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ORAL SUPPLEMENTATION IN DERMATOLOGY

INTRODUCTION:

Canadians purchase approximately $1.2 billion of oral vitamins and supplements, also known as 'nutraceuticals', each year.[1] Global retail sales of nutraceuticals have been valued at over $382 billion in 2019.[2] Health Canada does not review natural health products with the same rigor as over-the-counter and prescription drugs[3], and many of these products claim to have medical benefits for the skin, hair, and/or nails. As dermatologists, our patients often ask questions regarding the possible benefits of various oral supplements. These inquiries are related to topics ranging from skin rejuvenation, hair and nail health, photoprotection, to anti-oxidant and anti-inflammatory effects in conditions such as eczema, psoriasis, acne, and hidradenitis suppurativa. With growing patient interest and market share, there are an increasing number of clinical studies examining the potential effects of oral supplements on the skin. While there are thousands of products available, the scope of this article is centered on reviewing the evidence for three of the more commonly encountered ones: collagen, *polypodium leucotomos*, and omega-3 fatty acids. The ensuing discussion about the evidence for each one of these agents will be summarized according to the quality of studies[4] and the level of evidence outlined in **Table 1**.

COLLAGEN:

Oral collagen has been a popular product for many years. In 2016, the collagen market was valued at around $3.7 billion USD and is projected to reach $6.6 billion USD by 2025.[6] Commercially available products are typically derived from various origins such as marine, bovine and porcine sources. Oral collagen has been linked with both antioxidant and anti-inflammatory properties, as well as being associated with UV protection, skin hydration, and improvements in nail strength.[7] Collagen-derived products are metabolized in the gastrointestinal system into amino acids (most commonly di- and tri-peptides) before being absorbed into the blood circulation, but there is growing evidence to suggest that they might also be absorbed directly.[8] Animal studies have demonstrated that maximal absorption in the skin is reached at 12 hours after consumption, and that more than 85% disappears from the blood after 24 hours.[9]

Levels of Evidence for Therapeutic Studies*

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCTs (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	"Outcomes" research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

**From the Centre for Evidence-Based Medicine, http://www.cebm.net.*

Table 1: Levels of Evidence for Therapeutic Studies[5]

A recent systematic review and meta-analysis published in March 2021 evaluated the effects of oral collagen supplementation on skin; it included 19 randomized, double-blind, and controlled trials (RCTs) with a total of 1,125 participants aged between 20 and 70 years. It showed favorable results of collagen supplementation in terms of skin hydration (measured by corneometry in 10 out of 13 studies), elasticity (measured by cutometry in 11 out of 15 studies), and wrinkles (measured by silicone skin replicas with 3D topography analysis in 2 out of 4 studies, and photographic analysis in 2 out of 4 studies) after 90 days of use.[10]

Another 2019 systematic review examined the effects of collagen-derived dietary supplements on the skin and included 11 RCTs with a total of 805 patients.[11] That review concluded that these supplements are generally safe. Eight studies used collagen hydrolysate, at 2.5 grams per day (g/d) to 10 g/d, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3 g/d for 4 to 12 weeks, with notable improvement in skin elasticity and hydration. The last study using collagen dipeptide showed a dose-dependent relationship to anti-aging efficacy.[12] The majority of these 11 RCTs also used cutometry and corneometry to measure elasticity and skin hydration respectively. These systematic reviews suggest benefit for oral collagen supplements in skin aging. The level of evidence for using oral collagen supplementation for this is therefore 1A. Further studies are needed to elucidate medical use in skin barrier diseases such as atopic dermatitis and to determine optimal dosing regimens

POLYPODIUM LEUCOTOMOS:

There are a few manufacturers of this oral supplement available which is a South American species of fern plant, and claims to have antioxidant, photoprotective,

and anti-aging properties by inhibition of UV-induced reactive oxygen species generation.[13] There have been a number of studies that suggest evidence for photoprotection and photoaging with *polypodium leucotomos*.[14,15,16]

Although it has gained more "hype" in recent years, extracts of this fern have been used for the treatment of a variety of skin conditions since the 1970s, including psoriasis, atopic dermatitis, polymorphic light eruption, and melasma. To date, there is weak or no scientific evidence to support these uses.[17,18,19,20]

Only two RCTs evaluating this oral supplement have shown statistically significant outcomes. One randomized, double-blind, placebo-controlled study with 40 subjects demonstrated that 240 mg of *P. leucotomos* taken twice daily for 60 days resulted in an increased minimal erythema dose (MED) and reduced UV-induced erythema intensity at day 28.[21] Another recently published randomized, assessor-blinded prospective study with 44 vitiligo patients showed that 480 mg of oral *P. leucotomos* taken twice daily along with NB-UVB phototherapy demonstrated improved repigmentation as well as increased response rate to NB-UVB treatment compared to those on placebo and NB-UVB treatment.[22] The level of evidence to use oral *P. leucotomos* for UV protection and adjunctive therapy for vitiligo is therefore 1B.

OMEGA-3 FATTY ACIDS:

Most of the scientific research on oral omega-3 fatty acids (O3FAs) focuses on alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA is found in plant oils such as flaxseed, walnuts, soy, and canola oils, while EPA and DHA are found in fish, krill and fish oils (originally synthesized by microalgae).[23] Studies have suggested that O3FAs have antioxidant and photoprotective properties in the skin and may benefit eczema and psoriasis patients.

Although a deficiency of O3FAs can lead to skin disease such as dermatitis, there is no known lower threshold for the serum concentrations of O3FAs below which dermatitis can manifest.[24]

A review of 38 studies which met the eligibility criteria was published in 2020 examining the role of omega-3 supplementation in various dermatological conditions, The review included double-blind RCTs that showed statistically significant benefits in psoriasis, atopic dermatitis, acne, and skin ulcers.[25] The level of evidence for using omega-3 supplementation in these conditions is therefore 1B.

CONCLUSION:

The role of oral nutraceutical supplementation in skin health is a frequent source of patient inquiry and physician uncertainty. There is limited evidence for the efficacy and safety of many supplements in the treatment of dermatologic diseases, and I do not recommend them over the use of medically prescribed therapies. This article reviews the currently available evidence for three of the more common oral supplements that patients may inquire about. With the appropriate patients, I would discuss the potential benefit of oral supplementation, in addition to prescribed therapies, especially if they are not obtaining adequate amounts in their diet. For example, omega-3 supplementation is unlikely to clear a patient's psoriasis or dermatitis as monotherapy, but there is some evidence to suggest benefit. Similarly, *P. leucotomos* can be used as an adjunct to, not a substitute for, sunscreen and UV-protective clothing for photoprotection. I may suggest it to some of my vitiligo patients undergoing phototherapy in light of the recent publication. The use of supplements is not without cost, and so before a patient relies solely on oral collagen for anti-aging, it is important to ensure the patient understands the importance of healthy lifestyle choices (e.g. sun protection, not smoking, eating healthy, getting good sleep, regular exercise, and perhaps the use of a topical retinoid). In suitable patients, it may be reasonable to supplement collagen, *P. leucotomos*, and/or O3FAs given their ease of administration, low risk of adverse effects, and growing body of evidence to indicate their potential benefits.

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