between caffeine consumption and the inverse relationship with skin cancer are based around caffeinated coffee consumption. There are numerous active compounds (5-O-caffeoylquinic acid, diterpenes, and nicotinic acid) in coffee aside from caffeine that inhibit carcinogenesis at the molecular level.[29,45-47] The presence of these compounds and not caffeine could be responsible for the anticarcinogenic effects and reduction in the risk of melanoma. However, the lack of inverse associations between skin cancer and decaffeinated coffee consumption in several of these studies point toward a caffeine-dominated role. This is also supported by the inverse association seen with caffeinated black tea.[28]

A major limitation in the relationship between caffeine consumption and risk of skin cancer was the lack of reporting on absolute effects, such as absolute risk reduction and NNT. While numerous studies reported a RR reduction in skin cancer from

caffeine consumption, the calculation of absolute risk reduction by our team from the data provided in two studies revealed a disparity in the impact of caffeine on skin cancer prevention through a low absolute risk reduction and a high NNT.

Conclusion

Caffeine offers numerous positive benefits at the cellular level that have translated into few clinical applications and risk-reducing interventions. While further studies examining the implications of caffeine in dermatology are warranted, current evidence appears to be insufficient for caffeine's application in dermatology.

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Conflicts of interest

There are no conflicts of interest.

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