nutraceuticals

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Review

Comparative Assessment of Nutraceuticals for Supporting Skin Health

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Abstract: Background/Objectives: The term "nutraceuticals" refers to food and dietary supplements promoted for their health benefits in addition to their nutritional value. These products contain plant- or animal-derived nutrients, vitamins, minerals, trace elements, and similar compounds aimed at enhancing skin health and influencing visible skin quality. This review provides an overview of the current research on nutraceuticals and the scientific evidence supporting their effects on skin health. Methods: The literature on more than 50 selected nutraceuticals was examined to assess any clinically substantiated, beneficial effects on skin health. The assessment was based on scientific evidence, including the quality and quantity of empirically gathered and evaluated findings. Results: A total of 17 common dietary supplements, either as individual compounds or categorized into groups, along with some combination products, were identified as nutraceuticals with well-supported effects on skin health. These include, among others, vitamins A, B7, C, and E; collagen peptides; carotenoids; and various plant extracts. For many other nutraceuticals, clinical evidence for their effects on skin health is limited or insufficient. Conclusions: The literature indicates that many nutraceuticals marketed for skin health are more or less suitable for this application based on the evidence assessment.

Keywords: clinical evidence; dietary supplements; nutraceuticals; RCT; skin health

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1. Introduction

Nutraceuticals represent a modern generation of food and dietary supplements that claim health benefits. To date, numerous review articles have evaluated nutraceuticals [1–4]. Regarding skin, several reviews have addressed various aspects of skin health, focusing on a limited selection or special groups of nutraceuticals [5–8], particular aspects of skin health [9–14] or nutribiotics for skin care [15]. A recent review article demonstrates a clear connection between diet and skin health and provides recommendations for the use of certain key nutrients [16]. However, there has not yet been a comprehensive evaluation of commercially available nutraceuticals marketed for skin health in terms of their clinically proven efficacy.

This article aims to provide a comprehensive overview of the current state of science and research regarding the demonstrated effects of nutraceuticals on skin health. The main

objective of this review is to classify a broad range of commercially available nutraceuticals based on the availability and quality of published efficacy data. Health claims for nutrients are regulated in the EU by the European Food Safety Authority (EFSA). The EU Regulation 1924/2006 on nutrition and health claims on foods, commonly referred to as the Health Claims for Food Regulation, establishes uniform requirements across Europe for the use of such claims [17]. Nutritional claims describe specific nutritional properties of foods, such as their energy content or their content of nutrients or other substances. Health-related claims establish a connection between nutrients in a product and health benefits. They are strictly regulated and apply only to the nutrients contained in the nutraceuticals. Usually, health claims refer to the influence on structures and functions of the body.

In contrast, beauty claims relate to the appearance of the body [18], such as skin appearance. Beauty claims also require scientifically substantiated justification. However, they are not subject to EFSA review, as beauty claims cannot, by definition, be health claims at the same time. Scientific evidence of efficacy is nonetheless essential for beauty claims as well. To provide greater clarity regarding the skin effects of nutraceuticals, common nutraceuticals have been assessed for their suitability in influencing skin health based on the available studies and taking into account the evidence and relevance of data.

Due to the complexity of the topic, the wide range of nutraceuticals, and the great range of informative value of the existing studies, the subjective assessments of the authors play a decisive role in the classification of the substances. Therefore, this review can only be narrative in nature, although efforts were made to incorporate as many aspects of a systematic or scoping review as possible.

1.1. Nutraceuticals

The strict distinction that previously existed between the pharmaceutical and food markets is becoming more and more blurred. A health-conscious approach to one's own body has become commonplace, manifesting itself across all areas of life. Today, the focus extends to whether a food is beneficial or detrimental to health and to what extent foods can provide a physiologically active additional benefit. This trend is not entirely new: as early as the time of Hippocrates, the preventive value of nutrition for human health was recognized—yet he clearly distinguished between nutrition and medicine. This distinction remains relevant today: while nutrition is not a form of therapy, it constitutes an essential foundation for maintaining and promoting health.

To date, there is no clear regulatory definition for nutraceuticals (Table 1). The term "nutraceuticals" is a syncretic neologism derived from the English words "nutrition" and "pharmaceuticals". It was coined by the American physician Stephen De Felice, founder of the Foundation for Innovation in Medicine [19]. He used this term to describe foods or components of foods that provide a medical or health benefit, including the prevention and treatment of diseases. In contrast to pharmaceuticals, nutraceuticals are typically not synthetic substances developed for the treatment of specific conditions. They primarily contain nutrients and natural compounds that can be consumed as food or food ingredients. Unlike many pharmaceuticals, they are not xenobiotics and, thus, are generally well-tolerated, harmless, and safe even when used long-term.

Although there is often no clear distinction between nutraceuticals and other food categories, such as dietary supplements, foods for special medical purposes, functional foods, and novel foods, there has been considerable change in the literature over the last five years. Modern definitions define separate categories: "Nutraceuticals" are concentrated bioactive products that are typically offered as tablets, capsules, powders, or ampoules and are often used for therapeutic or preventive purposes. In contrast, the term "functional foods" refers to whole foods or food products that offer health benefits beyond basic

nutrition when consumed as part of a normal diet. Distinct definitions can also be found for dietary supplements and nutraceuticals: Dietary supplements are intended to supplement a deficiency (vitamins and minerals), but nutraceuticals go beyond that, imparting a therapeutic effect.

Nevertheless, the Dietary Supplement Health and Education Act (DSHEA) does not differentiate between nutraceuticals and dietary supplements. They are defined as products that contain isolated, sometimes chemically pure food ingredients in high dosages, provided in non-conventional food formats, and attributed with special health effects. They support nutrition and contain one or more of the following ingredients: vitamins, minerals, herbs, plant extracts, amino acids, or nutrients [20].

Table 1. Definitions for "Nutraceuticals" (According to Santini et al. 2018 [21]).

Source	Nutraceuticals Are...	
DeFelice, 1995 [19]	...	food or nutrient that provide medical or health benefits, including the prevention and treatment of diseases.
Zeisel, 1999; DSHEA [22]	...	dietary supplements that deliver a concentrated form of nutrients and natural active ingredients in food in a non-food-like manner to improve health.
Brower, 1998 [23]	...	all kinds of food or nutrients that have medical and health benefits and are suitable for prevention and therapy, among other things.
Merriam-Webster Dictionary, 2015 [24]	...	food as fortified food or dietary supplements that have a health value in addition to their nutritional value.
European Nutraceutical Association (ENA), 2016 [25]	...	dietary products that have health or medical effects that can be used, among other things, for prevention and therapy.

Nutraceuticals are also referred to as "food supplements", "functional foods", "superfoods", "whole foods", or "health foods". The EFSA categorizes these products as "food", "food ingredients", "foods for specific groups", "foods for specific medical purposes", "dietetic products", "traditional food", "novel food", or "novel food ingredients".

This document focuses exclusively on foodstuffs (including food ingredients such as nutrients and natural agents), encompassing dietary supplements but excluding medical devices and pharmaceuticals. Nutraceuticals encompass a vast array of plant and animal-derived nutrients, vitamins, and minerals. In various reviews, authors have attempted to classify and functionally categorize nutraceuticals [1,2], some of which have served as a basis for the development of this overview article.

1.2. Target Audience and Market

The target audience for these nutraceuticals comprises physically healthy individuals seeking to enhance their skin appearance and maintain skin health. The concept of "beauty from within" has gained widespread acceptance, supported by scientific evidence demonstrating nutrition's lasting impact on skin health [26]. Furthermore, the increasing life expectancy has led to growing demands for maintaining a youthful appearance. According to Global Industry Analysts' market analysis, the global nutraceuticals market is projected to reach USD 441.7 trillion by 2026, with an average annual growth rate of 7.8% (source: www.prnewswire.com/news-releases/global-nutraceuticals-market-to-reach-441-7-billion-by-2026--301491307.html (accessed on 27 March 2022). Currently, the European

market is the largest for nutraceuticals, followed by Asia and North America, with the Asian market experiencing the strongest growth.

1.3. Skin Physiology

The skin, functioning as a boundary organ, provides multiple protective barriers—physical, chemical, biological, and immunological against environmental factors. These barriers protect against external influences such as temperature extremes (heat and cold), environmental conditions (humidity, wind), physical contaminants (dust, dirt), dehydration, UV radiation, harmful substances, pathogens, and much more. In response to excessive UV exposure, the skin develops protective mechanisms like a thickening of the stratum corneum ("light callus") and an increase in melanin production, leading to skin pigmentation (tanning).

The skin contributes to thermoregulation through multiple mechanisms: Releasing of excess heat through convection and evaporation of sweat and water, constricting blood vessels, and causing piloerection (commonly known as "goosebumps") to maintain a constant body temperature in cold conditions. Notably, the stratum corneum (horny layer), being the outermost layer of the skin, and underlying epidermal layers undergo continuous renewal as a defensive mechanism against external influences. In the stratum basale, new cells are constantly generated, migrating upwards, keratinizing (transformation of keratinocytes into resistant corneocytes), and then undergoing programmed cell death.

The skin's intrinsic barrier function provides protection against pathogens (bacteria, viruses, fungi) as well as mechanical stress and irritative or allergenic substances, including fine particulate matter. In humans, this barrier consists of a multilayered, partially overlapping squamous epithelium (corneocytes) with a precisely organized intercellular lipid matrix composed of cholesterol, free fatty acids, and ceramides. Additionally, the stratum corneum contains water-binding substances (natural moisturizing factor) and sebaceous lipids on the surface. The acidic pH in the upper stratum corneum reduces colonization by pathogenic viruses and bacteria [27,28].

Furthermore, the epidermis contains nerve fibers that extend just below the stratum corneum, as well as inflammatory and immune cells. Beneath the epidermis lies the dermis, a highly elastic and tensile tissue extending into the subcutaneous fat tissue. It primarily consists of cellular elements (connective tissue cells, fibroblasts, and fibrocytes), along with structural elements (dermal fibers, collagen, elastin), all embedded in a gel-like ground substance known as the extracellular matrix. The dermis houses neural components (nerve fibers, tactile sensory cells, cold receptors), vascular elements (blood and lymphatic vessels), and appendages (hair follicles with smooth muscle fibers, sweat, and sebaceous glands). The dermal vasculature serves dual functions: Nutrient supply to the epidermis and significant contribution to the macroscopic skin appearance through moisturizing factors (e.g., hyaluronic acid) affecting skin turgor. During the aging process, the degradation of elastin and collagen becomes apparent through a loss of elasticity and firmness at the skin's surface.

The subcutis serves as a reservoir for heat and nutrients, cushioning underlying structures, dampening external pressure and impacts, and providing protection against heat loss. Recent findings suggest that subcutaneous adipose tissue also has additional functions, such as hormone production. Age-related loss or redistribution of subcutaneous fat is an important aspect of the appearance of older individuals.

1.4. Skin Health

Healthy skin significantly contributes to a person's attractiveness. The more uniform the pigmentation and the smoother the surface topography, the more appealing a face

appears [29]. Women with healthier skin are perceived as younger, an effect observed in both facial and body skin. Skin without visible abnormalities or lesions can appear up to five years younger. Skin health is a visible indicator of skin quality, characterized by four perceptual parameters: evenness of skin tone, evenness of the skin surface, skin firmness, and skin glow [30].

Skin health and quality are influenced by various factors. External, particularly chronic influences such as cold or heat, mechanical or chemical stress, mental strain, and environmental noxae like UV radiation or particulate pollution, can have a lasting impact on skin health. Additionally, age-related changes in skin function directly impact skin health. The progressive degradation of dermal components, specifically collagen and elastin, combined with decreased moisture retention due to reduced endogenous hyaluronic acid production, manifests as visibly diminished firmness and elasticity, leading to wrinkle formation [31,32]. Oxidative stress, characterized by an imbalance between free radicals and antioxidants, significantly contributes to skin aging through both epidermal and dermal damage [33].

With aging, transepidermal water loss (TEWL) as a marker of the "inside-outside" barrier is slightly reduced due to diminished blood circulation. However, the "outside-inside" barrier is compromised, primarily due to thinning of the skin, particularly the stratum corneum (the primary barrier location), and a slowed metabolism. These changes result in increased permeability and susceptibility to environmental irritants. Inflammatory skin diseases can disrupt both the "inside-outside" and "out-side-inside" skin barriers regardless of age.

The following outcome parameters were included in the literature-based review to evaluate improvements in one or more determinants of skin health:

- Skin hydration;
- Transepidermal water loss (TEWL);
- Skin elasticity/firmness;
- Wrinkle depth/wrinkle reduction;
- Collagen synthesis/collagen content;
- Skin roughness/surface smoothness;
- Skin density/dermal thickness;
- Skin appearance/subjective skin quality;
- Reduction in UVB-induced damage/photoprotection;
- Inflammatory markers/anti-inflammatory effects;
- Skin lipid composition/ceramide levels;
- Skin pigmentation/melanin content;
- Healing and regeneration from skin diseases;
- Oxidative stress markers;
- Sebum secretion/skin surface lipid levels.

Individual nutrition represents another crucial factor affecting skin health. Nutritional deficiencies, whether resulting from malnutrition or restrictive dietary practices, can manifest as visible skin conditions. Intervention studies suggest that supplementation with certain nutrients such as specific amino acids, carotenoids, flavonoids, and vitamins (particularly vitamins A, C, D, and E) can support skin health, enhance skin quality, and potentially delay skin aging.

To evaluate the efficacy of selected nutraceuticals in maintaining, protecting, and promoting skin health, we have compiled and assessed relevant studies according to their evidence levels.

2. Materials and Methods

This overview examines selected common nutrients that are marketed either as nutraceuticals or as components of nutraceuticals, claiming positive effects on skin health. The analysis primarily focuses on products available in the German market as of September 2024, though many of these products are distributed internationally.

The examined nutraceuticals and nutrients were categorized into three groups: 1. Ingredients with proven in vivo efficacy according to Evidence Level I, 2. Ingredients with less well-established efficacy according to Evidence Level II, and 3. Ingredients with insufficiently documented effects corresponding to Evidence Level III. The results of this categorisation were summarised as tables, along with relevant study references and resulting evidence levels. When clear categorization proved challenging, decisions were based on both the quantity and quality of available review literature.

While this review encompasses literature through December 2024 and aims to include the majority of commercially available and scientifically documented substances, it does not claim to be exhaustive. Due to the continually increasing variety of nutraceuticals, the growing number of clinical studies, and new scientific insights into mechanisms of action, the evaluation of the evidence can only represent a snapshot in time. Consequently, the assessment of the evidence and the number of substances with established efficacy may change over time.

2.1. Search Strategy and Criteria for the Assessment of Nutraceuticals Affecting Skin Health

This review article classifies nutraceuticals according to their beneficial effects on skin health, with classifications guided by the quality of empirically gathered and assessed scientific evidence. Scientific validation of claimed benefits remains the critical factor in assessment, as emphasized by Kalra EK (2003) [34]: "Nutraceuticals still need support of extensive scientific study to prove their effects with reduced side effects". The European Nutraceuticals Association (ENA) also bases its decisions on the level of scientific evidence for the nutraceuticals it presents (Table 1).

The assessment of evidence involved comprehensive literature research through PubMed (National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, USA) and Google Scholar (Google LLC, Mountain View, CA, USA) databases (through December 2024), encompassing preclinical and clinical studies, all types of reviews, and meta-analyses. Only studies providing a statement on the efficacy of the respective nutraceutical were included in the analysis. The availability of high-quality positive clinical studies and reviews was considered the key criterion for a positive evaluation. In addition to the number of available studies, the quality of the studies was primarily decisive for the classification, in the following ascending order: Reviews → Meta-analyses → Preclinical studies → Randomized controlled trials (RCT) → Placebo-controlled double-blind trials (PCDB). Nutraceutical dosage was largely disregarded due to inconsistent or missing dosage information across the reviewed literature. The evaluation of evidence is based on the finding that, where assessable, the dosages used in the cited studies generally align with the recommended intake ranges for the respective products despite some degree of variation.

2.2. Classification of Evidence

The most commonly used classification of evidence follows the recommendations of the Agency for Healthcare Research and Quality (AHRQ), which has gained worldwide recognition and has been the basis for other guidelines (e.g., S3 guideline for the diagnosis and therapy of bipolar disorders, 2012) and is partially modified and utilized by the Cochrane Collaboration (CC) and the German Cochrane Center [35,36]. Another example of a frequently employed classification of evidence is the international classification by

CEBM, which is somewhat more detailed but does not differ significantly in its fundamental classification from the AHRQ classification [37].

However, the strict classification according to AHRQ did not appear sufficiently practicable for evaluating nutraceuticals in the context of this review. Since the evaluated substances and products are not pharmaceuticals or medical devices but solely OTC products (nutraceuticals) with "cosmetic" effects, the assessment was simplified (Table 2) in accordance with the guideline "Dermocosmetics against Skin Aging" of the German Society for Dermopharmacy (GD) [38].

Table 2. Simplified Classification of Evidence.

Level I	Active ingredients with proven efficacy in vivo
Level Ia	Efficacy proven in placebo-controlled double-blind studies (PCDB studies)
Level Ib	Efficacy proven in other studies conducted with objectifiable methods (RCT or similar, no PCDB studies)
Level II	Active ingredients with proven efficacy in vitro
Level III	Other advertised active ingredients

Tables 3–5 provide an assessment of the evidence for all considered substances, as well as an overview of the available literature supporting the classifications. Furthermore, the tables indicate which substances are associated with health claims related to the skin. The evaluation of whether the effect of a substance is sufficiently substantiated is based on the following quality and quantity of the existing study literature:

Table 3. Categorization of nutraceuticals with supporting references: GROUP 1—ingredients with proven efficacy (clinical studies).

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Vitamins	Vitamin A HC	[1,10,13,16, 38–46]	[47,48]		[49,50]	[51]		Ia [1]	see β-carotene
	Biotin HC (Vitamin B7 or Vitamin H)	[13,38,40, 43,52–55]	[56]	[57]		[58]		Ia [2]	EFSA Health Claims, numerous reviews, one PCDB in combination, objectively measurable animal studies, (older) human studies, and studies on hair effects. Higher dosages: Medical product or drug
	Vitamin C HC	[1,3,4,7,8, 10,13,14,16, 32,38,40,43, 46,59–61]	[62]	[63,64]	[65]	[66–68]		Ia	Few substance-related PCDB, but undeniable skin effects. EFSA Health Claim, efficacy enhancement in combination with vitamin E.
	Vitamin E	[3,4,8,10, 13,14,16,38, 40,43,46,58, 59,69,70]	[71]	[63]		[67,68]	*Many topical studies*	Ib [2]	PCDB evidence of effectiveness only demonstrated in combination with vitamin C but supported by many other objectively measurable data. Studies required to determine the dose needed for maximum skin improvement.

Table 3. *Cont.*

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Fatty acids, Lipids	Omega-3 fatty acids (PUFA)	[1–4,7,13,16,43,72,73]	[74–77]	[63,78–81]	[82]	[83]		Ia	Numerous studies on various omega-3 fatty acids, often not involving the same substance but rather different PUFAs or fish or evening primrose oil.
	Ceramides	[4,10,12,84–86]	[87]	[88,89]	[90]	[91,92]		Ia	Several PCDB, preclinical investigations, and coherent reviews.
Collagen Peptides	Collagen peptides from cattle or pigs	[2,4,8,10,12,16,40,93–105]	[106–117]	[118–128]	[129–138]	[139–147]	[148]	Ia [1]	A large number of studies and meta-analyses, numerous double-blind RCTs, various collagen peptides (from pigs or cattle, e.g., Verisol®, Peptan®) with well-documented, product-specific PCDB, some combined with other nutrients (e.g., ELASTEN®). Verisol is also known as a component of various combination products.
	Marine/fish collagen peptides	[149–152]	[153]		[154–157]	[158]		Ia	(Marine) collagen peptides from fish, many studies, including substance-related PCDB.
	Chicken collagen peptides	[159]	[108,160,161]			[162,163]	[164,165]	Ia [2]	Not yet as well documented as other collagen peptides, but two PCDB with extracts and preclinical studies. Additional PCDB needed for effects on joints.
	Collagen-like peptides from non-animal sources				[166]			Ia	(Few) data available, one PCDB.
Carotenoids	ß-carotene	[3,4,7,10,12,14,16,167–169]		[170–172]	[173]	[174]		Ia	Precursor for vitamin A, for which there are undeniable effects and an EFSA Health Claim. PCDB available. Further studies required to determine dosing and possible health risks; increased risk of lung cancer is discussed.
	Lutein, zeaxanthin, astaxanthin	[3,4,8,13,175–178]		[179]	[180–183]	[184]		Ia	Clinical evidence of skin improvement, particularly for astaxanthin (PCDB), meta-analysis.
	Lycopene	[2,3,16]		[185]	[183]	[174]		Ia	One substance-related PCDB, otherwise unconvincing studies; studies needed to determine the optimal dose.

Table 3. *Cont.*

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Plant and animal substances/extracts	Polyphenols: Pinus extract (maritime pine bark extract), flavonoids, resveratrol	[7,10,12, 186–194]	[195,196]	[197–200]		[158,201–203]		Ia [2]	Studies partially with topical application or combination products, but alongside one PCDB in combination, many other objectively measurable studies. Bioavailability in humans remains an unresolved issue.
	Aloe vera gel	[2,3,12,204, 205]	[206–209]	[210]	[211,212]	[213]		Ia	Substance-related PCDB. Studies required to determine the optimal daily dose and possible health risks; studies also show effects with topical application of the extract.
	Sea buckthorn oil	[214–216]	[217]	[218, 219]	[220]			Ib	Numerous indications, some studies, currently one RCT evidence.
	Other extracts: Poly-podium leucotomos, pomegranate, bilberry extract, liquorice root extract	[221–225]			[226–231]	[232,233]		Ia	Substance-related PCDB.
	Hyaluronic acid	[12,214, 234]	[235]	[236]	[237–240]	[241]		Ia [1]	Several PCDB and a meta-analysis, but some weak effects and critical assessments. Extensive evidence in the literature.

[HC] EFSA Health Claim related to the skin is available; * Based on the classification scheme in Table 2; [1] Already evaluated as a dermocosmetic by the Society for Dermopharmacy (GD); [2] RCT not substance-related, in another area of application or in combination.

Ingredients with clinically proven effects (Group 1): This category encompasses all ingredients of the selected nutraceuticals whose efficacy has been demonstrated through in vivo placebo-controlled double-blind studies (PCDB, Ia) or other randomized controlled studies (RCT, Ib) using objective methods (Table 3). A positive efficacy claim requires either a substance-specific study with positive outcomes or an RCT in a related application area or in combination with other substances, supported by comprehensive clinical data and efficacy indicators.

Ingredients with less well-documented efficacy (Group 2): This category comprises nutraceuticals or ingredients studied only in lower-significance trials (lacking RCT/PCDB methodology), with limited research data, or without substance-specific or product-specific studies. It also includes ingredients whose efficacy has been demonstrated only in vitro or in combination with other substances (Table 4).

Ingredients with insufficiently documented effects (Group 3): This category encompasses all other nutraceuticals whose efficacy has only been described or postulated in reviews or other publications (Table 5).

Table 4. Categorization of nutraceuticals with supporting references: GROUP 2—ingredients with less well-documented efficacy.

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Minerals/trace elements	Zinc [HC]	[3,4,55,242,243]	[244]	[245]				II	Undisputed skin effects, EFSA Health Claim. But RCTs and studies to determine the dose required for maximum skin improvement are lacking.
	Manganese [HC]	[246,247]				[248]		II [2]	One RCT with a manganese-containing bitter melon extract shows strong photoprotective effects. EFSA Health Claim, but few literature data.
Amino acids	L-arginine, L-glutamine, L-leucine, etc.		[249]	[250]	[251]		[252]		Importance for the skin is undisputed, but no RCT or no substance-related clinical studies and only a few published data.
Secondary natural products	Polyphenols: Catechins from green tea extract, grape seed/skin extract	[7,8,10,12,14]				[253–257]	[258]	II [1]	No significant results with catechins from green tea (GTC), probably due to underdosing of the GTC; Pinus extract, flavanol-rich cocoa: see herbal and animal substances/extracts. Grape extracts: studies currently only in combination or topical.
Plant Extracts	Citrus/ rosemary extracts	[259]		[260, 261]				II	No RCT, or clinical studies only in combination and without placebo; additional studies required to verify the previous results.
	Acerola extract	[262]	[263]	[264]				II	No RCT so far, positive effects rather in combination with other substances. Advantageous: High endogenous vitamin C content.

Table 4. *Cont.*

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Probiotics and prebiotics	Probiotics (Lactobacillus, Bifidobacterium)	[2,7,8,12,15,265–270]	[271,272]	[272]				II	Many studies in children and/or with topical application; beneficial effects for the skin despite divergent study quality and data often described, but only one RCT.
	Galacto-oligosaccharides	[2,7,273]		[274]		[275,276]		II [2]	The available studies (in combination with bifidobacteria) suggest a significant improvement in skin properties (hydration and skin barrier function). Few literature references.
Other	Coenzym Q10	[3,4,7,8]	[277]	[278]	[279]			II	Undisputed skin effects, EFSA Health Claim. But RCTs and studies to determine the dose required for maximum skin improvement are lacking.

[HC] EFSA Health Claim related to the skin is available; * Based on the classification scheme in Table 2; [1] Already evaluated as a dermocosmetic by the Society for Dermopharmacy (GD); [2] RCT not substance-related, in another area of application or in combination.

Table 5. Categorization of nutraceuticals with supporting references: GROUP 3—ingredients with insufficiently documented effects.

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Vitamins	Vitamins B1, B2 [HC], B3 [HC], B5, B6	[1,10,280–283]		[284]				III	No conclusive clinical evidence so far, one RCT without significant results. EFSA Health Claims for B2 and B3.
	Vitamin D	[285–288]		[289]				III	Few, mostly very old or unsuitable studies with limited data and findings

Table 5. *Cont.*

	Nutraceutical/ Ingredient	Reviews	Pre-Clinical Data	Clinical Data	RCT Substance-Related	RCT in Combination	Other	Evidence *	Comments
Minerals/trace elements	Copper [HC]	[3,290–294]						III	Insufficient clinical studies. EFSA Health Claim.
	Selenium [HC]	[3,4,295]	[296]					III	RCTs and studies to determine the necessary dose are lacking, transition metal, higher doses are harmful (oxidative stress), EFSA Health Claims for connective tissue, skin and hair pigmentation.
Sec. natural products	Curcumin	[12,13,297–299]						III	Reviews, but no studies, EFSA Health Claims on hair and nails
Plant and animal substances	Phytosterols (except Aloe sterols)	[4,300–302]						III	No suitable studies to prove skin effects
	Polysaccharides	[4,303–305]						III	No study so far to prove positive skin effects with oral application
	Serenoa repens	[3,306]		[307]				III	Only studies with multi-combination preparations; conclusions on individual substances problematic.
Pre-biotics	Other prebiotics	[2,15,303–305]						III	No sufficient evidence so far; existing studies with focus on hair loss
Other	N-acetylcysteine)	[3]	[308]	[250]	[309]		[310]	III	No scientific evidence/studies

[HC] EFSA Health Claim related to the skin is available; * Based on the classification scheme in Table 2.

3. Results

3.1. Group 1: Active Ingredients with Clinically Proven Efficacy

3.1.1. Vitamins

Vitamin A

Refer to carotenoids: β-carotene, lutein, zeaxanthin, astaxanthin, lycopene.

Biotin (Vitamin B7 or Vitamin H)

Biotin supplements are used to maintain healthy skin and mucous membranes. Biotin deficiency can manifest in various symptoms across body systems. These include neurological symptoms such as depression, drowsiness, and hallucinations; sensory disturbances including muscle pain, hypersensitivity, and localized dysesthesia; digestive issues like loss of appetite and nausea; as well as dermatological changes including hair loss, changes

in hair color, brittle nails, and skin alterations. The German Society for Nutrition (DGE) recommends a daily biotin intake of 5–60 µg [39]. Biotin is generally regarded as safe and well-tolerated. Being water-soluble, excess biotin is eliminated through the kidneys, making overdose virtually impossible.

Substance and mechanism of action: Biotin (Vitamin B7, Vitamin H), belonging to the B-complex group, serves as a vital component in the fundamental metabolic regulation of carbohydrates, proteins, and fats. As a prosthetic group for enzymes, it plays an important role in the epigenetic regulation of gene function.

Evidence base: The beneficial effects of biotin on skin health have been thoroughly documented in comprehensive reviews and demonstrated in preclinical studies. Most human studies are dated and mainly address the role of biotin in maintaining healthy hair and nails. Two significant EFSA Health Claims support its efficacy, stating that "Biotin contributes to the maintenance of normal skin" and "Biotin contributes to the maintenance of normal hair". Numerous reviews, preclinical studies, and one PCDB study (in combination with silicon) have been found regarding biotin as a dietary supplement. Moreover, biotin supplements at higher dosages (5 mg and above) are approved as drugs for the treatment and prevention of biotin deficiency, which has been shown to cause skin problems. Considering all these aspects, the efficacy of biotin for maintaining skin health and its appendages can be regarded as established.

Vitamin C

Vitamin C is used in numerous nutraceuticals either as a sole ingredient or in various combinations with other vitamins, nutrients, or minerals. It is characterized by significant antioxidant effects and plays a crucial role in maintaining the skin's collagen network. Vitamin C has low toxicity and, even at higher doses (>1 g/day), causes only minimal side effects (e.g., diarrhea, gastrointestinal discomfort). The DGE recommends a normal daily intake of 20–125 mg [39].

Substance and mechanism of action: Vitamin C (L-ascorbic acid) is a natural, water-soluble vitamin found in high concentrations in fruits and tea. Unlike most animals, humans must obtain it through diet as they cannot synthesize it. It functions as a free radical scavenger with antioxidant properties, thereby reducing UVB-induced oxidative stress. Among others, the vitamin is essential for connective tissue formation, participates in the hydroxylation of essential amino acids for collagen synthesis, and neutralizes free radicals in the body. Its biologically active form, L-ascorbic acid, serves as a co-factor in collagen synthesis and, according to the literature, promotes both intra- and extracellular collagen formation.

Evidence base: Vitamin C stands as one of the most extensively studied anti-aging agents, with undisputed efficacy demonstrated through multiple studies, including PCDB. The EFSA has acknowledged its benefits with a specific health claim related to skin health: "Vitamin C contributes to normal collagen formation for the normal function of the skin". Research has particularly shown that its effects are significantly enhanced when combined with vitamin E.

Vitamin E

Vitamin E encompasses a group of tocopherols, tocotrienols, and tocosterols. Located in the lipophilic portion of cell membranes, it provides protection against UV-induced lipid peroxidation. It has been demonstrated that after oral intake, vitamin E is transported through the sebaceous glands and mechanically distributed across the skin surface, allowing it to exert antioxidant effects in the outermost cell layers.

Among the eight naturally occurring compounds categorized as vitamin E, α-tocopherol is most significant for humans, representing nearly 90% of vitamin E in the body.

Vitamin E supplements are commonly available for addressing deficiencies and frequently appear in other nutraceutical formulations. The DGE recommends a daily intake ranging from 11 to 15 mg [3,39]. While well-tolerated at recommended dosages, extended use of high doses may occasionally result in gastrointestinal issues.

Substance and mechanism of action: Vitamin E (tocopherol), a fat-soluble vitamin found naturally in oils, cereal germ, and nuts, is present in all animal cell membranes. Vitamin E has antioxidant, lipid-lowering, and antithrombotic properties. It exhibits antioxidant, lipid-lowering, and antithrombotic properties, functioning as a free radical scavenger to protect cell membranes, lipids, DNA, and lipoproteins from oxidative damage.

Evidence base: The protective effect of vitamin E on skin health against UVB damage has been extensively documented in numerous reviews and demonstrated through various studies, primarily using topical applications but sometimes also including oral administration. PCDB studies, however, have typically been conducted in combination with vitamin C. To date, there is no specific health claim for vitamin E regarding its effect on the skin. Nevertheless, based on the totality of available data and its classification as a dermocosmetic, its skin-related efficacy as a nutraceutical is considered established and classified with evidence level Ib (Table 3).

3.1.2. Fatty Acids, Lipids

Omega-3 Fatty Acids (PUFA)

Omega-3 fatty acids are essential fatty acids that the body cannot synthesize independently and must be obtained through dietary sources. For healthy individuals, normal dietary intake typically meets daily requirements. According to DGE recommendations, omega-3 fatty acid α-linolenic acid should constitute 0.5% of total daily energy intake, which corresponds to approximately 80 g of total fat for men with an energy reference value of 9.8 megajoules (2300 kcal; PAL 1.4) [39]. Omega-3 fatty acids occur naturally in algae, plants, and fish, primarily as fatty acid esters or triglycerides. While plant sources predominantly contain α-linolenic acid, fatty fish such as eel, carp, and sardines, along with algae, are rich in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Users should be aware of potential side effects, including digestive disturbances, reduced platelet aggregation, extended bleeding time, and mild transaminase elevations. According to recent assessments by the Consumer Advice Centre of North Rhine-Westphalia regarding cardiovascular diseases and diabetes, healthy individuals do not require additional omega-3 fatty acid supplementation. Furthermore, they warn that high-dose omega-3 products may pose significant health risks and could potentially interact with medications.

Substance and mechanism of action: Omega-3 fatty acids are long-chain polyunsaturated fatty acids (PUFAs) essential for human nutrition. Common nutraceutical ingredients include docosahexaenoic acid, eicosapentaenoic acid, or linoleic acid. When derived from plants, these fatty acids serve multiple functions: they provide energy through metabolism, become incorporated into cell membranes, and act as precursors for series-3 prostaglandins. Their beneficial properties include triglyceride reduction, antiarrhythmic effects, anti-inflammatory action, blood pressure reduction, and endothelial protection. The scientific literature also documents their photoprotective properties, particularly in increasing UV-induced erythema threshold.

Evidence base: The positive influence of omega-3 fatty acids on skin health is well-supported across numerous reviews. While many studies exist examining various omega-3 fatty acids, they frequently investigate combinations rather than individual substances. One notable PCDB study utilized evening primrose oil, which primarily contains omega-6 fatty acids and, like fish oil, is attributed with positive effects on the skin. These studies typically focus on UV-damaged skin or individuals with skin conditions such as psoriasis.

In cardiovascular diseases, on the other hand, according to a recent meta-analysis no positive effect of dietary supplementation with fish oil capsules could be demonstrated (Table 3).

Ceramides

Ceramides (sphingolipids) are essential components of lipid bilayers, acting as a permeability barrier in the stratum corneum of the skin. While present in nearly all organs and cell membranes, they are particularly concentrated in the skin and brain. Topically applied ceramides have been used for several years in medical skin care and for the prevention of skin diseases such as atopic dermatitis and psoriasis. Their oral application as nutraceuticals is relatively new but is now being offered for the treatment of dry skin and aging skin. While no general dosage recommendations exist, common supplements provide 350 mg for once-daily intake, with no reported side effects to date.

Substance and mechanism of action: Ceramides, belonging to the sphingolipid family, are predominantly found in the skin, where they form specific structures, and also occur in the brain and other organs. Through coupling with various saccharides or phosphorylcholine, they serve as basic modules of glycosphingolipids and sphingomyelin. As central molecules in sphingolipid metabolism, signaling ceramides influence various processes, including cell growth inhibition, apoptosis induction, cell differentiation promotion, and inflammatory reactions. Structural ceramides work together with cholesterol and free fatty acids to form double lipid layers in the stratum corneum between corneocytes due to their amphiphilic structure. This creates a natural barrier that prevents both moisture loss and foreign substance penetration. Any disruption of the balance of these substances may result in dry skin or pathological skin conditions [84].

Evidence base: The efficacy of oral ceramides for skin health and especially the epidermal barrier function has been investigated through numerous preclinical and clinical studies. While in vitro research has demonstrated anti-inflammatory effects, PCDB studies have shown improvements in skin hydration, TEWL, age-related skin symptoms, and atopic dermatitis. In particular, studies showing positive effects on skin hydration and TEWL provide strong evidence for their role in supporting skin health.

3.1.3. Collagen

Collagen Peptides

Collagen is the most important extracellular structural protein in ligaments, tendons, and cartilage, as well as in muscle fascia. In young and healthy skin, it comprises nearly 80% of the composition, forming a vital scaffold in the dermis, the middle layer of the skin, that provides strength and structure, thereby significantly influencing skin appearance. Nutraceutical formulations typically use enzymatically hydrolyzed collagen peptides, whose characteristics vary considerably depending on the hydrolysis parameters and collagen source [106,107]. These variations can be unequivocally determined using nanoLC-MS/MS measurements. The collagen peptides used in nutraceuticals are primarily sourced from bovine or porcine sources or are derived from chickens or marine animals (e.g., fish, jellyfish, or sponges) [108]. While no general dosage recommendations exist for collagen peptide nutraceuticals, studies indicate an optimal intake of 2.5 g per day, with higher doses of 5 g showing no statistically significant additional benefits. Specific side effects related to the substance are hardly known. Allergic reactions to collagen hydrolysates have not been documented so far, likely due to collagen being a highly conserved structural protein with almost 100% similarity across organisms from jellyfish to humans [109]. A 2019 review by Choi et al. confirmed that collagen supplementation is generally safe with no reported adverse effects [93].

Due to the heterogeneity of collagen peptides, consumers should prioritize products for which product-specific, ideally placebo-controlled studies have been conducted, demonstrating a specific benefit of the product itself for skin physiology.

Substance and mechanism of action: Collagen peptides are enzymatically obtained through hydrolysis of native collagen. Following oral intake, they undergo further enzymatic breakdown in the gastrointestinal tract through existing enzymes (e.g., pepsin, pancreatin) [110,153]. While natural digestion results in molecular weight-dependent fragmentation, remarkably, up to 16% of hydrolyzed collagen with a molecular weight of 2.9 kDa is absorbed undigested through the intestinal wall [111]. Industrial enzymatic proteolysis typically yields fragments of 16–26 amino acids in length. However, absorption is highest only up to tetrapeptides, indicating that body-specific proteases must assist in the breakdown of collagen fragments. The absorption of collagen protein fragments likely involves active transport. Overall, the exact transport pathway of collagen peptides across the intestinal wall has not yet been conclusively and in detail clarified [115,129].

The structural collagen fibers are formed as a triple helix from individual procollagen strands, which are typically sufficiently available between the cells of the deeper skin layers [94,95]. When transported via the bloodstream to these deeper skin layers, collagen peptides may stimulate fibroblasts to produce body-specific components of the extracellular matrix, including collagen, hyaluronic acid, and elastin. These processes result in structural changes within the dermis, leading to improved skin physiology and reduced wrinkle formation in aging skin [113,130,131]. A particularly notable finding is that collagen peptides closely matching human collagen, designated as [HC] peptides, demonstrate especially high effectiveness [106,141,142]. The mechanism of action has been explored in several studies but is only partially understood so far [112,117,129,132,133].

Evidence base and source-dependent differences:

Bovine and porcine peptides: Numerous clinical studies worldwide have consistently demonstrated the positive effects of nutraceuticals containing collagen peptides on skin elasticity, hydration, density, and roughness, thereby improving overall skin health. Research has established now that collagen peptide supplementation effectively counteracts UV-induced skin damage [105]. Most of these studies have focused on collagen peptides sourced from bovine or porcine origins (Table 3). EU regulations require BOV (Bovine Spongiform Encephalopathy, BSE) risk controls and traceable sourcing; porcine collagen is non-halal, and bovine is only halal if certified. Use in cosmetics may be restricted in halal markets or countries with strict animal-origin regulations.

Marine collagen peptides are broadly accepted and highly bioavailable, with favorable regulatory status and halal suitability. Human PCDB studies consistently confirm benefits for skin elasticity and hydration.

Chicken collagen peptides are clinically supported for dermal effects (PCDB studies with extracts are available) but are less common in cosmetics. Regulatory acceptance depends on hygienic processing; halal status requires certified sourcing.

Plant-based alternatives to collagen peptides primarily include so-called collagen boosters, which are designed to stimulate the body's own collagen production through certain nutrients or plant extracts, as well as synthetically produced collagen-mimetic peptides obtained through microbial fermentation. These alternatives do not contain real collagen. Evidence of their effectiveness for the skin is already available—a PCDB study has been identified—but is still limited and less conclusive compared to the data available for animal-derived collagen peptides.

Additionally, numerous positive study results exist for nutraceuticals that combine collagen peptides with other substances such as vitamins, minerals, plant extracts, and hyaluronic acid. The studies suggest that these active ingredients work synergistically,

enhancing the overall effect. For one combination product, scanning electron microscopy, combined with the suction blister method for the first time, revealed visible improvements in collagen structure after several weeks of application [123] (Table 6).

Table 6. Combinations of Ingredients in dietary supplements with supporting references.

Nutraceutical/ Ingredient	Examples	Review	Product-Related Proof		Evidence *	Comments
			Clinical	RCT		
Bovine or porcine collagen peptides, vitamins, and others	ELASTEN®	[12,93,99–101,104]	[118–120,122,123]	[141,142]	Ia	Very well-documented, product-specific RCTs, meta-analyses, also visualization of the collagen network before/after using scanning electron microscopy
	Doppelherz® system KOLLAGEN BEAUTY			[144]	Ia	One product-specific PCDB study
	Pure Gold Collagen®	[40,100]	[124]	[139,140]	Ia	Product-specific studies, including 1 PCDB study
Fish collagen, Pinus, vitamins, carotenoids and others	Fish-derived collagen peptide (FUJIFILM)	[12,100]		[145]	Ia	One product-specific PCDB study
	Evelle®			[201,202]	Ia	Several product-specific PCDB studies
	Vinh Wellness Collagen			[154]	Ia	One product-specific PCDB
	Cellergen® (Switzerland)			[158]	Ib	One single-blind RCT
Proteins, polysaccharides, vitamins, and others	Imedeen®	[254,311]	[312]	[313–316]	Ia	Well-documented, several product-specific PCDB studies
	Vivida®			[313]		One product-specific study
Hyaluronic acid, plant concentrates, biotin, vitamins, and others	Regulat-pro® Hyaluron		[236]	[239]	Ia	Several studies, including 1 PCDB study
Amino acids, vitamins, minerals	Fermented papaya fruit extract (*Carica papaya* L.)			[64]	Ib	Product-specific double-blind study vs. active control (antioxidants), but not against placebo
Citrus extract, rosemary extract	Nutroxsun®			[260]	Ib	One RCT on UVA and UVB protection
Licorice root extract, grape seed extract, grape pomace extract, vitamin C	Belight2®, SkinMedica®			[232,233]	Ib	Two product-specific RCTs on skin lightening
Various vitamins, zinc, niacin, biotin	Vitamin Haut&Haare (and many more in varying compositions)	[55]			III	No significant studies available to date

* Based on the classification scheme in Table 2.

3.1.4. Secondary Metabolites

Carotenoids: B-Carotene, Lutein, Zeaxanthin, Astaxanthin, Lycopene

Carotenoids represent a group of secondary plant metabolites that, while not essential for humans, are considered beneficial to health. They naturally occur in bacteria, plants (particularly fruits and vegetables), and certain fungi. Currently, no established daily dosage recommendations exist for carotenoids, as appropriate dosing depends on various factors, including the specific indication. While therapeutic doses may reach up to 180 mg/day without causing adverse effects or hypervitaminosis A, the EFSA considers a maintenance dose of β-carotene of up to 15 mg/day to be safe.

Of the approximately 50 known carotenoids, a subset exhibits provitamin A activity, meaning they can be converted into vitamin A in the body, with β-carotene having the highest activity. Consequently, β-carotene is the most important precursor of vitamin A in foods. Vitamin A is used therapeutically to address deficiency, inadequate intake, and skin disorders. Manufacturers claim that nutraceuticals containing vitamin A promote healthier skin, strengthen the immune system, and improve vision. According to EFSA, the following health claim is permitted: "Vitamin A contributes to the maintenance of normal skin". However, evidence of efficacy regarding skin health has primarily been demonstrated for topical formulations and for the precursor β-carotene. Vitamin A supplements, taken at the dosage recommended by the DGE [39] (approximately 1 mg/day), are well-tolerated but must not be taken in excess, as higher doses can be teratogenic.

Substance and mechanism of action: Carotenoids form an extensive class comprising over 600 fat-soluble plant pigments, all sharing a tetraterpenoid scaffold. Lycopene, the central compound in carotenoid biosynthesis, is believed to reduce collagen degradation in the skin and improve skin roughness. Through processes of cyclization, hydroxylation, and other functionalizations, lycopene serves as a precursor for all other carotenoids. β-carotene, the most well-known carotenoid, is used in the prevention and treatment of vitamin A deficiency, as a dietary supplement, in the management of erythropoietic protoporphyria, for pigment disorders, and in preventing "sun allergy". Other carotenoids include lutein and zeaxanthin, regarded as nutrients beneficial not only for the eyes (e.g., in age-related macular degeneration) but also for the skin. They are natural components of the dermis and epidermis. Particularly, lutein is believed to protect the skin from harmful light exposure, enhance skin moisture, improve elasticity, and support the dermis and epidermis against oxidative stress.

Vitamin A (retinol) is a fat-soluble vitamin with numerous physiological properties, found only in animal products and occurring primarily in ester form in the subcutaneous layer. Retinol is considered to act both as a prohormone and a prehormone. It is present in plant foods as carotenoid precursor. Its biologically active form is all-trans-retinoic acid (tretinoin, Retin A, vitamin A acid). Since all-trans-retinoic acid is a prescription medication not permitted in nutraceuticals, it will not be discussed in detail here. In non-pharmaceutical products, only less potent forms of vitamin A may be used, such as free retinol, retinyl palmitate, retinyl acetate, and retinaldehyde. These compounds are converted into the biologically active all-trans-retinoic acid in the skin.

To meet vitamin A requirements, humans can utilize not only retinol and retinyl esters but also provitamin A (β-carotene). The activity of dietary carotenoids as provitamin A is expressed in terms of retinol equivalents, where approximately 6 mg of β-carotene and 12 mg of other provitamin A carotenoids correspond to 1 mg of retinol equivalent.

In the human body, six carotenoids play a vital role: β-carotene, α-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin. Most of these function as antioxidants. Carotenoids, particularly lycopene (e.g., in tomatoes), are regarded as efficient scavengers of the highly reactive singlet oxygen.

Vitamin A is one of the skin's natural antioxidants. In a study involving cultured human skin fibroblasts, it was demonstrated that retinol induces the expression of the elastin gene and the formation of elastic fibers. This effect is based on the activation of nuclear receptors that bind to DNA and trigger transcription and gene expression of specific genes. RAR and RXR receptors are the two primary receptor families activated by vitamin A. They are transcription factors that activate the expression of specific genes.

Evidence base: β-Carotene is a precursor of vitamin A, which has undeniable effects on skin health. The EFSA has approved the health claim: "Vitamin A contributes to the maintenance of normal skin". Positive influences on relevant skin parameters or UV protection functions have been demonstrated for several carotenoids in PCDB studies, including β-carotene, zeaxanthin, and astaxanthin. Regarding lycopene, most studies are less convincing. Nevertheless, this substance can also be classified as effective, not least because of numerous review mentions and a PCDB study (Table 3).

Topical application of all-trans-retinoic acid has been shown to improve the overall appearance of the skin, fine and moderate wrinkles, skin roughness, pigmentation, and skin elasticity. Although direct studies on vitamin A supplements for skin health are lacking, research has shown that β-carotene, as a precursor of the vitamin, can provide UV protection and that nutraceuticals can substitute for vitamin A in cases of deficiency (Table 3).

Other carotenoids, such as astaxanthin, have also demonstrated positive effects on the skin, contributing to a favorable evidence assessment. While this evidence is promising, more research is needed to fully understand the effects of oral vitamin A and carotenoid supplements on skin health.

3.1.5. Plant and Animal Substances/Extracts

Polyphenols: Pine Extract (Maritime Pine Bark Extract), Flavonoids, Resveratrol

Pine extract, derived from the bark of the French maritime pine (Pinus pinaster subsp. atlantica), is available in standardized form, e.g., as Pycnogenol®. The extract contains polyphenols and is used in dietary supplements (100–500 mg/day) for photoprotection against UV-induced skin damage, as well as in cosmetics. Products containing pine extract are marketed for achieving significant improvements in skin hydration and elasticity. Side effects are rare, with mild digestive issues reported in 2.4% of study participants ("Pine Bark Extract Pycnogenol®—vitamine-ratgeber.com", available online: https://vitamine-ratgeber.com/weitere-vitalstoffe/pinienrindenextrakt-pycnogenol/ (accessed on 27 March 2025)).

Other notable polyphenols include catechins in green tea (see Section 3.2.3.), resveratrol (found in red grapes and wine and marketed as a dietary supplement due to its antioxidant properties), and flavonoids (present in cocoa).

Substance and mechanism of action: Maritime pine extract consists of 65–75% procyanidins, which are biopolymers composed of catechin and epicatechin units. These units are converted by the human gut microbiota into postbiotic active metabolites. The extract also contains antioxidant plant acids and bioflavonoids.

Green tea, an unfermented form of black tea, contains polyphenolic compounds such as epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG). Resveratrol belongs to the group of phytoalexins. The polyphenols found in cocoa are primarily flavonoids.

Polyphenols, which are also found in black tea, act as potent antioxidants by stimulating the synthesis of antioxidant enzymes and binding to free radicals. Additionally, polyphenol-rich extracts inhibit the onset and progression of chronic inflammatory diseases by significantly reducing the activity of NF-κB. They also decrease the release of

specific transcription factors, which leads to a reduction in the release of other inflammatory molecules, such as interleukins, prostaglandins, CRP, TNF-alpha, and COX.

Evidence base: Numerous clinical studies have investigated the effects of pine extract (e.g., Pycnogenol®) on skin health and appearance, although most of these studies used combination products or topical applications. Based on objective study results and a variety of supporting publications, the evidence for its effectiveness can be deemed sufficient.

In vitro, resveratrol has been shown to inhibit inflammatory cells and extend the lifespan of mice. Although clinical evidence for its influence on skin health currently exists only for combinations of resveratrol with other nutrients (e.g., pomegranate fruit extract), many other objective studies allow for a conclusion of effectiveness. A long-term study of the flavanols in concentrated cocoa demonstrated their positive effects on skin blood flow and skin quality (Table 3).

Aloe Vera Gel

The gel obtained from the inner leaf of the aloe vera plant is primarily known for topical use in skin care, as well as its application to wounds and sunburned skin. Less commonly recognized is its oral use as a nutraceutical for supporting skin health and pigmentation. Anthraquinone-free aloe gel is available as a novel dietary supplement and does not require medicinal approval. While general dosage recommendations are not yet established, commercially available gels or juices are typically recommended at a dose of 20–50 mL per day. Significant side effects have been reported only for anthraquinone-containing juices (see below) and topical preparations (burning sensation, allergic dermatitis, itching).

Substance and mechanism of action: Aloe vera gel is derived from the water-storing tissue of the leaves and contains a variety of active components, including polysaccharides, vitamins, minerals, essential oils, and phytosterols (such as cycloartenol and lophenol). Aloe leaves must always be peeled, as the unpeeled leaves contain anthraquinones, classified as "not safe" by the Federal Institute for Risk Assessment (BfR) and the EFSA due to severe side effects. Aloe vera gel and juice are attributed with antimicrobial, antioxidant, antiproliferative, anti-inflammatory, moisturizing, and anti-itch properties.

Evidence base: Based on the available in vitro and in vivo (PCDB) studies, the positive impact of aloe vera gel on skin health can now be regarded as established. However, further randomized controlled clinical trials are needed to provide more specific insights into the effectiveness and safety of the gel or juice (Table 3).

Sea Buckthorn Oil

Sea buckthorn berries are renowned for their high vitamin content, particularly in the treatment of cold illnesses and febrile infections. Sea buckthorn oil is used topically for skin care and is also claimed to support gut and heart health, as well as wound healing, when taken orally.

Substance and mechanism of action: Sea buckthorn oil, derived from the seeds, contains vitamin E, beta-carotene, and various omega-fatty acids, all of which have been shown to have positive effects on skin health (see above).

Evidence base: A PCDB study demonstrated positive skin effects from a mixture of sea buckthorn fruit and seed oil (Omegia® Softgel). Given the positive results from other studies and the supportive evidence for the individual components, the efficacy of sea buckthorn oil for skin health can now be considered well-established (Table 3).

Other Extracts: Polypodium leucotomos, pomegranate, blueberry extract, licorice root extract.

The fern Polypodium leucotomos, originally native to Central America, was used by the Maya as a "blood purification tea". It is now cultivated on plantations in various countries across Latin and South America. The fruit of the pomegranate (Punica granatum), widespread

in Asia and the Mediterranean, is utilized in various food applications. Extracts from both plants are commonly included in cosmetics due to their reputed skin care benefits.

Blueberry extracts are used for the symptomatic treatment of mild diarrhea, relief from a feeling of heaviness in the legs due to mild venous circulation disorders, and to support eye and heart health. While their use for skin health is primarily known as additives in cosmetics, some nutraceutical products also claim positive effects on the skin.

Licorice root extract, sweet and aromatic with a hint of licorice, is mainly known for treating inflammation, gastrointestinal complaints, and infections in the oral and throat areas. However, its use for skin improvement, particularly for skin lightening, is gaining increasing attention.

Substance and mechanism of action: The extract from Polypodium leucotomos contains various bioactive substances, including phenolic acids and flavonoids, which have antioxidant effects and contribute to protecting the skin from UV damage. Glycosylated flavonoids are thought to have anti-inflammatory properties and help neutralize free radicals. Triterpenes are known for their anti-inflammatory and antimicrobial properties. Polysaccharides (see below) are credited with supporting the immune system and exhibiting anti-inflammatory properties. Additionally, proteins and amino acids in the extract may help maintain skin structure and support regeneration.

Pomegranate extract also contains several skin-relevant substances, including polyphenols and flavonoids (mentioned previously), vitamin C, punicic acid, phytoestrogens, and phytosterols, all of which are believed to have skin-protective effects. Blueberry extracts contain similar substances, such as flavonoids, terpenoids, and anthocyanins. Licorice root extract also contains flavonoids and terpenoids, along with coumarin.

Evidence base: Positive effects of Polypodium leucotomos and Punica granatum on the skin have been described in several reviews. Clinical RCT evidence, including PCDB studies, supports these effects, leading to a positive evaluation of the evidence situation. Similar findings apply to blueberry extract, for which a recent PCDB study showed positive effects on skin aging and complexion. Several clinical studies on licorice root extract were identified, but mainly involving combination products (Table 3).

Hyaluronic Acid

Hyaluronic acid, found throughout the human body, is present in large amounts primarily in the skin, bones, intervertebral disks, joint fluid, and vitreous body of the eye. Its use in anti-aging cosmetics is based on the observation that the body's production of hyaluronic acid decreases with age. Consequently, hyaluronic acid has become a key ingredient in numerous dermocosmetics and is widely used for wrinkle filling. Recent studies have shown that the intake of nutraceuticals containing hyaluronic acid can improve skin moisture levels and elasticity, as well as reduce wrinkles. There have been no known side effects associated with the intake of hyaluronic acid (in capsule form) at the recommended dosages (100–200 mg per day).

Substance and mechanism of action: Hyaluronic acid is a long-chain, linear polysaccharide that serves as a key component of the extracellular matrix in the connective tissue of the skin. Due to its unique chemical properties, hyaluronic acid plays multiple mechanical roles in connective tissue. Its ability to bind large quantities of water relative to its mass ensures sufficient skin moisture, skin firmness, and resistance to pressure.

Evidence base: While efficacy has been well-demonstrated for topical application, especially for short- to medium-chain hyaluronic acid fragments in supporting skin health, recent studies have shown such effects with the oral intake of longer-chain hyaluronic acid molecules as well (Table 3). Despite some weak effects and critical evaluations, the efficacy can generally be regarded as established.

3.2. Group 2: Active Ingredients with Less Well-Documented Effectiveness

3.2.1. Minerals and Trace Elements

Zinc

Zinc is an essential trace element that cannot be synthesized by the body. Zinc deficiency, resulting from malnutrition or hereditary zinc deficiency syndromes, may manifest as impaired linear growth, skin eczema, diarrhea, and wound healing disorders.

Substance and mechanism of action: As a component of numerous enzymes and proteins, zinc plays a key role in numerous biochemical reactions in the body, including those related to skin health. It acts as an important cofactor for cellular activity and helps protect cells from lipid peroxidation, UV-induced cytotoxicity, and oxidative stress. In the skin, zinc is primarily found in the epidermis, where it is essential for epidermal proliferation and keratinocyte differentiation. Excessive zinc intake, particularly when copper intake is low, can impair copper absorption, potentially leading to anemia.

Evidence base: There is substantial evidence supporting the benefits of zinc for skin health, and the EFSA has published a health claim stating that "zinc contributes to the maintenance of normal skin, hair, and nails". However, RCTs specifically focused on skin health are still lacking. One earlier study found no skin-improving effects (Table 4).

Manganese

Manganese is a trace element important for bones, connective tissue, and metabolism. Symptoms of manganese deficiency (which is rare) may include an increased risk of infections, poor wound healing, dry skin, and graying hair. According to the DEG, children older than 7 years, adolescents, and adults require approximately 2 to 5 mg of manganese daily. Currently, there is no evidence suggesting that a manganese-rich diet, such as a plant-based one, is associated with adverse side effects. However, excessive manganese intake can lead to neurotoxic and motor disturbances.

Substance and mechanism of action: Manganese is an essential trace element that can be toxic at high doses and is a component of various enzymes. Intracellularly, manganese is mainly localized in the mitochondria, where it acts as an activator of specific enzyme systems. Manganese is also present in lysosomes and the nucleus. It acts as an activator for numerous enzymes involved in gluconeogenesis and collagen synthesis. In particular, it is important for antioxidant metabolism as a component of superoxide dismutase in the removal of oxygen radicals.

Evidence base: Despite numerous references in the literature, evidence for the role of manganese as a skin-affecting nutraceutical is limited. Regarding connective tissue, the EFSA has a health claim stating that "manganese contributes to normal connective tissue formation". In a PCDB study, a melon extract was used for supplementation instead of manganese supplementation. However, since the extract indirectly provided manganese through its manganese-dependent superoxide dismutase content, it is possible to infer—at least to some extent—the effect of manganese intake on skin health (Table 4). Nonetheless, as with zinc, the evidence remains insufficient.

3.2.2. Amino Acids

L-Arginine, L-Glutamine, L-Leucine, etc.

Amino acids are fundamental for human nutrition. A balanced diet typically ensures an adequate intake of essential amino acids through animal proteins or a well-combined mix of plant proteins. Cosmetics and nutraceuticals containing various essential and semi-essential amino acids are widely marketed in the beauty industry to maintain healthy, youthful-looking skin. Products featuring cysteine, arginine, creatine, glutamine, leucine, glycine, (hydroxy)proline, or lysine are common. The WHO recommends daily

intakes ranging from 4 mg/kg body weight (e.g., cysteine) to ≥30 mg/kg body weight (e.g., lysine, leucine). However, the dosages of commercially available products, particularly for individuals with low body weight, often exceed these recommendations.

Substance and mechanism of action: The essential amino acids for humans include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine and histidine are semi-essential, as they need to be consumed during specific life stages (growth, regeneration). Proteinogenic amino acids are the building blocks for body peptides and proteins, while non-proteinogenic amino acids serve as enzymes, hormones, or neurotransmitters. Over twenty proteinogenic amino acids are currently known, and as fundamental components of collagen peptides, they are indispensable nutrients for skin integrity.

Evidence base: Although the essential role of many amino acids in skin health is undisputed, there are only a few studies demonstrating the effects of individual amino acid supplementation on skin health, and substance-specific RCTs are still lacking (Table 4).

3.2.3. Secondary Natural Substances

Polyphenols: Catechins from Green Tea Extract, Grape Seed/Skin Extract

Polyphenols, including catechins found in green tea, are among the key constituents, along with caffeine. Grape seed extract is attributed with several health-promoting effects, including positive impacts on circulation, cardiovascular health, and wound healing. Similar benefits are associated with grape skin extract, which focuses on vascular health and protection against oxidative stress.

Substance and mechanism of action: The mechanisms of action of polyphenols have been briefly mentioned (see above).

Grape seed extract primarily contains phenolic compounds like catechins, proanthocyanidins, and flavonols, while grape skin extract mainly comprises polyphenols like oligomeric proanthocyanidin complexes (OPCs) and anthocyanins.

Evidence base: Animal studies and a few observational studies have shown that polyphenols from green tea significantly protect against UV-induced skin damage and immunosuppression following topical and oral administration. Despite one study with a negative result, they appear promising but need confirmation through clinical trials. No substance-specific RCTs for grape seed/skin extract have been found, and there is only limited evidence from combination products. Therefore, robust evidence for the efficacy of these polyphenols remains lacking (Table 4).

3.2.4. Plant and Animal Substances/Extracts

Citrus/Rosemary Extracts

Citrus and rosemary extracts are commonly used as food additives for preservation. As nutraceuticals, they are often combined with various other nutrients like vitamins or minerals. Pure extracts, such as blood orange extract, are also marketed for various therapeutic purposes. No side effects have been reported in connection with such extracts. The known interactions between grapefruit consumption and certain medications are attributed to the presence of furanocoumarins, which are not found in citrus extracts.

Substance and mechanism of action: Extracts from various citrus plants typically contain high levels of vitamin C, essential oils, flavonoids, and minerals. Rosemary extract mainly consists of essential oils (terpenes, carnosol, carnosic acid) and flavonoids. These extracts are considered relatively potent antioxidants, making them suitable for use in skin health disorders.

Evidence base: Evidence for the effectiveness of citrus and rosemary extracts is still insufficient. Although several studies exist regarding their impact on skin health, most

clinical trials, including PCDB studies, have been conducted with combinations of multiple substances or extracts, typically combining citrus extract with rosemary extract (Table 4).

Acerola Extract

Acerola is the drupe of a Malpighia species. While it resembles the native cherry in appearance, it is not related to it.

Substance and mechanism of action: Acerola is one of the richest natural sources of vitamin C. The fruit and its extract also contain provitamin A, vitamins B1, and niacin, as well as minerals like iron, phosphorus, and calcium. The effects of vitamins on the skin are described in Sections 3.1.1 and 3.3.1.

Evidence base: Currently, there are no PCDB studies available, and most research has investigated combinations with other substances. Due to the low level of evidence, a definitive demonstration of efficacy regarding skin health cannot yet be considered established (Table 4).

3.2.5. Probiotics and Prebiotics

Probiotics (Lactobacillus, Bifidobacterium)

Unlike probiotic foods containing live microorganisms, the efficacy of probiotic nutraceuticals—such as those used to improve atopic dermatitis—has been scientifically validated to some extent. For optimal effectiveness, a probiotic nutraceutical should contain at least 5 to 10 billion colony-forming units per dose. In general, probiotics are well tolerated. Possible side effects include bloating, abdominal pain, and diarrhea.

Substance and mechanism of action: Probiotic nutraceuticals typically contain several million to billions of viable bacteria in powder form, predominantly Bifidobacteria and Lactobacilli. Probiotics can partially stimulate or modulate the mucosal immune system. Through various mechanisms, they stimulate the production of secretory immunoglobulins located in the intestinal lumen or on mucosal surfaces. Additionally, probiotic bacteria can inhibit the growth of competing, potentially pathogenic bacteria.

Evidence base: There is a considerable body of evidence regarding the effects of topical and oral probiotics on skin health. However, no substance-specific PCDB studies have been conducted. Many studies were conducted in children, with a significant variability in study quality. The beneficial effects are often weak and critically questioned in some publications, meaning the overall evidence is still insufficient (Table 4).

Galacto-Oligosaccharides

Galacto-oligosaccharides are classified as prebiotics. They are used as additives in various foods and are also found in breast milk. Nutraceuticals containing galacto-oligosaccharides (e.g., from whey) are typically consumed in doses of 2.5 to 10 g daily. Possible side effects, particularly at high doses, may include bloating, abdominal pain, and diarrhea.

Substance and mechanism of action: Galacto-oligosaccharides are reducing oligosaccharides consisting of one to seven galactose units and one glucose unit. They act as prebiotics by being "non-digestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or more beneficial bacterial species in the colon, thus improving host health" (Gibson and Roberfroid, 1995 [317]). The stimulation of health-promoting bacteria leads to numerous beneficial effects, such as enhanced immune function, improved nutrient absorption, and the production of hydrogen as an antioxidant. In the context of skin health, the application of nutraceuticals containing galacto-oligosaccharides is suggested to reduce moisture loss and minimize wrinkle areas.

Evidence base: Previous studies suggest a significant improvement in skin properties (hydration and skin barrier function). However, the number of studies conducted is

still quite limited, and most have been carried out in combination with Bifidobacteria. Thus, the efficacy of these nutraceuticals for supporting skin health remains insufficiently substantiated (Table 4).

3.2.6. Others

Coenzyme Q10

Coenzyme Q10 is an endogenous substance that is partly obtained from food but also synthesized in the body. In rare cases where the need for Q10 is elevated, nutraceuticals can help to prevent or compensate for a deficiency. A normal value for an adult is considered to be 0.85 µg/mL of coenzyme Q10 in plasma. The daily requirement for a normal-weight individual is approximately 50 mg (maintenance dose). The risk of overdose is low, as excess coenzyme Q10 is immediately converted to inactive forms and broken down. Symptoms such as abdominal pain, digestive disorders, and cold-like symptoms can occur only in cases of acute overdose of 1000 mg daily.

Substance and mechanism of action: Coenzyme Q10 is a naturally occurring ubiquinone produced by the body, found in mitochondria, blood, and cell membranes. As a nutraceutical, it is used to counteract skin aging and contribute to skin smoothness. Coenzyme Q10 plays a key role in cellular energy metabolism by participating in electron transfer in the respiratory chain and ATP production. It also has antioxidant properties, protecting membranes from oxidative damage.

Evidence base: The evidence base for nutraceuticals containing coenzyme Q10 is rather weak, as there are no clinical studies meeting scientific standards that demonstrate efficacy in relation to skin health beyond review articles. A PCDB study showed no significant reduction in skin wrinkles or improvement in skin smoothness (Table 4).

3.3. Group 3: Ingredients with Insufficiently Documented Effects

3.3.1. Vitamins

Vitamins B1, B2, B3, B5, B6, Vitamin D

The literature provides numerous indications that B vitamins, such as thiamine (Vitamin B1), riboflavin (Vitamin B2), niacinamide (Vitamin B3), pantothenic acid (Vitamin B5), and pyridoxine (Vitamin B6), play a significant role in skin health. For instance, a deficiency in thiamine may delay wound healing and impair the "maturation" of collagen fibers. A lack of riboflavin could promote the development of skin tumors, while pyridoxine deficiency may be associated with skin hypersensitivity. Supplementation with pantothenic acid is suggested to aid wound healing, and niacinamide is appreciated for its smoothing effects in cosmetic products. Vitamin D is widely used for alleviating atopic dermatitis and, often in conjunction with calcium, for maintaining bone health.

Substance and mechanism of action: The B vitamins comprise a group of eight water-soluble vitamins that serve as precursors for coenzymes. They are chemically and pharmacologically completely different substances found in both animal and plant foods, such as fish, liver, dairy products, broccoli, and spinach. Deficiency symptoms vary widely, from fatigue to skin rashes, inflammation, and even muscle wasting. Niacin is thought to help stabilize the skin's barrier function, while vitamin D is well-known for its protective role against UV radiation.

The daily intake for niacin recommended by the DGE is between 13 and 18 mg. In Germany, this intake is typically exceeded by the standard diet, normally ensuring an adequate supply of niacin. When nicotinic acid is supplemented at high doses instead of nicotinamide, it can cause facial flushing, redness in the neck and arms, a sensation of heat, urticaria with intensely itchy wheals, and general skin itching, commonly referred to as "flushing symptoms". Very high doses, reaching gram levels, can lead to diarrhea,

nausea, vomiting, and even result in jaundice and liver damage. Supplements containing nicotinamide are typically offered in doses ranging from 50 to 500 mg per capsule. Unlike nicotinic acid, nicotinamide is not associated with flushing and exhibits very low hepatotoxicity.

Thiamine, as thiamine pyrophosphate, plays crucial roles as a coenzyme in decarboxylation reactions and is found in high concentrations in neurons as thiamine triphosphate (TTP). Pyridoxine, in its active form, pyridoxal phosphate, serves as a coenzyme involved in various biochemical reactions in cellular metabolism. Pantothenic acid is vital for the synthesis and breakdown of carbohydrates and fats as a component of coenzyme A and the acyl-carrier protein of fatty acid synthase. Pyridoxine, in its pyridoxal phosphate form, catalyzes elimination reactions, transaminations, and decarboxylations in amino acid metabolism. Niacin is an essential component of the coenzymes NAD+ and NADP+, which facilitate reversible hydrogen binding.

Evidence base: Despite the frequently described effects and an EFSA Health Claim for riboflavin and niacin concerning skin health ("...contributes to the maintenance of normal skin"), substantial clinical evidence supporting the efficacy of B vitamins (except biotin) or vitamin D as nutraceuticals for skin health is currently lacking. Most publications focus on the protective effects of these vitamins against UV radiation (Table 5).

3.3.2. Minerals and Trace Elements

Copper

Copper is an essential trace mineral obtained through the diet. The DGE recommends a daily intake of 1 to 1.5 mg of copper for healthy adults, although only about 25% of this amount can be absorbed. High concentrations of copper can lead to gastrointestinal disturbances, colic, or liver damage and may induce oxidative stress.

Substance and mechanism of action: As a trace element, copper is indispensable for the body, contributing to the elasticity, stability, and growth of connective tissues, bones, ligaments, tendons, and muscles. It is also vital for energy metabolism and melanin formation. Copper exhibits antioxidant properties and is required for collagen and elastin synthesis.

Copper is a key component of various enzymes, including monoamine oxidase, cytochrome c oxidase, and superoxide dismutase. Although copper deficiency is relatively rare due to sufficient dietary intake, it can occur in preterm infants and lead to impaired keratinization and pigmentation of hair. Copper appears to play a significant role as a cofactor in enzymatic reactions involved in the cross-linking of collagen fibers.

Evidence base: Copper is commonly found in various skin care products, particularly in the form of copper peptides, which are used to prevent age spots and wrinkle formation and to tighten connective tissue. There are two specific EFSA Health Claims for copper: "...contributes to normal skin pigmentation" and "...contributes to the maintenance of normal connective tissues". However, substantial clinical studies and investigations supporting its use for skin health are still lacking (Table 5).

Selenium

Selenium is an essential trace element, present in the human body at levels of 5–15 mg as a component of various selenoproteins. The daily required intake is approximately 0.1 mg.

Substance and mechanism of action: Selenium is primarily ingested through organic compounds (e.g., selenocysteine) in the diet and is absorbed through the intestinal mucosa in proportion to the amount consumed. In the bloodstream, selenium is predominantly transported bound to selenoprotein P.

In addition to supporting pancreatic function, selenium is part of the amino acid selenocysteine, which acts as a cofactor for glutathione peroxidase and thyroxine-5′-deiodinase.

Selenium deficiency is relatively uncommon in Europe and primarily manifests as impaired thyroid function and reduced antioxidant protection.

Evidence base: The EFSA has established a health claim for selenium regarding skin health: "Selenium contributes to the maintenance of normal skin, hair, and nails". However, reliable clinical evidence for the effects of selenium on skin health, as mentioned in various reviews, has yet to be identified.

3.3.3. Secondary Natural Substances

Curcumin

Curcumin, the main component of turmeric, has been used in traditional Indian and Chinese medicine. In Ayurvedic medicine, it is employed to treat respiratory diseases, liver disorders, anorexia, rheumatism, and sinusitis, while traditional Chinese medicine uses it to alleviate abdominal pain. In the EU, health-related claims for (turmeric-containing) dietary supplements are not permitted.

Substance and mechanism of action: Curcumin is a polyphenol derived from the rhizome of the turmeric plant. It is believed to have anti-inflammatory, antioxidant, antimicrobial, and antimutagenic effects. The acceptable daily intake (ADI) is given as a maximum of 3 mg/kg body weight. Potential, albeit rare, side effects include diarrhea, headaches, skin rashes, and yellow stool discoloration.

Evidence base: Two meta-reviews have indicated that supplementation with curcumin-containing products may lower CRP levels. However, reliable data and studies specifically addressing its application for skin health are still lacking.

3.3.4. Plant and Animal Substances/Extracts

Phytosterols (excluding Aloe Sterols)

Phytosterols, also known as phytosterines, are secondary plant compounds classified as sterols. They primarily occur in fat-rich plant materials such as wheat germ, sunflower seeds, sesame, soybeans, and pumpkin seeds. In the context of benign prostatic hyperplasia, drugs, and specific dietary supplements are commercially available. There is evidence suggesting that phytosterols may impair the absorption of fat-soluble vitamins, resulting in reduced levels of carotene, vitamin E (α-tocopherol), and lycopene.

Substance and mechanism of action: Phytosterols are a group of chemical compounds found in plants, serving as structural components in plant cell membranes, similar to cholesterol in animal cell membranes. They are attributed with cholesterol-lowering, anti-atherogenic, and potentially anti-carcinogenic properties, though their precise mechanisms of action remain unclear. It is thought that phytosterols inhibit cholesterol absorption in the small intestine through competitive mechanisms. However, the BfR recommends limiting the consumption of phytosterol-enriched foods to individuals with elevated cholesterol levels due to a potentially increased atherogenic risk. Regarding skin health, it is assumed that orally ingested phytosterols are transported to the skin after absorption and contribute to the composition of surface lipids.

Evidence base: Studies demonstrating positive skin effects from the oral administration of phytosterols are still awaited (Table 5).

Bioactive Polysaccharides

Natural bioactive polysaccharides are regarded as effective modulators of the physiological structure, function, and health of the gastrointestinal tract. They are commonly used to treat inflammatory bowel diseases to exert immunomodulatory effects and certain beneficial impacts on the gut microbiota and its metabolites.

Substance and mechanism of action: Polysaccharides are carbohydrates consisting of a large number (at least eleven) of monosaccharides (simple sugars) linked by glycosidic bonds. This class of substances is widely distributed in nature and is needed for various functions, including energy storage, immune recognition structures, and molecular building blocks for the extracellular matrix.

Evidence base: Currently, only studies involving multi-ingredient formulations have been identified, making it difficult to draw conclusions about the effectiveness of individual substances (Table 5).

Serenoa Repens

Saw palmetto extract, derived from the fruit of the saw palmetto (Serenoa repens), is used as a herbal medicine for alleviating the symptoms of benign prostatic hyperplasia and for treating androgenetic alopecia.

Substance and mechanism of action: The main components of saw palmetto extract include phytosterols and plant oils containing free fatty acids. It also contains flavonoids, long-chain sugar molecules, and essential oils. The exact mechanisms of action are not yet fully elucidated. Anti-inflammatory and anti-androgenic effects attributed to the fatty acids and phytosterols are under discussion. Another potential mechanism involves the inhibition of 5-alpha-reductase, an enzyme that converts testosterone to dihydrotestosterone. Mild side effects, such as nausea, diarrhea, constipation, and sexual dysfunction, have been reported in connection with saw palmetto use.

Evidence base: Some studies suggest that Serenoa repens, when used as a standalone treatment compared to placebo, results in, at best, a small improvement in urinary symptoms or quality of life over three to six months. Positive effects were also noted in two smaller studies involving men with mild to moderate androgenetic alopecia. However, studies regarding its application for skin health are still lacking.

3.3.5. Probiotics and Prebiotics

Other Prebiotics

The targeted use of prebiotic substances in cosmetic products to support skin health by influencing the skin microbiome is increasingly pursued. Prebiotics aim to restore the balance of resident bacteria on human skin, which is important for both appearance and health. Utilizing the prebiotic principle, known from the food sector for specifically promoting gut microbiota to enhance immune function, pathogenic bacteria are inhibited while beneficial bacteria are fostered.

Substance and mechanism of action: Prebiotics are defined as indigestible food components that can be metabolized by specific bacteria in the intestinal microbiota. They are intended to specifically promote the growth of beneficial bacteria, thereby exerting positive effects on the health of the host.

Evidence base: Currently, robust scientific evidence or studies demonstrating the effectiveness of prebiotics in improving skin health are unavailable (Table 5).

3.3.6. Others

N-Acetylcysteine (NAC)

N-acetylcysteine (NAC) is primarily known for its oral, inhalative, and intravenous applications to liquefy mucus and facilitate its expulsion in chronic bronchopulmonary diseases associated with impaired mucus production and transport. Daily use is also claimed to benefit skin appearance.

Substance and mechanism of action: NAC is a prodrug form of L-cysteine and a precursor to glutathione, which is present in all cells of the body, particularly in erythrocytes.

Glutathione plays a vital role as an antioxidant and enzyme cofactor. It helps neutralize free radicals, thus reducing oxidative stress. L-cysteine is also necessary for the biosynthesis of coenzyme A. The exact mechanism of action of NAC is not definitively established; its mucus-dissolving effect is believed to arise from the cleavage of polysaccharides in bronchial secretions.

Evidence base: Some studies have indicated that topical application of NAC can improve various skin parameters. However, sufficient scientific evidence regarding skin effects from oral NAC is still lacking. A PCDB study has been conducted, but it did not yield conclusive results (Table 5).

3.4. Combinations of Individual Substances

The majority of commercially available nutraceuticals aimed at supporting skin health contain more than one nutrient. A selection of common combinations is listed in Table 6. Amino acids, peptides, or plant extracts are often combined with vitamins and/or minerals to enhance or complement the positive effects of individual substances. However, this approach presents several issues: Generally, it is possible that the effects of individual substances may not necessarily synergize, and in some cases, even inhibitory interactions could occur. Therefore, positive effects observed from individual nutrients cannot automatically be assumed to apply to combinations of those nutrients (Tables 3–5).

A positive evidence rating is only assigned to combination products for which at least one product-specific randomized controlled trial is available. This applies to most of the products listed in Table 6, particularly to nutraceutical products combining collagen peptides or proteins with vitamins and often some other bioactive ingredients. To some extent, it also applies to products that include hyaluronic acid, amino acids, or specific plant extracts in combination with vitamins, minerals, or other functional ingredients.

3.5. Digestion and Absorption of Nutraceuticals

The bioavailability of nutraceuticals depends largely on their digestion, intestinal uptake, and subsequent transport. These processes vary considerably depending on the chemical nature, molecular size, and solubility of the compound. The review of the relevant literature has identified the following key mechanisms:

(a) Modes of intake: Hydrophilic micronutrients (e.g., vitamin C, B vitamins, zinc) and peptides (e.g., collagen peptides) are typically taken in liquid, powder, or capsule form. Lipophilic substances (e.g., carotenoids, coenzyme Q10, omega-3 fatty acids) require fat-based formulations to support solubility and micelle formation. Polysaccharide-rich ingredients (e.g., aloe vera, hyaluronic acid) are commonly consumed as gels or liquid extracts. Formulation strongly affects dissolution and absorption.

(b) Breakdown (digestion) processes: Proteins and polysaccharides undergo enzymatic digestion before absorption. Collagen peptides, though pre-hydrolyzed, are further degraded by pepsin and pancreatic enzymes into oligopeptides and amino acids. Polysaccharides like fiber or hyaluronic acid are largely indigestible and reach the colon, where gut microbiota may ferment them. Most micronutrients do not require digestive processing.

(c) Transport and absorption mechanisms: Hydrophilic compounds use specific transporters: sodium–vitamin C co-transporters (SVCT), sodium-dependent multivitamin transporter (SMVT, e.g., for biotin and pantothenic acid), proton-coupled oligopeptide transporter 1 (PEPT1, for di- and tripeptides), and Zrt- and Irt-like protein 4 (ZIP4, for zinc). Lipophilic molecules are absorbed via passive diffusion from bile salt micelles, sometimes facilitated by transporters such as fatty acid translocase (FAT/CD36). Peptides such as collagen fragments are absorbed primarily via PEPT1.

(d) Site of absorption: Most nutrients are absorbed in the duodenum and jejunum. Some, like vitamin B_{12}, are absorbed in the ileum via receptor-mediated endocytosis. Microbially activated compounds (e.g., polyphenols) and polysaccharides primarily exert their physiological effects in the colon after undergoing microbial transformation.
(e) Transport routes: Hydrophilic nutrients and small peptides enter the liver via the portal vein for further metabolism or distribution. Lipophilic compounds are incorporated into chylomicrons and reach systemic circulation via the lymphatic system. Non-absorbable components (e.g., fibers, probiotics) remain in the gastrointestinal tract and interact locally with gut cells or microbiota.
(f) First-pass effect: Hydrophilic micronutrients, amino acids, and peptides may undergo partial first-pass metabolism in the liver. In contrast, lipophilic substances initially bypass hepatic metabolism via lymphatic transport but are eventually processed after chylomicron remnants are taken up by the liver.

3.6. Adverse Effects and Tolerability

Nutraceuticals, like all foods, medicines, and other preparations, can potentially trigger intolerances to individual or multiple ingredients. Allergic and immunogenic reactions, including anaphylactic shock, cannot be entirely ruled out. While the risk of side effects is generally assumed to be lower due to the relatively low dosages of ingredients and their typically minimal systemic efficacy compared to pharmaceuticals and other therapeutics, the likelihood of adverse effects increases with prolonged use and, in combination products, with the number of ingredients included.

The incidence of adverse effects from nutraceuticals can only be partially inferred from study results due to often limited participant numbers and inadequate study designs. Therefore, it is advisable to systematically document all reported suspected side effects using a "nutrivigilance" approach, similar to pharmacovigilance for pharmaceuticals, to identify potential clusters and associated risks.

Examples of adverse effects that are sometimes controversially discussed in the literature include the generation of oxidative stress at higher dosages of copper-containing products and an increased risk of lung cancer associated with beta-carotene (30 mg) after prolonged intake by smokers [318]. For fat-soluble vitamins, it is important to note that they can accumulate in the body and should generally be administered at relatively low doses.

Moreover, the use of polyphenols, despite their promising beneficial effects, is not always without potential risks. At higher doses, they may protect cancerous cells in addition to healthy cells, cause headaches or gastrointestinal side effects such as nausea, and even reach toxic levels, for instance, by inducing pro-oxidant effects [319].

Hyaluronic acid and its salts can cause intolerances, as well as allergic and immunogenic reactions. However, studies on beauty products containing hyaluronic acid have not reported any intolerances at the typical dosages used. Non-purified hyaluronic acid may contain endotoxins such as lipopolysaccharides. The hyaluronic acid found in supplements is typical of pharmaceutical quality and, thus, sufficiently pure. Hormone-mimetic substances like phytosterols may also lead to adverse effects, especially with prolonged use. Unlike nicotinamide, the intake of nicotinic acid can frequently lead to transient skin flushing (niacin flush), depending on various factors such as dosage, formulation, and medical condition. Accordingly, the recommended maximum daily dosages for the two substances differ significantly: 4 mg per day for nicotinic acid and 160 mg per day for nicotinamide [320].

The good tolerability of vitamins, minerals, trace elements, collagen peptides, fatty acids, and carbohydrates at the specified intake amounts has been demonstrated in selected studies and is particularly highlighted in reviews. The nutritional effects of these nutri-

ents are generally not associated with side effects, even with prolonged intake. Natural substances like hyaluronic acid or curcumin are regarded with more caution in this regard.

The dosage form of nutraceuticals, such as gummies, chocolates, or similar products, should be viewed critically. So-called "beauty sweets" often suggest skin benefits through their ingredients, but they typically contain high sugar levels. Regular consumption of such products over an extended period contributes significantly to glycosylation, which can negatively affect skin quality [321].

4. Discussion

A closer examination of the data for more than 50 selected individual substances and combinations reveals that only a subset of these nutrients has scientifically validated efficacy in supporting skin health. The most important criterion is whether the benefits are supported by high-quality clinical studies, preferably including at least one substance-specific or product-specific PCDB study. The analysis has shown that the health claims formulated by the EFSA for certain nutraceuticals related to various aspects of skin health do not automatically allow for conclusions about the evidence base concerning skin health. A critical assessment of the evidence particularly applies to combination products, for which product-specific evidence is required.

It should be noted that the quality of studies may not always be satisfactorily assessed due to partially missing methodological details, which has led to downgrading evidence ratings in some cases. Moreover, due to the lack of clear dosage information in many studies, it cannot be ruled out that in individual cases, a dose that was too low has impeded the demonstration of efficacy.

The applications related to skin health emerge from the thoroughly described body of research. Original studies, reviews, and assessments facilitate the determination of purpose and suitability for various nutraceuticals. This documentation aims to present the available options for positively influencing skin health.

In this review, approximately 17 common dietary supplements or (groups of) substances for skin health, as well as some combination products, are identified as nutraceuticals with proven and sufficiently substantiated effects. These include vitamins A, B7, C, and E, collagen peptides, carotenoids, and several plant extracts. Other substances, despite many marketing claims and some existing health claims, were found to have limited (e.g., zinc, acerola) or insufficiently substantiated (e.g., many B vitamins, copper, curcumin) effects on skin health.

For various nutraceuticals where evidence from randomized controlled trials is insufficient or questionable, other forms of supporting data are available—such as non-RCT studies, positive assessments or indications from reviews, or even EFSA Health Claims related to skin health. In such cases, it seems appropriate to evaluate the full body of available evidence for each respective substance in order to determine whether it should be assigned to Group 2 (ingredients with less well-documented efficacy) or to Group 3 (ingredients with insufficiently documented effects). In this way, substances such as certain minerals, amino acids, plant extracts, and probiotics were assigned to Group 2, while ingredients, including, among others, certain vitamins, minerals, trace elements, and plant- or animal-derived compounds, were allocated to Group 3. For Biotin, vitamin E, and some polyphenols, it even appeared justified to assign them to Group 3 despite the lack of typical substance-specific RCT evidence, as at least one PCDB study in combination with vitamin A is available and the overall body of data is substantial.

The highlighted differences in the efficacy among these substances may serve as guidance for the targeted and successful use of these nutrients or nutrient complexes to

support skin health. A differentiated consideration of efficacy, tolerability, and safety forms the basis for best practices in application.

To establish the efficacy of a combination product, specific studies are necessary. References to evidence from studies on individual substances alone are not sufficient due to potential additive, synergistic, and inhibitory effects; at best, they can only support the findings from product-specific studies. Therefore, it is generally recommended that for products with multiple ingredients, product-specific studies should be prioritized, preferably PCDB studies. This ensures the verification of the product in its specific composition, quality, and delivery form.

In favor of a wide range of nutraceuticals and a better overview of the associated literature, this review does not provide a comprehensive and detailed presentation of clinical data, in contrast to other reviews. It is based on published studies and other reviews but ultimately reflects the subjective assessment of the authors regarding the classification into evidence groups due to the heterogeneity and divergence of extensive data. For a more reliable assessment of the evidence, substance-related or product-specific clinical studies with recognized scientific design (RCT, PCDB) would be necessary for all evaluable nutraceuticals, which would significantly limit the number of products involved. It can be expected that in the coming years, the number of nutraceuticals available on the market to support skin health, as well as the number of clinical studies validating their efficacy, will continue to increase.

5. Conclusions

The data presented here regarding efficacy, tolerability, and safety demonstrate that nutraceuticals with strong evidence for their effectiveness are generally suitable for practical application regarding skin health. The unexpectedly low number of only 17 nutraceuticals with demonstrated efficacy—out of approximately 50 products evaluated- highlights a persistent gap between marketing claims and the actual scientific evidence supporting product effectiveness. On the other hand, many of the most widely used nutraceuticals, such as various vitamins, collagen peptides, omega-3 fatty acids, and hyaluronic acid, fall into the category of substances for which this review attests a sufficiently documented effect.

The number of clinical studies continues to increase year by year, which means that a reclassification might be required in the future—either upgrading the level of evidence in cases of positive clinical results or downgrading it if future studies fail to confirm efficacy. In principle, future evidence could also influence the safety profile of individual nutraceuticals, although—based on the current data—significant safety concerns appear unlikely for those products generally categorized as dietary supplements.

The proposed classification of nutraceuticals for skin health may support consumers and healthcare professionals in identifying products with a higher probability of clinical benefit. Nonetheless, many aspects of nutraceutical efficacy remain beyond the scope of this review, as a comprehensive comparison of the numerous commercially available products would exceed its intended focus. That said, several recent reviews have addressed other relevant properties of selected nutraceuticals and may offer answers to more specific questions.

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