Applying Red Seaweed-Derived Compounds in Acne Vulgaris Care

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Acne vulgaris (AV) is a chronic skin disease of the pilosebaceous unit affecting both adolescents and adults. Its pathophysiology includes processes of inflammation, increased keratinization, sebum production, hormonal dysregulation, and bacterial Cutibacterium acnes proliferation. Common AV has been treated with antibiotics since the 1960s, but strain resistance has emerged and is of paramount concern. Macroalgae are known producers of substances with bioactive properties, including anti-viral, antibacterial, antioxidant, and anti-inflammatory properties, among several others. In particular, red algae are rich in bioactive compounds such as polysaccharides, phenolic compounds, lipids, sterols, alkaloids, and terpenoids, conferring them antioxidant, antimicrobial, and anti-inflammatory activities, among others. Thus, the exploration of compounds from marine resources can be an appealing approach to discover new treatment options against AV.

Keywords: antibacterial ; Cutibacterium acnes ; inflammation ; Rhodophyta ; seaweed extracts

1. Pathophysiological Targets for the Management of Acne Vulgaris

A thorough literature analysis revealed that the general pathogenesis of AV is well established and amply described, but there is not yet a consensus regarding the whole pathophysiology, mechanisms, and order of events that lead to AV lesions. More recent reviews and research articles focus on the role of immune and inflammatory responses, bacterial dysbiosis, and the interplay between all of these factors [1][2][3], as opposed to older studies in which *Cutibacterium acnes*, sebum, and hormones were usually the main characters [4][5][6]. There have been several advances in the understanding of the role of each aspect in the cascade of events in AV, and the dominant factors and triggers that are interconnected in a highly complex manner are the following: (a) hormonal influence, mostly due to excessive androgen production and growth factors; (b) hyperseborrhea, triggered by the hormonal stimulation of the sebaceous glands; (c) comedogenesis, hyperkeratinization and the formation of comedones due to excessive sebum accumulation and abnormal epithelial desquamation; (d) microbial proliferation and dysbiosis, especially involving *C. acnes*, owing to a lipid-rich and anaerobic environment in the pilosebaceous unit; and (e) immune response and inflammation, as a consequence of pro-inflammatory molecules and activated pathways induced by the bacterium, hormonal disequilibrium, changes in sebum composition, and cytokine secreted by keratinocyte hyperproliferation and keratinization [4][7][8][2][3][5][9][10][11][12][13][14][15] (**Figure 1**). Acne-related factors are detailed below.

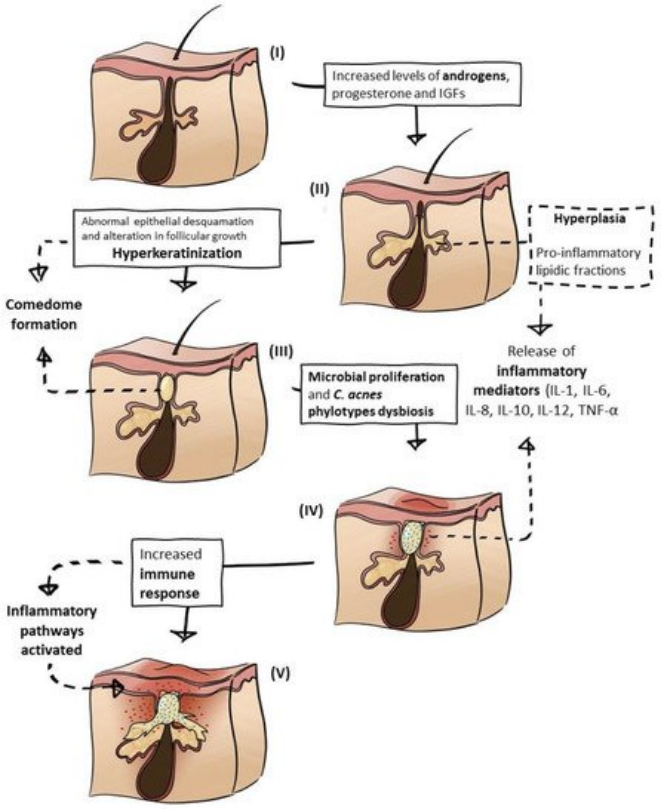

Figure 1. Acne vulgaris pathophysiology process schematics. (I) Pilosebaceous unit in normal conditions; (II) hormonal imbalance triggers seborrhea; (III) comedogenesis; (IV) microbial proliferation and inflammatory mediators' release; (V) immune response followed by inflammation. The arrows represent the interplay between triggers.

1.1. Hormonal Influence

Endogenous hormones—such as androgens, estrogen, progesterone, and insulin-like growth factors (IGFs), among others—play a critical role in the acne pathogenesis flow. Individuals that suffer from acne usually have high levels of androgens, progesterone, insulin, and IGFs, and, on the contrary, low levels of estrogen [8][16][17][18].

Androgens are the most important hormones controlling sebaceous gland activity, because they affect the sebaceous gland enlargement, sebocyte proliferation, and lipid metabolism, thus playing a crucial role in acne pathogenesis [19]. Free androgens are produced by the adrenal gland and gonads, but the most involved in acne are the androgens locally produced in the sebaceous glands. Inside the sebaceous glands is dehydroepiandrosterone sulphate (DHEAS), an adrenal precursor hormone that, by the action of steroid sulfatase, is converted into dehydroepiandrosterone (DHEA). The steroid metabolizing enzyme pathway expressed in the sebaceous glands seems to be initiated by 3β-hydroxysteroid dehydrogenase, which converts DHEA into androstenedione, then 17β-hydroxysteroid dehydrogenase converts androstenedione into testosterone, and finally, 5α-reductase converts testosterone into 5α-dihydrotestosterone (5α-DHT). DHT is three to ten times more potent than testosterone [20] when it comes to androgen receptors interaction, wherein the activity of 5α-reductase has a tremendous impact because its increased activity leads to the bigger size proportions of sebaceous glands. Furthermore, DHT increases lipidic production, not only by increasing the proliferation of sebocytes but also through the magnification of the mRNA levels of proteins involved in cholesterol, fatty acid, and triglyceride synthesis [8][21][22].

The growth hormone (GH) is secreted by the pituitary gland and can be found in sebaceous glands and hair follicles [23]. Diseases involving GH excess, such as acromegaly, are frequently associated with sebum overproduction, leading to acne development [21]. Furthermore, GH stimulates the production of IGFs, and, in particular, women evidencing acne lesions have higher levels of IGF-1, compared with androgens, sebaceous gland growth, and lipogenesis [19][24][25]. Naturally, IGF-1 levels tend to rise during puberty by the action of increased GH secretion, the same as for the levels of testosterone [26]. Features directly related to acne include the IGF-1 capacity to stimulate adrenal synthesis, resulting in increased androgen levels; IGF-1 also induces the proliferation of sebocytes; receptors of IGF-1 are expressed in sebaceous glands and hair follicles; IGF-1 mediates lipogenesis by the influence on the increasing expression of sterol regulatory element-binding proteins (SREBPs) transcription factor, which regulates the geneses involved in lipidic biosynthesis, and also by activating MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) pathways; IGF-1 is able to stimulate 5α-reductase, sebocyte proliferation, and androgen receptor signal transduction [8][21].

1.2. Seborrhoea

The typical regions of the skin that are affected by acne are the face and upper torso, as they are densely populated by sebaceous glands [4]. Those glands are cutaneous appendages that secrete an oily substance (sebum) within hair follicles through sebaceous ducts [27]. Sebum is a mixture of lipids—namely a combination of wax esters, triglycerides, steroid esters, and squalene [28]—protecting the skin against friction due to natural lubrication; by acting as a barrier, it retains water molecules helping to keep the skin moist and healthy [19]. However, hyperseborrhea, excessive sebum production associated with overactive sebaceous glands, is a major etiopathogenetic factor directly associated with AV, because it contributes to all three mechanisms described below—comedogenesis, microbial proliferation, and inflammation—whereas the disease is not seen in the absence of sebum [7].

It is possible that not only the amount of sebum is a key factor in acne; the alteration of sebum composition may also have a determinant role. For instance, lipidic fractions of sebum are proinflammatory, contributing to the inflammatory cell and tissue process, ultimately resulting in the development of acne lesions [28][29]. For example, squalene peroxide induces inflammatory responses in keratinocytes by increasing IL-6 production and lipoxygenase (5-LOX) activation [30]. Moreover, modifications in the sebum ratio of saturated/unsaturated fatty acid are triggers of innate immunity response and follicular inflammation, being a main character in early inflammatory pathways of acne [24][28]. Additionally, changes in the oxidant/antioxidant ratio also represent a cause for acne's initial development [9]. Further acne-related lipid-enzymes are liver X receptor-α (LXR-α) and cyclooxygenase 2 (COX-2), which regulate inflammation and lipid synthesis. LXR-α is expressed in sebaceous glands, sweat glands, and hair follicles, and controls the transcription of the genes involved in fatty acid and lipid synthesis. During inflammatory events, COX2 release is stimulated by cytokines that were activated by NF-κB [31].

1.3. Comedogenesis

Increased androgen production, the accumulation of sebum, and the adhesiveness of keratinocytes lead to follicle blockage and the occlusion of the pilosebaceous ducts, resulting in the formation of microcomedones that are the primary type of acne lesions [32][33]. These hard structures, microcomedones, are formed within the hair follicle, more precisely in the infundibulum, and are connected with the sebaceous gland via a keratinized duct. The set of the hair follicle and sebaceous gland constitutes the pilosebaceous unit [27]. As a pleomorphic disorder of the pilosebaceous unit, acne microcomedones evolve into comedones owing to sebum and keratin accumulation accompanied by follicle expansion [34], and these can be closed (white heads) or open (blackheads), but they may progress to inflammatory lesions, such as pustules, papules, cysts, and nodules [5], eventually leaving scars [8].

Keratinocyte IL-1 secretion is another triggering step in the comedogenesis process, mostly as a consequence of *C. acnes*-mediated Toll-like receptor (TLR) activation. IL-1 also contributes to sebocytes hypercornification. Comedone formation is a result of a combination of some factors, such as the response to androgen production; sebum alteration, production, and oxidation; *C. acnes* proliferation, and recruitment of cytokines to the pilosebaceous unit [32].

1.4. Inflammatory Response

The AV pathophysiological cascade ends with the inflammatory process, but, at the same time, it also follows the whole process from the beginning, by activating the immune system and/or by the release of molecules that activate inflammatory pathways [35]. There are many inflammatory mediators involved, as mentioned before, e.g., proinflammatory lipids (at the hyperseborrhea process), cytokines (mostly involved by recruitment of *C. acnes*), and chemokines (stimulated by bacterial antigens). There is also the role of proinflammatory cathelicidins, peptides from macrophage lysosomes, and members of the immune system with immunomodulatory and antimicrobial functions [32].

It seems that the main factor influencing the inflammatory process is the activation of the immune system by *C. acnes*, when the bacterium overpopulates sebocytes, through TLRs and nod-like receptors (NLRs) that segregate IL-1 and other cytokines, activating inflammatory pathways [32]. Furthermore, the keratinocyte stimulated-*C. acnes* production of reactive oxygen species (ROS) induces nitric-oxide production in macrophages, contributing to the magnification of the inflammatory response [36].

2. Seaweed Extracts and Compounds to Address AV Disease

Numerous studies have identified red seaweeds as significant producers of valuable metabolites with antibacterial and anti-inflammatory activities, thus representing a potential resource in the battle against AV, a chronic disease of which the management involves the mitigation of these symptoms.

2.1. Antibacterials from Red Macroalgae

The study by Choi and co-workers [37] employed methanol solid–liquid extractions from *S. latiuscula*, resulting in an extract capable of inhibiting *C. acnes* growth. This seaweed is known to have high amounts of bromophenols, which can explain the antibacterial effect, because these compounds are known to be toxic to some bacteria [37]. The work of Barreto and Meyer (2006) aimed to isolate lanosol ethyl ether from *O. serrata*, which is a brominated phenol and a halogenated metabolite, showing high bacteriostatic and mild bactericidal activity [38]. Organobromine compounds are naturally produced by seaweeds for chemical defense and are usually found in Rhodophyta. Besides lanosol, examples include acetogenins (brominated nonterpenoid metabolites), which are mainly found in the genus *Laurencia* [39]; bromoform from *Asparagopsis taxiformis* [40]; brominated monoterpenes, also in the genus *Laurencia* [41], but also in *Plocamium cartilagineum* [39]; and indoles from *Rhodophyllis membranacea* [39]. These bromine compounds confer several bioactivities, including antimicrobial, antioxidant, anticancerogenic, and anti-diabetic activities [42], emphasizing the high value of red seaweed-derived compounds. Another example showing the antibacterial activity conferred by organobromine compounds is the study by [43], which used *Asparagopsis armata* supercritical CO_2 extractions to find an inhibition halo of 23 mm (at 10 mg·mL^{-1}) in contact with a *C. acnes* culture. Such results seem to be in accordance with a variety of cosmeceutical products which recently became available in the market that incorporate *A. armata* extracts. For instance, ASPAR'AGE™, formulated by SEPPIC (La Garenne-Colombes, France), promises a lotion with an extract containing MAAs that reduce the visible effects of age, and Asparcid P®, from Exsymol (Monaco-Ville, Monaco), claims to possess cytostimulating action and antimicrobial activity.

2.2. Extracts and Compounds from Red Macroalgae Targeting Other Mechanisms of AV

The literature search on anti-sebum compounds or extracts from Rhodophyta, even when it comes to macroalgae in general, revealed a complete absence of published studies. Despite this fact, SEPPIC (La Garenne-Colombes, France), a cosmetic company, own red seaweed-incorporating products in the market claiming to possess anti-sebum properties. The incorporation of macroalgal extracts in the skincare line product WESOURCE (SEPPIC) revealed an anti-sebum effect (34% reduction after 56 days), observed when oily skinned volunteers were tested using CONTACTICEL™ (SEPPIC, La Garenne-Colombes, France) [44], a skin-care product that contained extracts from *Acrochaetium moniliforme*, a red seaweed product under the patent WO2016162648A1. Furthermore, similar results were obtained with a brown seaweed, revealing in vivo sebum regulation—29.3% lower sebum in 23 days—providing visible mattifying effects on volunteers subjected to *Laminaria saccharina* extract [44]. Because both cosmetic products are effective in the reduction of facial sebum, using active ingredients obtained from two macroalgae, despite no scientific publications being found, at least some red and brown seaweeds may be considered to have anti-sebum properties in vivo.

Hyperlipidaemia, a condition characterized by high levels of lipids in the blood, e.g., cholesterol, was associated with patients exhibiting acne. In accordance with this, high levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) were found in the blood of both male and female subjects [45][46]. A study by Liu et al. (2017) showed the improvement of carbohydrate and lipid metabolism in rats which were hyperlipidaemia-induced by high fructose (HF) intake, when fed with a *Gelidium amansii*-supplemented diet. *Gelidium amansii* supplementation resulted in the decrease of glucose, leptin, insulin, and TNF-α blood levels [47]. Moreover, it also reduced the accumulation of hepatic lipids, namely TG and the total cholesterol (TC) content, while increasing the excretion of bile acid and faecal lipids [47]. Further studies are required to prove Rhodophyta's anti-hyperlipidaemia properties, but evidence already shows the potential of using this biomass to reduce the lipid levels in acne patients.

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