Dietary supplements in dermatology: A review of the evidence for zinc, biotin, vitamin D, nicotinamide, and *Polypodium*

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Dietary supplements are commonly recommended by dermatologists in the treatment of skin, hair, and nail disorders. This review of oral over-the-counter supplement use in dermatology summarizes current evidence for the use of zinc, biotin, vitamin D, nicotinamide, and *Polypodium* in the management of common dermatologic disorders. Evidence for the safety and efficacy of these supplements is limited. Very few large-scale randomized controlled trials exist for these over-the-counter supplements, particularly biotin and *Polypodium*. The lack of standardized dosing and standardized outcome measures makes comparison across existing studies challenging, and the lack of adverse events reporting in the majority of studies limits analysis of supplement safety. The most promising evidence exists for the use of nicotinamide in preventing nonmelanoma skin cancers. There is some evidence for the role of vitamin D in decreasing melanoma risk and progression in some individuals and for the photoprotective role of *Polypodium*, although additional high-quality studies are needed to determine appropriate dosing. Current evidence is insufficient to recommend the use of biotin or zinc supplements in dermatology. Large-scale randomized controlled trials investigating safety and efficacy are needed before widespread incorporation of these oral supplements into the general practice of dermatology. (J Am Acad Dermatol 2021;84:1042-50.)

Key words: biotin; niacin; nicotinamide; OTC; OTC supplements; over-the-counter; over-the-counter supplements; *Polypodium*; supplements; vitamin D; vitamins; zinc.

Dietary supplements are used by the majority of US adults.[1,2] Their designation as supplements allows these products to be marketed without stringent monitoring by the US Food and Drug Administration.[3] Despite the lack of rigorous assessments of the safety and efficacy of oral over-the-counter (OTC) supplements, as many as 66% of dermatologists reported recommending these supplements to their patients, most commonly for their purported benefits in skin, hair, and nail health.[4] We critically reviewed the available evidence for commonly recommended oral OTC supplements (see supplemental materials for search strategy; available via Mendeley at https://data.mendeley.com/datasets/w29wp46nf4/1).

ZINC

Zinc, an essential metal ion, has important catalytic, structural, and regulatory roles within the cell.[5] Rapid resolution of skin and hair findings in acrodermatitis enteropathica with zinc replacement therapy has suggested a role for zinc supplementation in promoting dermatologic health.[6] Zinc supplementation can be delivered through zinc sulfate (23% zinc) or zinc gluconate (14% zinc). Although zinc sulfate has a higher elemental zinc content, zinc gluconate reportedly has a less bitter, metallic taste.[7]

Studies of zinc supplementation for alopecia are limited to the treatment of alopecia areata. A double-blinded trial examining the efficacy of oral zinc sulfate (220 mg twice daily) in alopecia areata found

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that, although serum zinc levels increased significantly following supplementation, there was no clinical improvement in disease extent or activity.[8] An observational, uncontrolled study examining hair regrowth after oral zinc gluconate (50 mg/day) for alopecia areata observed hair regrowth in 66.7% of patients—within these patients, serum zinc levels increased to a significantly greater degree compared to patients who did not achieve a response.[9] The hair regrowth observed in these patients may have coincided with the natural course of the disease, so firm conclusions concerning the efficacy of zinc supplementation for hair regrowth cannot be established.

CAPSULE SUMMARY

- Few randomized controlled trials examine the safety and efficacy of oral over-the-counter dietary supplements marketed for dermatologic conditions.
- Although there is some evidence for clinical uses of vitamin D, nicotinamide, and *Polypodium*, insufficient evidence exists to recommend supplementation with biotin or zinc.

Evidence for oral zinc in acne vulgaris treatment is conflicting. A recent review identified 12 studies using varying doses of oral zinc as a single-agent supplement for acne, including 6 randomized controlled trials (RCTs), 3 controlled studies, 2 uncontrolled studies, and 1 case report. Three RCTs found no significant difference in acne severity between zinc and placebo groups,[10-13] whereas 3 RCTs found significant improvement in zinc groups.[14-16] The RCTs examined oral zinc sulfate given in varying doses, with higher and more frequent dosing in RCTs demonstrating no improvement. The most common adverse effects reported included nausea/vomiting,[12,14,15] diarrhea,[12,14] and indigestion.[15] Current evidence for zinc in acne is limited to a small number of RCTs with relatively small sample sizes, inconsistent dosing, and a lack of standardized outcome measures, which limits the interpretation of their results.

The use of oral zinc gluconate (90 mg/day) for Hurley stage I and II hidradenitis suppurativa (HS) has been investigated in 1 uncontrolled study and 1 retrospective study with oral zinc and topical triclosan (2%).[17,18] Both studies showed symptomatic improvement in patients with HS treated with zinc. Gastrointestinal adverse effects were reported in 18% and 22% of study participants,[17,18] which may limit widespread use.

Zinc supplementation has also been studied in wound healing. A controlled study of 20 young men undergoing pilonidal sinus excision found that the group treated with zinc sulfate 220 mg 3 times per day healed at a significantly faster rate.[19] Other studies have examined the efficacy of a high-protein, vitamin-enriched oral nutritional formula containing zinc for pressure ulcer healing. Significant reduction in pressure ulcer area was observed in the nutritional formula groups for all studies, including 2 RCTs,[20,21] 1 controlled trial,[22] and 1 uncontrolled trial.[23] The controlled study additionally compared the efficacy of a formula containing both L-carnosine and elemental zinc (34 mg/day) compared to L-carnosine alone.[22] Although significant improvement was observed in both formula groups compared to control, no significant difference in wound healing was observed between groups with or without zinc in the nutritional formula. RCTs examining the efficacy of zinc alone are needed to justify the use of zinc supplements in wound healing. Table I[24] reviews recommendations and levels of evidence by use.

BIOTIN

Biotin, or vitamin B7, is an essential coenzyme for 5 carboxylases involved in fatty acid synthesis, amino acid catabolism, and gluconeogenesis.[25] Frank biotin deficiency is rare. Marginal biotin deficiency may be encountered in pregnancy, smoking, and with long-term anticonvulsant use.[25] Despite the rarity of biotin deficiency, biotin supplement intake is relatively common. A 2016 study found the 30-day prevalence of biotin-containing supplement intake in US adults to be 29% (95% confidence interval, 27-31) from 2011 to 2012.[1] A limited number of studies have examined the efficacy of biotin in treating hair and nail disorders. Biotin therapy was shown to promote normal hair growth in 2 case series of familial uncombable hair syndrome.[26,27] In a series of patients experiencing alopecia after valproic acid treatment, biotin supplementation resulted in subjective improvement of alopecia.[28,29]

Evidence for biotin supplementation in nail disorders is limited to 1 clinical study,[30] 1 subjective survey,[31] and several case series.[32-34] The clinical study found that nail thickness increased significantly after biotin therapy in 8 patients with brittle nails.[30] RCTs studying biotin supplementation in hair and nail disorders are severely lacking.

The adequate intake for biotin is 30 μg/day for adults, which is easily achieved through a well-balanced diet including biotin-containing

Abbreviations used:

AD:	atopic dermatitis
AK:	actinic keratosis
EASI:	Eczema Area and Severity Index
HS:	hidradenitis suppurativa
NMSC:	nonmelanoma skin cancer
OTC:	over the counter
PDT:	photodynamic therapy
PLE:	*Polypodium leucotomos* extract
RCT:	randomized controlled trial
SCORAD:	Scoring Atopic Dermatitis
UV:	ultraviolet

foods, such as meat, eggs, fish, nuts, seeds, and certain vegetables. Biotin toxicity has not been reported at doses up to 200 mg orally and 20 mg intravenously.[35] However, biotin supplementation has been shown to interfere with routine immunoassays, including troponin T, thyroid-stimulating hormone, and antithyroid antibodies, yielding inaccurate test results.[36] The benefits of biotin supplementation remain unsubstantiated, and its use may lead to misdiagnosis of potentially serious conditions. Recommendations and levels of evidence are summarized in Table II.[37]

VITAMIN D

Studies showing that vitamin D deficiency is more common in patients with atopic dermatitis (AD) and psoriasis suggest a role for vitamin D in the pathogenesis of these common skin disorders.[38,39] Two early studies on the efficacy of vitamin D supplementation in AD showed conflicting results. An RCT comparing the efficacy of vitamins D and/or E against placebo found significant reduction in Scoring Atopic Dermatitis (SCORAD) in patients with AD after 60 days of treatment with either vitamin D or E. The greatest improvement was observed in participants treated with both.[40] A smaller RCT in children with AD found significant improvement in the Investigator Global Assessment of patients treated with vitamin D compared to placebo but no significant improvement in the Eczema Area and Severity Index (EASI) score.[41] Based on these studies, a 2012 Cochrane review of dietary supplements in AD found there to be insufficient evidence to recommend the use of vitamin D in AD.[42]

Since then, a number of RCTs have examined the impact of vitamin D supplementation on AD severity scores using a variety of doses and treatment intervals. With the exception of 1 RCT,[43] these studies have, overall, found that vitamin D supplementation significantly reduces SCORAD[44-46] and EASI scores,[47] *Staphylococcus aureus* colonization, and erythema index.[46] A cross-sectional, non–placebo-controlled study additionally found a significant reduction in both SCORAD and mean total immunoglobulin E level after vitamin D supplementation, perhaps suggesting an immunoregulatory role for vitamin D.[48] The discrepancy between the results from these studies may be related to the population studied, time of year, location, or degree of vitamin D deficiency at baseline.

Evidence for the use of oral vitamin D in psoriasis is scarcer. Uncontrolled studies suggested that vitamin D supplementation resulted in improved psoriasis and psoriatic arthritis severity.[49-52] More recently, however, several RCTs have shown vitamin D supplementation to have little impact on psoriasis severity. Although 1 study reported significant improvement in the Disease Activity Score–28,[53] no significant improvement in Psoriasis Area and Severity Index score after vitamin D supplementation was observed in the remaining RCTs.[53-56]

In vitro studies have shown that 1,25-dihydroxyvitamin D3 protects keratinocytes against ultraviolet (UV)-induced apoptosis and formation of mutagenic cyclobutane pyrimidine dimers.[57,58] Studies in humans have primarily been limited to observational studies examining the relationship between vitamin D levels and nonmelanoma skin cancer (NMSC) risk and have shown mixed results.[59-62] Observational studies suggest that lower vitamin D levels are correlated with poorer melanoma prognosis.[63-66] One RCT of 36,282 female participants evaluated the impact of daily calcium (1000 mg) with vitamin D3 (400 IU) on the incidence of NMSC and melanoma over 7 years. No difference in melanoma or NMSC was shown between the supplement and placebo groups; however, women with a history of NMSC taking calcium and vitamin D showed a significantly lower risk of melanoma compared to the placebo group.[67] Participant groups were comparable in terms of age, race/ethnicity, education, body mass index, smoking history, geographic region, sun exposure, and cancer history. Family history of skin cancer was not documented, however, and may be a confounding variable.

A meta-analysis of vitamin D status and the risk and prognosis of melanoma and NMSC found no association between vitamin D intake and cutaneous melanoma or NMSC risk.[68] A statistically significant positive association between high vitamin D levels and risk of NMSC was found, suggesting that sun exposure may be a confounding variable in many of the existing studies. No association was found between serum vitamin D levels and cutaneous

Table I. Zinc

Use	Dose	Recommendation	Adverse effects	Level of evidence*
Alopecia areata	Variable	Insufficient data for conclusive recommendation	Nausea	IIA
Acne	Variable	Insufficient data for conclusive recommendation	GI adverse effects	IB
Hidradenitis suppurativa	90 mg/day zinc gluconate	Insufficient data for conclusive recommendation	GI adverse effects	IIB
Wound healing	220 mg TID zinc sulfate	Insufficient data for conclusive recommendation	NR	IIA
Contraindications: Supplementation above the tolerable upper limit (40 mg elemental zinc per day) in pregnant and lactating women is contraindicated.[24]				

GI, Gastrointestinal; *NR*, not reported; *TID*, 3 times daily.
*Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines: level IA evidence includes evidence from meta-analysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both.

Table II. Biotin

Use	Dose	Recommendation	Adverse effects	Level of evidence*
Alopecia	10 mg/day	Insufficient data for conclusive recommendation	NR	III
Brittle nails	2.5 mg/day	Insufficient data for conclusive recommendation	NR	III
Contraindications: There are no known contraindications to biotin use. Biotin does cross the placenta and is secreted into breast milk, but the significance of this, if any, is unknown.[37]				

NR, Not reported.
*Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines: level IA evidence includes evidence from meta-analysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both.

melanoma risk, but, in individuals with melanoma, vitamin D levels were inversely associated with Breslow thickness at diagnosis.[68] These studies suggest that, although there are insufficient data to recommend vitamin D to reduce NMSC risk, vitamin D may have an impact on melanoma risk and prognosis, particularly in high-risk individuals. The results of a phase 3 RCT investigating the impact of vitamin D supplementation on cutaneous melanoma outcome are awaited.[69]

Vitamin D toxicity, although rare, can occur.[70] Symptoms of vitamin D toxicity are related to hypercalcemia and are observed after excessively high vitamin D doses (50,000-2,604,000 IU/day).[70] No adverse effects were reported in the described studies because vitamin D supplementation was given within recommended limits.[71] Table III[71,72] summarizes recommendations for each indication and available level of evidence.

NICOTINAMIDE

Nicotinamide, a form of vitamin B3, is a precursor for nicotinamide adenine dinucleotide,[73] which is the substrate for poly—adenosine diphosphate—ribose polymerase (PARP). PARP is a nuclear enzyme that is activated in response to oxidative DNA damage to promote DNA repair.[74] Following studies indicating that oral niacin prevents UV-induced immunosuppression and carcinogenesis in mice,[75] studies of the immunomodulating effects of nicotinamide in dogs with cutaneous lupus have shown promising results.[76] Studies of the efficacy of nicotinamide for cutaneous lupus in humans have yet to be performed.

Two small randomized trials evaluated the photoprotective effects of nicotinamide in humans after solar-simulated UV exposure and photodynamic therapy (PDT).[77,78] Nicotinamide showed no effect in decreasing the minimal

Table III. Vitamin D

Use	Dose	Recommendation	Adverse effects	Level of evidence*
Atopic dermatitis	Highly variable	Insufficient data for conclusive recommendation	NR	IB
Psoriasis	Highly variable	Insufficient data for conclusive recommendation	NR	IB
NMSC prevention	Highly variable	Insufficient data for conclusive recommendation	NR	IB
Melanoma prevention	Highly variable	Yes, in high-risk individuals	NR	IB
Contraindications: There are no known contraindications to vitamin D intake. Vitamin D supplementation should be approached cautiously in individuals with hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma.[72] Vitamin D levels in breast milk remained unchanged with supplementation of at least up to 2000 IU/day.[71]				

NMSC, Nonmelanoma skin cancer; *NR*, not reported.
*Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines: level IA evidence includes evidence from meta-analysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both.

Table IV. Nicotinamide

Use	Dose	Recommendation	Adverse effects	Level of evidence*
Photoprotection	500 mg daily-TID	No, reduces UV-induced immune suppression in the skin, but not erythema	NR	IB
AK clearance	500 mg daily-BID	Reduces AK count while receiving treatment	Rare nausea, diarrhea	IB
NMSC prevention	500 mg BID	Reduces rate of new NMSCs and AKs while receiving treatment	NR	IB
Contraindications: Nicotinamide is contraindicated in the case of hypersensitivity to niacin or niacinamide. Nicotinamide does cross the placenta, but the significance of this, if any, is unknown.[37]				

AK, Actinic keratosis; *BID*, twice daily; *NMSC*, nonmelanoma skin cancer; *NR*, not reported; *TID*, 3 times daily; *UV*, ultraviolet.
*Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines: level IA evidence includes evidence from meta-analysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both.

erythema dose compared to placebo, but photoimmunosuppression was significantly reduced in the nicotinamide group in both studies. In a phase 2 double-blinded RCT, the relative reduction in actinic keratosis (AK) count from baseline to 4 months of treatment was significantly lower in the nicotinamide group compared to placebo.[79] The relative reduction in AK count was more pronounced in patients treated with nicotinamide 500 mg twice daily (35%) compared to patients treated with 500 mg/day (29%).[79] Two smaller studies found that nicotinamide supplementation over 6 months in kidney or liver transplant recipients also led to a substantial decrease in size and number of AKs compared to placebo.[80,81]

A phase 3 RCT of nicotinamide supplementation for 12 months in patients with a recent history of NMSCs found that the rates of new NMSCs and AKs were significantly reduced while receiving treatment compared to placebo; however, no evidence of benefit was observed after 6 months of discontinuing nicotinamide.[82] Available evidence suggests that nicotinamide may be a useful addition to the standard of care for patients at high risk for NMSCs, although its chemopreventive benefit does not persist after discontinuation of the supplement. Because the vast majority of nicotinamide studies were conducted by the same group of investigators practicing in Australia, additional RCTs including a more diverse patient population would be useful in determining the generalizability of these results.

Nicotinamide toxicity has been reported at doses above 3.5 g/day. Signs of overdose include disturbances in liver enzymes, which may lead to

Table V. *Polypodium*

Use	Dose	Recommendation	Adverse effects	Level of evidence*
Photoprotection	240 mg BID	Reduces sunburn frequency and intensity	NR	IB
Idiopathic photodermatoses	240 mg BID	Improves subjective symptoms	NR	IIB
Melasma	240 mg BID-TID	Insufficient data for conclusive recommendation	NR	IB
AK clearance	240 mg BID-TID	Improves efficacy of PDT in clearing scalp AKs	NR	IIA
Contraindications: There are no known contraindications to *Polypodium*.				

AK, Actinic keratosis; *BID*, twice daily; *NR*, not reported; *PDT*, photodynamic therapy; *TID*, 3 times daily.
*Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines: level IA evidence includes evidence from meta-analysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both.

reversible hepatotoxicity.[83] The recommended upper limit of nicotinamide is 900 mg/day.[84] Long-term efficacy and safety data of nicotinamide are not yet available. Recommendations and levels of evidence are summarized in Table IV.[37]

POLYPODIUM

Polypodium leucotomos, a species of fern native to the tropical Americas, was first investigated in Honduras as a therapeutic agent for psoriasis.[85] *Polypodium leucotomos* has been studied in vitro for its antioxidant and direct photoprotective effects.[86-89] Studies of *Polypodium leucotomos* extract (PLE) given before UV irradiation in healthy individuals have shown that PLE administration is associated with a significant reduction in UV-induced erythema[90,91] compared to non-PLE treated control individuals. The largest randomized clinical trial to date investigated the safety and efficacy of PLE in 20 participants compared to placebo for 60 days. Individuals pretreated with PLE showed increased minimal erythema dose, decreased UV-induced erythema intensity and decreased likelihood of experiencing multiple sunburns from baseline to day 60 compared to placebo.[92] These results theoretically suggest that PLE could likewise be useful in decreasing UV-induced erythema in rosacea-prone individuals, although no studies of PLE in rosacea have yet been performed.[93]

Additional studies have investigated the role of PLE in skin disorders. Two studies showed subjective improvement in idiopathic photodermatoses after 15 days of PLE,[94,95] whereas the use of PLE in melasma has shown conflicting results.[96,97] No significant difference in melanin index between PLE and placebo groups was detected in either study; however, in 1 study, the Melanin Area and Severity Index score improved in patients with melasma receiving PLE.[97] One controlled study has investigated PLE as an adjunct to PDT for the treatment of AKs. Oral PLE beginning 1 week after PDT significantly improved the scalp AK clearance rate compared to PDT alone.[98] Although the precise antioxidant and photoprotective mechanisms of PLE have yet to be fully elucidated, these preliminary studies indicate that PLE may prove to be a useful adjunct to standard-of-care treatments in photodermatoses, melasma, and actinic damage. Table V summarizes recommendations and levels of evidence.

CONCLUSIONS

Evidence for the safety and efficacy of commonly recommended supplements in dermatology is remarkably limited. In particular, large-scale RCTs studying the efficacy and safety of biotin and *Polypodium* are severely lacking. Insufficient evidence exists to recommend the use of zinc in alopecia, acne, HS, or wound healing, and gastrointestinal adverse effects are relatively common. Vitamin D may have a role in decreasing melanoma risk/progression, particularly in high-risk individuals with a history of NMSC, but there is insufficient evidence to recommend vitamin D for AD, psoriasis, or prevention of NMSC. Studies on the use of nicotinamide in preventing NMSC are promising, but it should be noted that its chemopreventive effect does not persist after nicotinamide discontinuation. The use of OTC supplements is not without cost to the patient, and supplements without sufficient evidence for their use should not be routinely recommended. High-quality investigations into the safety and efficacy of these supplements with standardized dosing, outcome measures, and adverse effects reporting are greatly needed.

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