cosmetics

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Review

Spirulina for Skin Care: A Bright Blue Future

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Abstract: *Spirulina* stands out as a sustainable bioactive microalga with health-promoting properties, and an important active ingredient of natural cosmetics products. Currently, *Spirulina* has been incorporated in topical skin-care formulations, such as a moisturizing, antiwrinkles, antiaging and antiacne agent. Furthermore, this microalga is used by cosmetic formulators to promote healthy sunscreen protection, to treat skin pigmentation disorders and to heal wounds. Most of commercial cosmetics claim a large range of *Spirulina* properties, including antioxidant, revitalizing, remineralizing, moisturizing, protecting alongside cleansing and shining action, both for hair and for skin. In this review, recent cosmetic applications of *Spirulina* are revised, by highlighting its ability in improving skin appearance and health. Additionally, the analysis of the *Spirulina* cosmetic benchmark is discussed. Looking at the current emergence of the beauty industry, many *Spirulina* extracts and dry powder/flakes, both the starting ingredient and final *Spirulina*-based cosmetic products, are available on the market. In this industrial field, *Spirulina*—mainly *Spirulina platensis* and *Spirulina maxima*—is used either as a powder, like in the case of cheaper products, or as a phycocyanin-rich blue extract, particularly in the luxury market. It is likely that, in the coming years, diversity, quality and topical applications of *Spirulina* will rapidly increase.

Keywords: *Spirulina*; microalga; cyanobacteria; natural cosmetics; skin care; skin health

Citation: Ragusa, I.; Nardone, G.N.; Zanatta, S.; Bertin, W.; Amadio, E. *Spirulina* for Skin Care: A Bright Blue Future. *Cosmetics* **2021**, *8*, 7. https://doi.org/10.3390/cosmetics8010007

Received: 20 October 2020
Accepted: 14 December 2020
Published: 14 January 2021

1. Introduction

Since ancient times, botanical extracts have been extensively used in cosmetics and skin care products. In recent decades, researchers have turned their interest towards microalgae and cyanobacteria for the preparation of healthy and nutrient natural products, both as food and cosmetics [1,2].

Between the microalgae, *Spirulina* (Arthrospira) is one of the most promising species, due to its precious content of phytochemicals and its greener and more sustainable production chain. *Spirulina* is a unicellular cyanobacterial-type microalga, which grows at pH 10–12. The genus *Athrospira* includes a great variety of species (see, i.e., ref. [3]), such as the most popular *Spirulina platensis* and *Spirulina maxima*. These two algae types differ in both ultrastructural and morphological characteristics, alongside in their geographic origin: the *Spirulina platensis* is mainly found in Africa and Asia, while *Spirulina maxima* is widespread in California and Mexico [4]. The safety of *Spirulina* utilization is well justified by its long history of use—this microalgae has been cultivated for centuries, and is still commonly consumed in Africa and in Chad—and by a plenty of in vivo/vitro studies [5–8].

Spirulina is considered also highly sustainable due to a multiplicity of synergic factors [1,9]: (i) it is easily grown in "bioreactors" under solar light with considerable savings in water, soil and (ii) without the need of pesticide or herbicide. (iii) This pretty simple production process requires minimal operator training and technical supervision thus ensuring a high economic impact. (iv) After cultivation the whole microalgae is used, unlike other fruit and vegetable crops where root, stem and leaf systems are all byproducts, (v) helping to save energy, cutting greenhouse gas emissions and the overall environmental

impact. All these advantages are furthermore strengthened by the fact that (iv) *Spirulina* is highly dense and rich of nutrients and of phytochemicals [4,8–11]. Since the chemical composition of a given spirulina is strongly influenced by the genus and by the cultivation conditions, the list reported in Table 1 have to be considered as an example.

Table 1. Phytochemicals of *Spirulina* [12].

Name	Amount for 100 g of Raw Material	Unit
Water	90.67	g
Calcium, Ca	12	mg
Iron, Fe	2.79	mg
Magnesium, Mg	19	mg
Phosphorus, P	11	mg
Potassium, K	127	mg
Sodium, Na	98	mg
Zinc, Zn	0.2	mg
Copper, Cu	0.597	mg
Manganese, Mn	0.186	mg
Selenium, Se	0.7	µg
Vitamin C, total ascorbic acid	0.9	mg
Thiamin	0.222	mg
Riboflavin	0.342	mg
Niacin	1.196	mg
Pantothenic acid	0.325	mg
Vitamin B-6	0.034	mg
Folate, total	9	µg
Folate, food	9	µg
Folate, DFE	9	µg
Choline, total	6.5	mg
Vitamin A, RAE	3	µg
Carotene, beta	33	µg
Vitamin A, IU	56	IU
Vitamin E (alpha-Tocopherol)	0.49	mg
Vitamin K (phylloquinone)	2.5	µg
Fatty acids, total saturated	0.135	g
14:0	0.004	g
16:0	0.127	g
18:0	0.004	g
Fatty acids, total monounsaturated	0.034	g
16:1	0.017	g
18:1	0.018	g
Fatty acids, total polyunsaturated	0.106	g
18:2	0.064	g
18:3	0.042	g
Tryptophan	0.096	g
Threonine	0.306	g
Isoleucine	0.331	g
Leucine	0.509	g
Lysine	0.312	g
Methionine	0.118	g
Cystine	0.068	g
Phenylalanine	0.286	g
Tyrosine	0.266	g
Valine	0.362	g
Arginine	0.427	g
Histidine	0.112	g
Alanine	0.465	g
Aspartic acid	0.597	g
Glutamic acid	0.864	g
Glycine	0.319	g
Proline	0.245	g
Serine	0.309	g

In general, the main components of spirulina are proteins, carbohydrates and lipids. Among the various proteins, the most relevant (total amount around 60% on a dry weight basis) are phycobiliproteins, namely phycocyanin, allophycocyanin, and phycoerythrin. Besides proteins, the other well represented category is that of fatty acids. The main lipids found in *Spirulina* are γ-linolenic acid (18:3, n-6) from omega-6 family and palmitic acid (16:0) both known for their pharmaceutical potential to prevent cardiovascular diseases, hypercholesterolaemia and other disorders.

Furthermore, this alga is also a rich source of many other valuable compounds, such as several minerals and vitamins. The most commonly identified minerals are potassium, calcium, magnesium, selenium, iron and zinc. Among the vitamins, B vitamins are the most abundant. Its presence confers to the algae properties of in DNA repair, electron transfer, fatty acids synthesis and one-carbon metabolism [13]. Finally, in addition to phycobiliproteins mentioned before, other relevant *Spirulina*'s pigments are carotenoids and chlorophyll, whose colored compounds find potential interest in the food sector. Furthermore, these pigments exert potential health benefits over ingestion. There is evidence that the pigments consumption has enhanced the immune body response thus reducing the risk of developing degenerative chronic cardiovascular diseases, and certain types of cancer [14,15]. Nonetheless, *Spirulina* carries also out other pharmacological activities, i.e., enhancing body immunity against pathogenic bacteria, fungi, RNA viruses, including influenza and coronavirus [11,16–19] and preventing inflammatory diseases or cellular oxidative stress [20–22].

These features make this alga an attractive new ingredient, especially for the formulation of green and ecofriendly cosmetics [23]. In this context, a recent trend is using *Spirulina* food supplements as "nutricosmetics" that not only help to prevent diseases and become healthier, but also they enhance the natural beauty of skin, nails and hair [24–26].

However, despite the interest of the cosmetic-market in the natural-derived skin care products, up to now few studies have recommended the use of cyanobacteria for topic well-being treatments. In connection to the wide-ranging interests of our company in developing sustainable and innovative extracts [27,28] and high-quality food supplements, medical devices, foods for special medical purposes, probiotics and cosmetics [29]; in this paper we briefly review recent publications about cosmetic applications of *Spirulina*, with a focus on its potential activities and uses for improving appearance and skin health.

2. Benefits of *Spirulina* for Skin Care Formulations

To date, few research have aimed at studying and demonstrating the *Spirulina*'s healthy effect on the skin. The most of cosmetic actions, supported by the literature and claimed by the market, are firstly the antiage one, including moisturizing, antioxidant and brightening proprieties, and secondly the antiacne and wound healing properties. The most relevant articles about this topic, which were published during the last few years, are classified in Figure 1, Table 2 and in the hereafter discussion.

Figure 1. Current application of *Spirulina* in skin care.

Table 2. Selection of recent studies about the skin care benefits of *Spirulina* herein discussed.

Topic	Study Object	Outcome of the Study	Year	Reference
Antiage—Moisturizing	*Spirulina* in dermocosmetic formulations	Benefits on hydration, skin barrier function and oil control. Antiaging effects.	2015	[30]
	Spirulina fermented extracts for skin care applications	The enzymatic fermentation increased the efficiency of spirulina in inducing skin hydration and osmotic protecting activities	2018	[31]
	Dermatological effect of peptide extract of *Spirulina*	Stimulation of fibroblast proliferation and on the glycosaminoglycans and collagen's synthesis; anti-aging benefits	2018; 2006	[10,32]
Antiage—Antioxidant	Sunscreen formula with algae as active ingredients	Synergistic effect of the contemporary use of UV-filters and *Spirulina*; increase skin protection and appearance	2012	[33]
	Spirulina as antioxidant for sunscreen formulation	Benefits on health of the dermis and the skin elasticity, reduction of skin hyperpigmentation, protection against photoaging and inhibition of ROS-induced damage to the dermis.	2017	[34]
Antiage—Brightening	Antimelanogenic effect of c-phycocyanin from *Spirulina*	C-phycocyanin dose-dependent decrease of tyrosinase activity and melanin content. Best result with 0.1 mg/mL of Cpc.	2011	[35]
	Spirulina for skin whitening cosmetics	Great potential to treat pigmentary disorders. High activity toward tyrosinase inhibition	2018	[36]
Wound healing	In vivo wound healing activity of spirulina extracts	Significant improvement in the wound healing activity. Best result with ointment containing 10 % *w*/*w* of petroleum ether extract	2011	[37]
	In vivo and in vitro wound healing effect of crude *Spirulina* extract and phycocyanin	Promising wound healing activity of crude *Spirulina* extract. Activity related to the presence of a mixture of phycocyanin and carotenoids.	2013	[38]
	Wound healing and antioxidant activities of *Spirulina* extract incorporated in skin cream	Cell proliferation, migration and immunoactivity were increased by incorporation of crude algae extracts in the formulation. *Spirulina* had no genotoxic effect on human peripheral blood cells.	2017	[39]
	Spirulina- polycaprolactone (PCL) nanofiber wound dressing to improve cutaneous wound healing	PCL-nanofibers containing *Spirulina* extract were demonstrated to be effective on dermal wound healing in a rat model. Additional Alginate impregnation increased the adhesiveness and moisture of the skin and expedited wound healing without causing cytotoxicity.	2016, 2017	[40,41]
Antiacne	Formulation and Development of Topical Antiacne Formulation of *Spirulina* extract	Topical application of phycocyanin rich ointment successfully employed in the treatment of acne against *P. acne* and *S. epidermidis*.	2018	[42]
	In vitro evaluation of face mask containing extract and biomass of *Spirulina platensis* and its antibacterial activity	The face mask was able to inhibit *Cutibacterium* acnes with a diameter of inhibition zone was 10 ± 0.4 mm. The antibacterial activity was due to the presence of alkaloids, steroids, saponins and phenol in *S. platensis* extract.	2019	[43]

2.1. Antiage

2.1.1. Moisturizing

Skin aging is a complex process that depends on both a genetic predisposition and external factors, and causes functional and structural skin damage. Water molecules play a pivotal role in maintaining the skin structural proprieties: indeed, water binds the dermal proteins, such as collagen, and ensures the tissue thickness. Therefore, aged skin is poor of bounded water and has weak hydration networks, which make skin look less and less glowy and firm. Typically, UV radiation, pollution, a poor diet and an unhealthy lifestyle are the main causes of skin aging, and therefore of the loss of moisture together with the decrease of skin barrier.

Currently, the increase in life expectancy and the growing interest in a youthful appearance have led the cosmetic market to formulate antiage products with moisturizing and wrinkle reduction effects. Considering that beauty companies are also involved in searching sustainable raw materials and active ingredients, the studies on the antiaging effects of algae, like *Spirulina*, aroused great interest in recent years [44,45].

In this context, Delsin et al., in 2015 firstly promoted the use of *Spirulina* as an innovative ingredient for dermocosmetic products. They showed how the microalga improves the epidermis structure and acts as a hydration booster with positive results on skin barrier function, particularly to skin protection and antiage, and oil control [30]. Delsin's research team prepared a gel-cream, formulated with the following ingredients: fatty alcohols, ammonium acryloyldimethyltaurate, NP copolymer and methylphenyl polysiloxane, phenoxyethanol and parabens, BHT and distilled and deionized water. This formulation was on the one hand supplemented gel cream containing 0.1% (*w*/*w*) of dry extract of *Spirulina* (FGA) and, on the other hand, it was gel cream free from the active alga(vehicle—FGV). They were both applied twice daily on the participants face area. In particular, 40 female healthy participants, aged between 18 and 39 (young group) and 40 and 65 (mature group), with phototypes II, III or IV, took part in the clinical study. Both groups were divided into two subgroups, composed of ten people each: the first group used the formulation containing *Spirulina* extract while the second one used the vehicle gel-cream. For comparison data were collected before or after the application of the cream (in total 28 days). The parameters considered were: skin hydration, trans epidermal water loss (TEWL), skin microrelief, sebum content (on the forehead region), dermis echogenicity and morphological and structural epidermal features (in the periorbital region), before and after the aforementioned trial period. Among these parameters, trans epidermal water loss is the most important for revealing the skin barrier quality and, consequently, the skin moisture content. The results showed a significant increase of the stratum corneum water content, a reduction of TEWL (Figure 2) and the amount of sebum on the skin (Figure 3), and an enhancement of the echogenicity of the dermis and the distribution of keratinocytes.

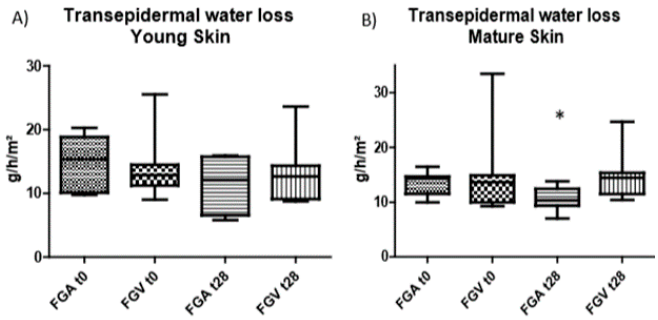

Figure 2. Transepidermal water loss before (t0), and after 28 days (t28) of application of the formulations FGA (gel cream containing 0.1% of *Spirulina* extract) and FGV (gel cream without *Spirulina* extract) in young skin (18–39 years) (**A**) and mature skin (40–65 years) (**B**). (* Kruskal–Wallis, $p < 0.05$). Published by ref. [30].

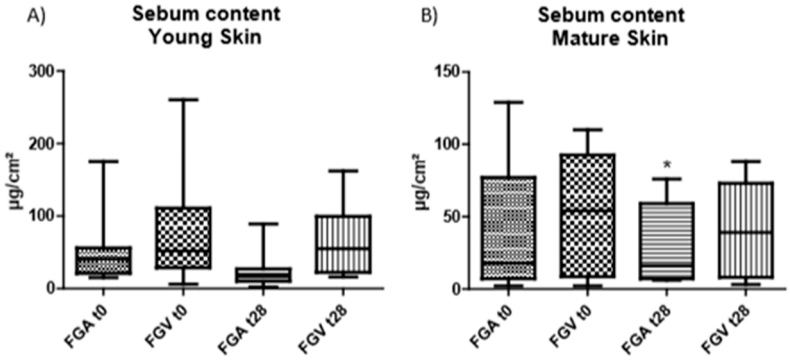

Figure 3. Sebum content of the skin before (t0), and after 28 days (t28) of application of the formulations FGA (gel cream containing 0.1% of *Spirulina* extract) and FGV (gel cream without *Spirulina* extract) on young skin (18–39 years) (**A**) and mature skin (40–65 years) (**B**) (* Kruskal–Wallis, $p < 0.05$). Published by ref. [30].

As result of this study, the *Spirulina*'s fatty acids, such as α and γ linolenic acid, inhibited isoenzyme type 1 metabolism and improved the oily skin appearance. The polysaccharides contained in the alga extract, instead, stimulate the cell division process and contribute to the keratinization processes or to renew the stratum corneum. Vitamins, minerals and proteins contained into the alga may further contribute in improving skin microrelief and hydration.

Therefore, *Spirulina* extract was essential to improve the hydrolipidic character, regenerate the skin tissue thus protecting and moisturizing the skin. These effects were greatly visible on the mature group. To further investigate the behaviors of the spirulina in the skin care, in 2018 F. Apone et al. tested and compared two *Spirulina* with the analogous unfermented. The reported data show a greater effectiveness of the enzymatically fermented extract in moisturizing and protecting the skin cells [31].

Another important aspect related to skin aging is the peptides reduction in the dermis extracellular matrix. Peptides are a short chain of amino acidic residues, which are involved in several physiological processes, such as inflammation, immune response and skin remodeling, and stimulate the synthesis of structural proteins (collagen and elastin). For this reason, cosmetic products that are rich in peptides may prevent the onset of wrinkles and signs of aging [46]. As most cyanobacteria, *Spirulina* contains several bioactive compounds, notably proteins (53–62%). A large number of peptides have been screened, fractionated and purified from *Spirulina* extracts and further used into pharmaceuticals and cosmetic applications. With this purpose, in 2006 a French research team patented a dermatological peptide extract of *Spirulina*, claiming positive effects on the stimulation of fibroblast proliferation and on the glycosaminoglycans and collagen's synthesis [32]. Moreover, a few years later, also Wang Z. et al., presented a study about antiaging peptides extracted from *Spirulina platensis* at the 13th International Congress on amino acids, peptides and proteins in Vienna [10].

2.1.2. Antioxidant

The antioxidant potential of blue-colored cyanobacteria is of great interest in the cosmesis. Pigments can be used as natural colorants in make-up products, like eyeliner and lipstick, and as antioxidant agents, which protect against UV radiation [1,23]. Indeed, *Spirulina* contains a lot of photosynthetic pigments like chlorophyll and especially phycocyanin, which determine a long-lasting green-blue coloration in cosmetic formulas (Figure 4) [47].

In 2012 Dr. Lotan A. (Nidaria Technology Ltd., Israel) patented some biologic sunscreen formulas, which included a blend of algae as active ingredients [33]. The claimed activity was the synergistic effect of the simultaneous use of UV filters and algae, which absorb sunlight, "convert it in energy source", protect the skin and improve its appearance. The patent argues that "the agent primarily responsible for the improved effect on the

skin is the incorporation of the algae" and *Spirulina* was one of the tested algae (*Spirulina*, *Dunaliela*, *Hematococus*, *Nannochlorosis* and *Tetraselmis*). However, despite the importance of this statement, an undeniable scientific demonstration is missing. The patent proposed three formulations containing 10% *w*/*w* non-viable intact algae, a topical gel and both W/O and O/W emulsions.

(**a**) (**b**)

Figure 4. Two formulas made by AromataGroup: (**a**) Mermaid Instant Mask with spirulina and rameic chlorophyll and (**b**) Marble Lipbalm with spirulina extract. Published by ref. [47].

Few years later, C. Souza et al., further developed a stable and effective sunscreen formulation containing a mixture of UV filters and antioxidants (using *Spirulina* between the others). As such it further encourages researchers to design more efficacious and reliable sunscreens (Table 3) [34]. As an antioxidant, *Spirulina* may reduce skin hyperpigmentation and protect skin against sun-induced damages (e.g., photoaging) by inhibiting ROS-induced damage to the dermis. Both visual and rheological analyses revealed that the sunscreen formulations were stable during the study period. Therefore, the inclusion of UV filters Tinosorb® S, Tinosorb® M, Uvinul® APlus and Uvinul® T150, along with *Spirulina* dry extract and dimethylmethoxy chromanol-loaded solid lipid nanoparticles (DMC-loaded SLN) did not alter the physical stability of the cream. Such formulations were characterized by a pH range between 5.3 and 5.8, suitable for topical application. DMC-loaded SLN were successfully produced with a high inclusion rate (approximately 96%, after 24 h) and stability (54 days). These formulations exhibited a non-Newtonian and pseudoplastic behavior and, in terms of safety, according to the sensorial analyses, they did not irritate the skin.

Table 3. Composition of the sunscreen cream based on UV filters and antioxidants. Published by Ref. [34].

Composition [a]	**Concentration (% *w*/*w*)**		
	Formulation Codes		
	F1	**F2**	**F3**
Oil phase [b]	12.6	12.6	12.6
Preservative	0.8	0.8	0.8
Aqueous phase	3.1	3.1	3.1
Bis-ethylhexyl methoxyphenyl triazine—Tinosorb® S	-	4.0	4.0
Diethylamino hydroxybenzoyl hexyl benzoate—Uvinul® APlus	-	1.0	1.0
Ethylhexyl triazone—Uvinul® T150	-	4.0	4.0
Methylene bis-benzotriazolyl tetramethylbutylphenol—Tinosorb® M	-	6.0	6.0
Spirulina dry extract	-	-	0.1
DMC-loaded SLN [c]	-	-	10.0
Water solvent q.s.	100 g	100 g	100 g

[a] Qualitative composition was reported in accordance with INCI (International Nomenclature of Cosmetic Ingredient). [b] Quantitative composition of oil and aqueous phases were previously reported by ref. [48]. [c] DMC final concentration into F3 formulation was 0.05% (*w*/*w*). DMC-loaded SLN: dimethylmethoxy chromanol-loaded solid lipid nanoparticles.

The C. Souza's research team examined the photoprotective effects of the developed formulations, both in vitro and in vivo, and highlighted the pivotal contribution of the addition of *Spirulina*. The in vitro UVA protection of formula F2 and F3 was evaluated by the UVA/UVB ratio and by the critical wavelength. The in vivo SPF values of both formulations were nearly 30 while the in vitro SPF values of formulations F2 and F3 were respectively around 2.5-times and 3.0-times higher than those obtained in vivo. Therefore, in vitro results suggest that the combination of *Spirulina* and SLN loaded DMC with UV filters improve the SPF value. However, in vivo tests did not adequately confirm this result. It has been observed that, while in vitro experiment measures the formulation transmittance, the in vivo procedure determines the effective ability to prevent inflammatory reaction (erythema) triggered by solar radiation. This means that *Spirulina* increase the light scattering properties without furnishing enough anti-inflammatory activity.

To further clarify the benefit of using *Spirulina* into the formulations, a 3-month single-blind clinical study has been carried out with 44 healthy participants (30–50 years old), during which the water content of stratum corneum, TEWL, dermis echogenicity and skin elasticity and pigmentation were measured. The results showed that *Spirulina*-supplemented sunscreen significantly improves both the health of the dermis and the skin elasticity after 84 days of the treatment, with respect to the sunscreen itself. Moreover, as previously stated by Delsin et al. [30], topically applied *Spirulina* regenerates the skin barrier and reduces the loss of water.

2.1.3. Brightening

Skin hyperpigmentation is an aesthetic issue, which raises a growing concern in the current cosmetic market. Currently, whitening products are pivotal in the antiage skin care routine, since they reduce spots and skin dyschromia caused by UV exposure. The pigmentogenesis begins inside melanocytes, which are a type of cell located between the keratinocytes in the basal layer of epidermis. During the mentioned process, tyrosinase plays an important role in controlling the production of melanin and then in coloring hair, skin and eyes. In fact, this multicopper enzyme facilitates the transformation of L-tyrosine in L-dihydroxyphenylalanine (L-DOPA), which in turn oxidizes itself and becomes DOPA-quinone. A set of spontaneous cascade reactions leads to the creation of a pigment polymer, called melanin, which is released to the surrounding keratinocytes [49]. Both the abnormal loss and the overproduction of melanin may generate serious esthetical and dermatological skin disorders in humans, such as *Acanthosis nigricans*, melasma, Cervical poikiloderma, Lentigines, Periorbital hyperpigmentation, neurodegeneration associated with skin cancer risk and Parkinson's disease. The most reliable strategy to treat such pigmentary disorders so far is to use inhibitors of the tyrosinase.

In the last decades, a huge number of natural and artificial inhibitors have been suggested for the production of hypopigmentation pharmaceuticals, antibrowning agents and skin whitening cosmetics [36,50–53] (Table 4). Arbutin, kojic acid and hydroquinone are among the best-known inhibitors, even though their use is currently limited because of certain side effects, among which irritation and allergies. Indeed, hydroquinone in cosmetic products is also forbidden by the EU and the FDA [54]. As a result, the use of *Spirulina* as a safer and greener tyrosinase inhibitor might have a huge potential application in the field. The effect of *Spirulina* on skin pigmentation was examined in detail by S. Sahin et al., in 2018 [36]. They demonstrated that this microalga has a big potential for the inhibition of tyrosinase and might be used for the development of skin whitening cosmetics, totally effective and safe. S. Sahin showed a high inhibitory effect on mushroom tyrosinase activity of *Spirulina*'s extracts. Moreover, the tyrosinase activity remarkably reduced in a dose dependent manner. In particular, the IC50 values of tyrosinase inhibition with *Spirulina* water and ethanol extracts were found as 1.4×10^{-3} and 7.2×10^{-3} g/mL, respectively. The values just mentioned were compared with other known natural tyrosinase inhibitors, and were found to be bigger than the IC50 value of kojic acid (IC50 = 2.8×10^{-4} g/mL).

Overall, the whitening activity of *Spirulina* may be related to the presence of a phytocomplex containing vanillic acid—as the main phenolic acid component—caffeic acid and ferulic acid, which all synergically act to inhibit the enzyme. Another important component that could be responsible for this antimelanogenic effect is the c-phycocyanin, which has also antioxidant properties, as mentioned above. In fact, in 2011 a research team from Taiwan studied how this protein modulates the tyrosinase expression, both in transcriptional and post-transcriptional levels [35]. The outcomes of the study show that C-phycocyanin inhibits the pathway of p38 mitogen-activated protein (MAP) kinases, by downregulating the CREB activation and then the melanocyte inducing transcription factor (MITF) expression. At the same time, C-phycocyanin fits in the physiologic retro-control mechanism, that is a post-transcriptional pathway that downregulates an over synthesis of melanin. In doing so, the influence of the blue protein increases the cAMP levels (Figure 5) that trigger the MAPK/ERK pathway, which in turn phosphorylates the MITF on Serine 73. This last step results in an increased transcriptional activity and, at the same time, in the protein binding with ubiquitin monomers, which ends with the degradation of the transcription factor. Li-Chen Wu and his team studied the concentrations needed to suppress the tyrosinase activity and the following melanin content as well. As shown in Figure 6, the enzyme activity decreased in line with the pigment concentration, according to a C-phycocyanin dose-dependent trend. In particular, the enzyme activity was reduced from 75.7% to 65.7% and the pigment concentration from 56.2% to 47.5%, using a C-phycocyanin treatment with a range from 0.05 to 0.1 mg/mL. The higher concentration (0.2 mg/mL) was excluded from the study results because it affected the viability of B16F10 melanoma cells, even though it contributed to a great decrease in both tyrosinase activity and melanin content.

Table 4. Natural blends with inhibitory activity of tyrosinase. Published by Ref. [36] and references therein.

Compounds	IC50	Substrate
Ethanol extract of *Cudrania tricuspidata* twig	1.14×10^{-4} g/mL	L-tyrosine
Steppogenin from *C. tricuspidata*	2.52 ± 0.66 μM/7.26×10^{-7} g/mL	L-tyrosine
Oxyresveratrol from *C. tricuspidata*	2.85 ± 0.26 μM/6.96×10^{-7} g/mL	L-tyrosine
Trans-dihydromorin from *C. tricuspidata*	21.54 ± 0.84 μM/6.55×10^{-6} g/mL	L-tyrosine
Quercetin from *C. tricuspidata*	54.58 ± 0.89 μM/1.65×10^{-5} g/mL	L-tyrosine
Dihydrokaempferol from *C. tricuspidata*	N100 μM/N2.88×10^{-5} g/mL	L-tyrosine
Protocatechuic acid from *C. tricuspidata*	N500 μM/N7.71×10^{-5} g/mL	L-tyrosine
Naringenin from *C. tricuspidata*	N500 μM/N1.36×10^{-4} g/mL	L-tyrosine
Kojic acid (standard tyrosinase inhibitor)	50.43 ± 1.75 μM/7.17×10^{-6} g/mL	L-tyrosine
Kojic acid (standard tyrosinase inhibitor)	0.67 mM/9.52×10^{-5} g/mL	L-DOPA
85% ethanol extract of *Hesperethusa crenulata* bark	8.6×10^{-4} g/mL	L-tyrosine
Water extract of *H. crenulata* bark	1.09×10^{-3} g/mL	L-tyrosine
Methanol extract of *H. crenulata* bark	1.42×10^{-3} g/mL	L-tyrosine
Methanol extract of *Magnolia denudata*	3.34×10^{-3} g/mL	L-tyrosine
Methanol extract of *M. denudata* var. *purpurascens*	1.06×10^{-2} g/mL	L-tyrosine
50% methanol extract of *Podocarpus elongatus* leaves and stem	4.7×10^{-4} and 1.4×10^{-4} g/mL, respectively	L-DOPA
50% methanol extract of *P. falcatus* leaves and stem	2.9×10^{-4} and 3.5×10^{-4} g/mL, respectively	L-DOPA
50% methanol extract of *P. henkelii* leaves and stem	3.7×10^{-4} and 0.4×10^{-4} g/mL, respectively	L-DOPA
50% methanol extract of *P. latifolius* leaves and stem	4.1×10^{-4} and 3.6×10^{-4} g/mL, respectively	L-DOPA
Dieckol from *Ecklonia cava*	20 μM/1.49×10^{-5} g/mL	L-tyrosine
Cinnamic acid	2.10 mM/3.11×10^{-4} g/mL	L-DOPA
Ferulic acid	0.559 mM/1.09×10^{-4} g/mL	L-tyrosine
Caffeic acid	0.037 mM/6.67×10^{-5} g/mL	L-tyrosine
Ethanol and water extract of *A. platensis*	1.4×10^{-3} and 7.2×10^{-3} g/mL, respectively	L-DOPA

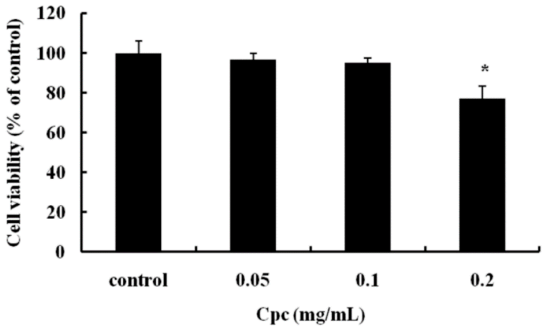

Figure 5. Effect of C-phycocyanin (Cpc) on B16F10 murine melanoma cell viability. The asterisk (*) indicates a significant difference from control group (*, $p < 0.05$). Published by Ref. [35].

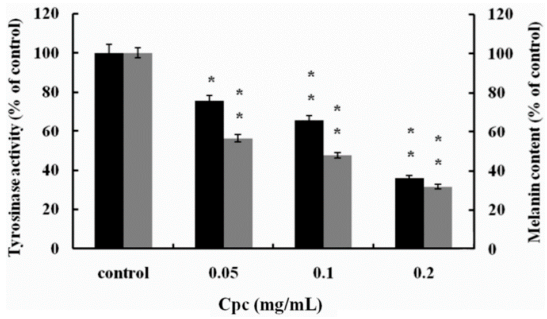

Figure 6. Effect of C-phycocyanin (Cpc) on tyrosinase activity (black) and melanin content (grey). The asterisk (*) has been used to denote a significant difference from control group (*, $p < 0.05$; **, $p < 0.01$). Published by Ref. [35].

2.2. Wound Healing

Skin wound is a disruption of intact tissue, which leads to a loss in functional and anatomic continuity. Environmental conditions, accidents but also skin issues, like dryness and dermatitis, might be some of the trigger factors. Wound healing is, instead, a complex process involving inflammatory system, synthesis of structural proteins, migration and proliferation of both parenchymal and connective tissue cells. Full recovery is complex and, sometimes, chronic diseases or bacterial infections may further undermine the healing process.

In 2011, *Spirulina* was investigated for its effectiveness in wound healing, due to its flavonoids and triterpenoids, which act as astringent and antimicrobial agents [37]. The *Spirulina* wound healing effect of dry extracts, obtained in petroleum ether, chloroform and methanol was tested on rats and monitored for 16 days. Specifically, the wound contraction—as the percentage reduction in wound area—and its closure time were controlled. A significant improvement in the wound healing activity was noticed with the three extracts aforementioned. The best result was obtained in the ointment with *Spirulina* petroleum ether-based extract at 10% *w*/*w*. In 2013, Gur et al. studied the impact of the crude *Spirulina* extract and the phycocyanin isolated from the crude *Spirulina* extract on cultures of human keratinocyte, by using in vitro and in vivo models of wound healing [38]. They observed that *Spirulina* extract showed the best growth stimulation at 33.5 µg/mL dose of treatment, which declared a cell activity ranging from 100% to 270% after 72 h. Cell viability has also improved with phycocyanin and it was measured, even up to 213%. Cell activity and proliferation difference between *Spirulina* extract and phycocyanin were noted not to be important ($p > 0.05$) at the range of doses (33.5–0.0335 µg/mL) examined. It was also discovered that 1.25% of C-phycocyanin has a superior effect on the in vivo efficiency, compared to other preparations with *Spirulina* extract, on the 7th day. Overall, the proliferation and growth stimulation activities of *Spirulina* extract seem to be directly connected to the presence of both phycocyanin and carotenoids, which synergistically

contribute to the wound healing and tissue regeneration. A few years later, Gunes et al. developed natural skin creams enriched with bioactive *S. platensis* extract, and studied its wound healing, genotoxic and immunoreactive effects in vitro to evaluate the potential use of *Spirulina* in biomedical and pharmaceutical sector [39]. The in vitro cell culture tests demonstrated that *Spirulina* extracts showed significant effects on fibroblast cell proliferation and migration. Fibroblasts are mesenchymal cells that enable tissue preservation by secreting extracellular matrix, and they are in charge of the inflammation and scar formation, during the wound healing process. A skin-care cream, which incorporates 1.125% of *Spirulina* extract, presented the biggest proliferative effect on skin cells with an increase of Type 1 collagen immunoreactivity. The micronucleus assay, which shows DNA damage, demonstrated that *Spirulina* based cream had no genotoxic effect on human peripheral blood cells. Additionally, *Spirulina platensis* also revealed a strong antioxidant property, due to its superoxide dismutase (SOD) activity with values up to 8.0 U/mL of SOD in *Spirulina* extract. All these features lead the blue-green microalga to be suitable for biomedical and cosmetic applications, particularly for wound dressings as well as sunburns, erythema and photoaging.

More recently a Korean research team absorbed *Spirulina* in an engineered-tissue, to evaluate its wound healing potential [40,41]. They selected nanofibers of polycaprolactone (PCL) as a supporting material suitable for tissue regeneration. PCL, which is an FDA-approved polymer, is also biocompatible, biodegradable and known to favor the oxygen absorptivity, the drainage capability and the water evaporative control, which are critical factors for the skin regeneration. In a study, *Spirulina* aqueous extract was absorbed on the nanomaterial and the wound regeneration was evaluated using an in vivo wound model [40]. In this specific regard and from a bioethical view, we contest such use of an animal for analysis in the cosmetic field and we strongly recommend the stakeholders to find other cruelty free alternatives to perform efficiency tests. In general, *Spirulina*-PCL helped to regenerate wounds and enhanced skin regeneration, by improving the antioxidant mechanism against the reactive oxygen species (ROS) of fibroblast under oxidative stress (Figure 7). Nevertheless, the developed nanofibers had a restricted capability to moisturize wounded skin because of the hydrophobicity of PCL.

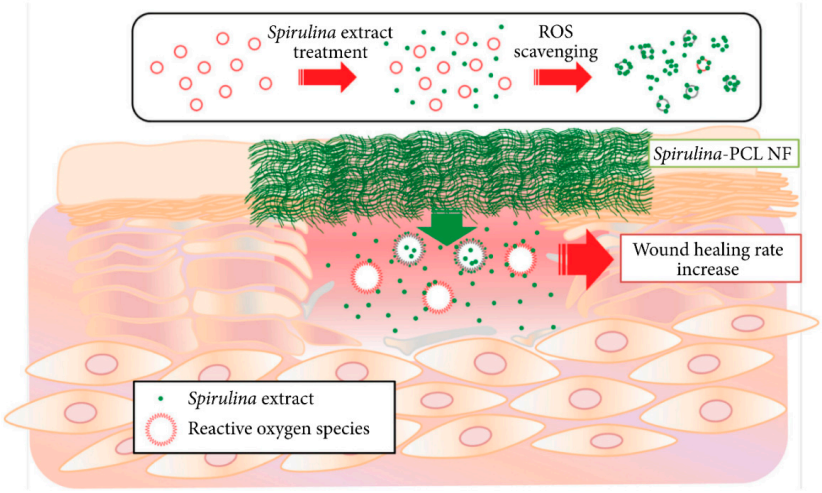

Figure 7. Schematic design of the *Spirulina*-PCL nanofibers application to cutaneous wound. Published by Ref. [40].

To resolve the issue of the hydrophobic behavior of *Spirulina*-PCL nanofibers, the alginate was added in a following step due to its high hydrophilicity and absorbing capability [41]. Alginate (Alg) has a hydrophilic structure that consists of alpha-L-guluronic acid and beta-D-mannuronic acid, which can accommodate large amounts of water. The study revealed that *Spirulina* extract-alginate saturated polycaprolactone

nanofibers (*Spirulina*-Alg/PCL) effectively accelerated the tissue regeneration in a rat model (3.7% *w*/*v* of *Spirulina* extract). When this patch was applied to the animal's wounds, the extracellular matrices were rearranged faster than those treated with the simple patch support without *Spirulina*. In comparison to the earlier developed *Spirulina*-PCL nanofibers, alginate improved the moisture preservation and adhesiveness of the *Spirulina*-Alg/PCL nanofibers, in addition it accelerated the regeneration of full-thickness wounded skin in the rat model.

2.3. Antiacne

Acne is an epidermis disorder correlated to a sebum hypersecretion in deformed follicles, which implies inflammation and comedones formation. The anaerobic *Cutibacterium* acnes (also known as Propionibacteriumacnes) plays a role in the inflammation process because it hyperproliferates in the sebaceous lipid environment and produces reactive oxygen species (ROS) and proinflammatory compounds. This cytokine cascade also induces the follicular wall rupture of sebaceous glands and a consequently variation in the sebum composition. Acneic skins are low in linoleic acid and, therefore, their barrier skin function is compromised. Such a lesion pathway may also help the colonization of other bacteria like the *Staphylococcus epidermis* (*S. epidermis*). Indeed, although this *Staphylococcus* is a commensal skin microbiome bacterium, it was found in acne as well [55].

Acne disorder affects several people, mostly during adolescence, and it may lead to a lack of the self-confidence, resulting in body shame. Since acne-inducing bacteria shown side effects and an increasing resistance towards the synthetic drugs like tetracycmidrule, many alternative approaches have been explored in the last decades. Among them, the topical applications of cosmetic formulas containing botanicals as safer active ingredients are the more suitable [56].

Currently, the cosmetic market is strongly interested in formulating antiacne products with a special focus on natural active ingredients, in addition to topical medication [57]. With this purpose, in 2018 Nihal et al. developed a topical antiacne formulation using *Spirulina* extract rich in phycocyanin protein [42]. The latter protein, as already mentioned, is known to be responsible for most of the natural *Spirulina* benefits. The phycocyanin was successfully extracted from the alga by using sonication and the cold-maceration process and then it was purified by the dialysis method. The authors thus studied its antimicrobial and anti-inflammatory activities. In particular, the antioxidant activity was found to be dependent on phycocyanin concentration in the range between 0.05 and 0.3 $mg \cdot mL^{-1}$.

The antimicrobial property was evaluated, both in an oily-based (FA) and water-based (FB) formula, against *Cutibacterium acnes* (*C. acnes*) and *S. epidermis*, by evaluating the minimal inhibitory concentration (MIC) and the dimension of the zone of inhibition (Table 5). The results shown that the water-based formulation was more effective in inhibiting bacteria proliferation than the oily-based one and confirmed the *Spirulina* antiacne property.

More recently, Setyaningsih's research team further explored the antibacterial activity of a *Spirulina*-based face mask [43]. *Spirulina* used in this study was specifically grown to increase the amount of phycocyanins, flavonoids, alkaloids and phenolic compounds, to enhance his anti-inflammatory and antibacterial properties. As reported in Table 6, the formula composition includes polyvinyl alcohol and HPMC as polymers, and both extract of *Spirulina platensis* and its native biomass as active ingredients. During the study, three masks were formulated: the first one with *Spirulina*, the second one free from any active ingredients and the third one with clindamycin. The latter is a common antimicrobial topic drug and its antibacterial activity against *C. acnes* was evaluated in vitro. While the free-*Spirulina* face mask did not affect the bacteria proliferation, a similar inhibition behavior was observed with the alga extract and the synthetic antibacterial drug. Indeed, although the concentration of active ingredients incubated per well was different, the zone of inhibition was comparable: 10 ± 0.4 mm for the *Spirulina* mask and 12 ± 1.1 mm for the clindamycin one.

Table 5. Composition, characteristic and activity of anti-acne formulations. Published by Ref. [42].

Parameters	Oily Formula—(FA)	Water Formula—(FB)
Ingredients	Paraffin hard (5%) Wool fat (10%) Cetostearyl alcohol (10%) White soft paraffin (50%) Liquid paraffin (15%) *Spirulina* extract (10%)	PEG400 (12%) PEG4000 (18%) Stearyl alcohol (28%) Glycerine (17%) Water (q.s.) *Spirulina* extract (10%)
Explanation	Color-intense blue Odor-waxy	Color-intense blue Odor-odorless
Uniformity of weight	Comply with the standard	Comply with the standard
Globule diameter	5.29 mm	5.44 mm
pH	6.1 ± 0.06	6.8 ± 0.09
Loss on drying	35% *w*/*w*	47% *w*/*w*
Consistency	Good	Good
Viscosity	198 ± 0.4 cps	175 ± 0.2 cps
Spreadability	8.1 ± 0.11 g·cm/s	8.6 ± 0.12 g·cm/s
Diameter of zone of inhibition (mm)	23.4 ± 1.0 (*P. acne*) 21.3 ± 1.4 (*S. epidermis*)	26.1 ± 1.2 (*P. acne*) 24.6 ± 1.6 (*S. epidermis*)
MIC	1.6 ± 0.4 mg/mL (*P. acne*) 2.1 ± 0.6 mg/mL (*S. epidermis*)	1.5 ± 0.1 mg/mL (*P. acne*) 1.8 ± 0.2 mg/mL (*S. epidermis*)

Table 6. Composition, characteristic and activity of antiacne face mask. Published by Ref. [43].

Parameters	Face Mask
Ingredients	Methylparaben (0.01 g) HPMC (0.2 g) Glycerine (0.25 g) PVA (0.6 g) Distilled water (100 g) Extract of *S. platensis* (0.25 g) Biomass of *S. platensis* (0.75 g)
Organoleptic	color: Green consistency: Semisolid
Viscosity	7306.7 ± 9.2 cP
pH	6
Spreadability	1.1 cm
Homogeneity	homogenous
Odor	Specific *Spirulina*
Antibacterial activity	Positive inhibit *C. acnes*
Diameter of zone of inhibition (mm)	10 ± 0.4 0 a 12 ± 1.1 b

a: Face Mask without *Spirulina*. b: Face Mask without *Spirulina* and with clindamycin.

Therefore, *Spirulina* is shown to be a promising natural cosmetic ingredient with high antibacterial activity against acne pathogens.

3. *Spirulina* Benchmark

Spirulina is the biggest cultivated microalga in the world and it gives rise to over 30% of the worldwide microalgal biomass production [58]. *Spirulina* is cropped in several countries,

including various African States, Argentina, Burma, Chile, China, Cuba, India, Israel, Japan, Mexico, Myanmar, Pakistan, Thailand, the USA and Vietnam. Japan, the USA and Europe are the main importers of *Spirulina* powder. As a whole, over 128,000 tons of *Spirulina* was internationally consumed in 2016, and its revenues reached US$ 718.7 Mn [59]. In the upcoming years the global *Spirulina* market is expected to grow since its use is rising enormously across the world. The reason behind the overall *Spirulina* market growth might be to increase awareness about natural food products all over the world, to prefer plant protein sources and to follow the regulation on synthetic colors. Therefore, the market will be estimated at almost US$ 2000 Mn by 2026, with a global *Spirulina* consumption of more than 321,000 tons [59].

As for the emerging beauty industry, many *Spirulina* extracts/powders and *Spirulina*-based products are available on the market, and claim a wide variety of skin-benefits. Furthermore, it is likely that diversity, quality and topical type of applications of *Spirulina* will rapidly expand in the following years.

Considering *Spirulina* as an active ingredient in the cosmetic industry, dry or liquid concentrated extracts are generally preferred—but not exclusive—over the raw powder of the alga, due to final products functional and esthetical reasons. There is evidence that both properties and behaviors of the *Spirulina* extracts are strongly influenced by the extraction procedure and by the chosen solvent. Selected commercial suppliers of *Spirulina* extracts/powders are reported in Table 7.

Table 7. Selected commercial *Spirulina* extracts/powders for skin care applications.

Company	Type	Key Benefits/Claims	Ref.
Bio-Botanica (USA)	Hydroglyceric liquid *Spirulina platensis* extract	Skin conditioning benefits	[60]
Sensient Cosmetic Technologies (France)	Dry extract of *Spirulina platensis* supported in dextrin, sodium citrate and sodium phosphate	Antioxidant potential with radiant skin effect and revitalizing benefits	[61]
SEPPIC (France)	Water-blue algae extract	Antiradical, anti-inflammatory, photoprotective and cells renewal effects	[62]
Phenbiox (Italy)	Water *Spirulina platensis* extract, stabilized by citric acid, sodium benzoate and potassium sorbate	Antioxidant potential	[63]

Bio-Botanica (USA) produces a liquid blend of *Spirulina platensis* extract in glycerin and water. This extract offers skin conditioning benefits and can be used in a variety of personal care formulations [60]. NatPure® APX, developed by Sensient Cosmetic Technologies (Saint-Ouen-l'Aumône, France-headquarter), is instead a dry extract of *Spirulina platensis* supported in dextrin, sodium citrate and sodium phosphate, and has antioxidant potential with a radiant skin effect and revitalizing benefits [61]. Spiruline AP® is a water-soluble blue algae extract, supplied by SEPPIC (France-headquarter). This brand claims that its extract has excellent antiradical, anti-inflammatory, photoprotective and cells renewal effects. It may be used as an active ingredient for antiaging skin products [62]. In Italy, a water *Spirulina platensis* extract—stabilized by citric acid, sodium benzoate and potassium sorbate—is supplied by Phenbiox [63].

The fact that more *Spirulina* extracts/raw material for cosmetics are currently on the market further demonstrates that the interest of the sector in this alga is rising. Some relevant commercial examples of *Spirulina*-based cosmetic products are listed in Table 8.

Looking at the current beauty products available in the market, *Spirulina*—mainly *S. platensis* and *S. maxima*—is used either as a powder, generally in cheaper products, or as a phycocyanin-rich blue extract, particularly in the luxury market. Overall, most of the cosmetics available on the market claim a large range of *Spirulina* benefits, including antiaging, revitalizing, remineralizing, moisturizing, protecting alongside cleansing and shining action, for both hair and skin. Furthermore, while some of the claims like "mattifying" or "purifying" are probably due to the whole blend of the ingredients, the moisturizing and illuminating effects may be directly attributed to the *Spirulina* action instead.

Table 8. *Spirulina* benchmark on skin care products.

Cosmetic Product	INCI *Spirulina*	Key Benefits/Claims	Company	Product's Photo	Ref.
KELLY powder mask	*S. platensis* powder	Peel-off for dry skin	PuroBIO cosmetics (Bari, Italy)		[64]
Spirulina Santè Methode face line	*S. maxima* extract	Antiaging serum, balancing cleansing milk, restorative tonic, antioxidant	Santè Naturels (Milano, Italy)		[65]
Face, hand, milk cream, SPF 50 +/30/15, after sun, hair oil, tanning oil	*S. maxima* extract	Regenerating, moisturizing, antiaging properties	DONI DEL MARE -HAZE COSMETICS (Milano, uniPV, Italy)		[66]
Crème spiruline liftante rides	*S. maxima* extract	Wrinkle-lifting and anti-aging with progressive action	ELLA BACHÈ Nutridermologie—(Paris, France)		[67]
Face cream, face serum	*S. maxima* extract	Immediate brightness effect. The skin is more toned, and smooth, visibly nourished and revitalized	Institut ESTHEDERM—(Paris, France)		[68]
Mattifying, purifying clay mask	*S. platensis* powder	Effective against blemishes. It minimizes the appearance of pores, removes excess sebum and fights congestion, without drying the skin out	REN Skin care—(UK)		[69]
Marin Complex Deep Restorative Cream	*S. maxima* extract	Restore and rejuvenate without risk of irritation	Zelens—(UK)		[70]

Table 8. *Cont.*

Cosmetic Product	INCI *Spirulina*	Key Benefits/Claims	Company	Product's Photo	Ref.
Powercell Skinmunity Emulsion	*S. platensis* extract	Stimulates revitalization, smoothes wrinkles, intensely hydrates the skin	HELENA RUBINSTEIN—(Australia)		[71]
Face cream, face serum	*S. platensis* extract	Nourishing, revitalizing, moisturizing, antioxidant, detox	SUKIN SKINCARE—(Australia)		[72]

4. Conclusions and Future Perspectives

As herein reviewed, *Spirulina* is a potential bioactive ingredient, for developing effective and safe cosmetics. In recent years the skin-care benefits of *Spirulina* products have been investigated by both academics and company researchers. *Spirulina* contains a set of synergistically acting components, such as peptides, polyunsaturated fatty acids, vitamins, minerals and antioxidant phytonutrients, which provide a full healthy action to the formulation.

Several *Spirulina* extracts/powders and alga-based skin care products are available on the market and this field is expected to further grow in the following years. As a formulating ingredient, *Spirulina*—*S. platensis* or *S. maxima*, as the major genes—is used as a dry or liquid concentrated phycocyanin-rich blue extract in the luxury products, or as raw powder in the cheaper formulations. A number of topical *Spirulina*-based formulations claim a large range of behaviors, including antioxidant, revitalizing, remineralizing, moisturizing, protecting alongside cleansing and shining action, for both hair and skin. Therefore, these products might be topically used like a booster of hydration, antiwrinkles, antiaging and antiacne agents. At the same time, *Spirulina* might be incorporated in skin-care formulations to promote healthy sunscreen protection, to treat skin pigmentation disorders and to achieve wound healing benefits.

Despite the recent progress, the topic should be further investigated: other skin benefits, actions or applications might occur and the role of the phytocomplex and its action pathways need a further exploration. In addition, the human health risks (skin-toxicity, allergies, etc.) should also be studied in greater depth to refine cosmetic spirulina-based products in the long-term.

For instance, the antibacterial activity of *Spirulina* might suggest to study how this alga affects the skin microbiome in deeper details. Taking care of skin commensal bacteria, thus avoiding skin dysbiosis, is an emerging topic in both cosmetic and dermatological fields. Skin dysbiosis is correlated to the incidence rate of skin disease, due to the hyperproliferation of some bacteria that normally colonize hair follicles and glands [73]. To conclude, there is a need to pursue research about *Spirulina* antimicrobial skin activity to further support the use of this microalga for the treatment of skin dysbiosis.

Author Contributions: Conceptualization, I.R., G.N.N., S.Z. and E.A.; writing—original draft preparation, I.R. and E.A.; writing—review and editing, I.R. and E.A.; project administration, E.A., W.B. and S.Z.; funding acquisition, W.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Labomar S.p.a.

Acknowledgments: The author would like to thank Alessia Marcato for her help in editing the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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