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A Review

Marine natural products as novel therapeutic approaches in Psoriasis: A comprehensive review

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Psoriasis is a chronic immune-mediated inflammatory skin condition that presents with white, patchy silvery scales with redness and inflammation. These clinical presentations arise due to the hyperproliferation of keratinocytes and modulation of cytokine pathways. The aim of the study is to assess available literature for the usage of marine biomolecules for the management of autoimmune inflammatory disorders than can be implemented for psoriasis. Conventional therapies include topical, phototherapy, targeted biologics and systemic agents which are used to control the disease. In addition, these allopathic medicines have a substantial possible risk of side effects and expected toxicity. Consequently, this provokes the demand for the development of new medications, particularly for psoriasis and other related chronic inflammatory conditions. Up to date, terrestrial natural resources have been well exploited in all standpoints of research including autoinflammatory diseases. Thus, exploring natural products from marine origin might be a distinct perspective. In many literatures, it has been proven that marine natural products have various beneficial effects like anti-inflammatory, antioxidant, immunosuppressive, and antimicrobial properties, which makes them promising treatment strategies for psoriasis management. This review deals with the critical understanding of marine sources with bioactive potential for treating psoriasis and other inflammatory illnesses.

Keywords: Anti-inflammatory activity, Antioxidant, Autoimmune disorders, Marine metabolites, Plaque psoriasis

Introduction

Autoimmune diseases represent a group of multidimensional conditions characterized by the dysregulation of immune response in which the body's immune system mistakenly attacks its own cells[1]. Among these, psoriasis is a prevalent inflammatory skin disorder that usually manifests with red, salmon-coloured scaly patches or plaques with silvery scales. These lesions are well-demarcated and significantly cause pain, swelling, and discomfort in area of the skin, elbow, joints, nails, and scalp. In psoriasis, autoantibodies target keratinocytes, leading to hyperproliferation and cytokine modulation. The primary immune cells involved in psoriasis are T-cells, which disrupt the epithelial immune microenvironment of the skin. Despite affecting the skin, psoriasis leads to systemic inflammation, which is associated with co-morbid complications like vascular inflammation, an increased risk of cardiovascular events, depression, and other related autoinflammatory diseases. About more than 125 million people worldwide are affected by psoriasis, and over 30% of these patients have a greater risk of developing complications such as psoriatic arthritis[2].

The onset of psoriasis is highly associated with the genetic susceptibility gene HLA-C*06. Other specific alterations in keratinocytes occur due to epigenetic factors, including genetic and environmental triggers. Based on their clinical features, psoriasis is sub-categorized into chronic plaque psoriasis or psoriatic vulgaris, erythroderma, flexural, guttate, generalized pustular psoriasis, palmoplantar pustulosis, and psoriatic nail disease[3]. In addition to the physical symptoms faced by the patient, psoriasis significantly affects the mental health, social disability, and overall quality of life of the individual. Moreover, it can influence various aspects of a patient's life, such as career, relationships, work, financial burden, social and psychological health, *etc*.

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Current treatments for psoriasis remain limited due to their multifaceted pathophysiological mechanisms, and there is no compromising therapy at all[4]. Conventional drugs used to control psoriasis have a higher risk of infections, myelosuppression, and hepatoxicity. This highlights the need for novel therapeutic approaches that target underlying disease pathophysiology with fewer side-effects.

Recent literature states that marine-derived active compounds are substantially more abundant than terrestrial resources[5]. It is because 70 percent of the earth is covered by ocean, which is the shelter to several unexplored biodiversity that constitutes about 80 percent of all flora and fauna. Marine organisms such as algae, sponges, invertebrate phyla (tunicates), coelenterates (soft corals and sea whips), echinoderms (sea cucumbers and starfish), and bryozoans have evolved and undergone various environmental stress to produce secondary metabolites such as lipids, nucleic acids, peptides, and polysaccharides, which provide unique and distinctive structures[6]. These substances, result in a wide range of biochemical properties comprising anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory benefits, which can also be potential anti-psoriatic agents[7]. Thus, this review explores the importance of marine natural products as a potential novel treatment approach for psoriasis, based on existing research.

Pathophysiology of psoriasis

The main hallmark in the pathophysiology of psoriasis is hyperproliferation of keratinocytes and the involvement of various immune mechanisms. The skin is generally made up of two essential layers; superficial epidermis, and the deeper dermis, which constitutes of epithelial tissues and collagenic connective tissues. The skin also contains nerve endings, skin appendages like sebaceous and sudoriferous glands, and the tiny vasculatures[8]. Among these, keratinocytes play an indispensable role in the pathogenesis of psoriasis. It comprises of multiple layers called stratum basale, which is the deepest layer that consists of intermediate keratin filaments and proliferating keratinocytes. The successive layers that overlie the stratum basale are the stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum, where keratinocytes differentiate continuously to form corneocytes. Besides non-immune cells, keratinocytes are also composed of immune cells such as antigen-presenting cells, Langerhans cells, mast cells and skin-associated lymphoid tissue (SALT)[4].

When exposed to endogenous and exogenous triggers, as mentioned in (Table 1), abrupt modifications in intracellular signalling and extracellular cytokines arise, which initiates inflammatory signalling cascade. It also initiates both first-line defense mechanisms and cell-mediated adaptive immunity followed by the release of self-nucleotides and cathelicidin antimicrobial peptides (CAMP) from damaged cells. Subsequently, antigen-presenting cells such as toll-like receptors activate plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs), which further activates clonal expansion[8]. Inflammatory cytokines are released via activation of T-cells in nearby lymph nodes and migration of CD8+ T cells to class 1 major histocompatibility complex (MHC) on keratinocytes and melanocytes, thus stimulating keratinocyte proliferation. Pro-inflammatory and inflammatory mediators including interferon-α (IFNα), interferon-β (IFNβ), tumor necrosis factor (TNF), IL-12 and IL-23 further promotes activation of T helper cells like T_H1, T_H17 and T_H22 cells that stimulates IL-1, IL-17 and IL-22 along additional cytokines (IL-1, IL-8, IL-12, IL-18, IL-20, IL-24, IL-15, IL-17, IL-19, IL-23, TNF-α and IFN-γ) and chemokines (CXCL 9, CXCL 10, and CXCL 11) and foster IL-1 modulates T_H17 to release IL-23. Transcriptional intracellular pathways like NF-κB and JAK/STAT are upregulated. Clinical presentations including acanthosis, hyperplasia and parakeratosis are initiated. To recruit additional inflammatory cells, Vascular endothelial growth factor (VEGF) receptors express more and recruit adhesion molecules which induce vasodilation and angiogenesis. These changes are ancillary to psoriatic skin lesions, developing Auspitz sign, rete ridges, and micro abscess of Munro[9].

Recently, certain studies have stated that an imbalance of sphingolipid metabolism, which includes ceramides and sphingosine, has the potential to trigger psoriasis. Catabolism of glycosphingolipids and sphingomyelin gives rise to ceramides that have antiproliferative and apoptotic effects. Ceramides are crucial components of the stratum corneum and thus any alterations to their composition might lead to increased susceptibility to environmental triggers and inflammatory cascade that compromises the skin barrier. In addition, dysbiosis of the skin microbiome which includes changes in microbial diversity and composition is also implicated in the pathogenesis of the disease. The key role lies in epidermal barrier dysfunction, where they can trigger many signalling pathways and immune cell dysregulation[10].

Table 1 — Endogenous and Exogenous triggers that induce psoriasis

Types of triggers	Example of triggers	Description
Endogenous	Genetic predisposition	Immune-related genes particularly HLA-Cw6 predispose immune dysfunction and triggers epithelial immune microenvironment in psoriasis
	Oxidative stress	Often correlated with other exogenous triggers like smoking, environmental hazards, UV radiation *etc*., that damages the skin barrier and ROS balancing capacity and activates pro-inflammatory cytokines.
	DNA mutations	Oxidative stress also leads to mutations in DNA sequences and cause damage; associated gene in psoriasis HLA-C*6 allele located in chromosome 6 of MHC gets affected and enhance autoimmune response.
	Protein Oxidation	Typically affects the amino acids in DNA, imbalances the production of antioxidant defense process and regulatory molecules of skin cell turnover involved in various cellular metabolic process in keratinocytes.
	Lipid peroxidation	Plays a key role in oxidative stress as lipids involves in protecting skin barrier, disruption leads to oxidative stress, dysregulated immune system via signalling pathways and causes abnormal keratinocyte differentiation.
Exogenous	Infections	Existing or new infections can cause psoriasis, for example in case of guttate psoriasis, streptococcal pharyngitis is the trigger, especially in children and teens.
	Smoking & Alcohol	Toxins that are produced after smoking and alcohol consumption can trigger systemic inflammation that disrupts immune system and worsens skin lesions.
	Mechanical trauma	Physical injury or wound on the skin like starches, sunburns, can provoke psoriasis at the site of injury which is called as Koebner phenomenon.
	Xenobiotics	Drugs like anti-malarials, β-adrenergic blockers, lithium, and some NSAIDS can induce psoriasis
	Environmental hazards	Climate change due to pollution, cold and dry weather with less humidity can trigger psoriasis. UV radiation is another common environmental factor that induces skin barrier damage.

*This table describes types of triggers that induce the immunopathogenesis of psoriasis at keratinocyte level

After exposure to triggers, keratinocytes release self-nucleotides that activate toll-like receptors and relevant immune cells for presenting the antigen and dendritic cells undergo clonal expansion simultaneously. This, in turn, activates T-cells to produce more cytokines and inflammatory mediators that change the composition of the epithelial barrier and immune microenvironment. Thus, the changes in the keratinocyte perspective affect its morphological features and lead to acanthosis, angiogenesis, and parakeratosis (Fig. 1).

Disease management of psoriasis

Standard treatment is based on the assessment of disease severity in individuals using the Psoriasis Area and Severity Index (PASI). Estimated Body Surface Area (BSA) would help in distinguishing mild, moderate and severe conditions. Topical therapy, including steroids, topical calcineurin inhibitors, Vitamin D analogues, keratolytics and add-on therapy, is the first-line treatment used for psoriasis after assessing the affected BSA (if < 10 %) and medical history. Disadvantages like limited penetration of the drug due to altered skin physiology in case of psoriatic skin, sensitivity, rebound effect of glucocorticoids, and skin atrophy occur. Phototherapy using narrow-band ultraviolet radiation B (NB-UVB) is suitable for monotherapy for psoriasis. For those patients who have failed to respond to NB-UVB or for those whose action is consistent with a short duration, Psoralen plus ultraviolet-A radiation (PUVA) therapy should be taken into consideration. Various alternatives are available as systemic therapy for treating psoriasis[11]. They can also be classified as non-biologics and biologics, which are used to treat moderate-severe forms of psoriasis. A brief description of drugs that are used to treat psoriasis is mentioned in (Table 2).

Marine Bio-active compounds with anti-psoriatic activity and their applications

The origin of life evolved 4 billion years ago from the oceans. They are the host of an extensive variety of biological and chemical components. Marine organisms

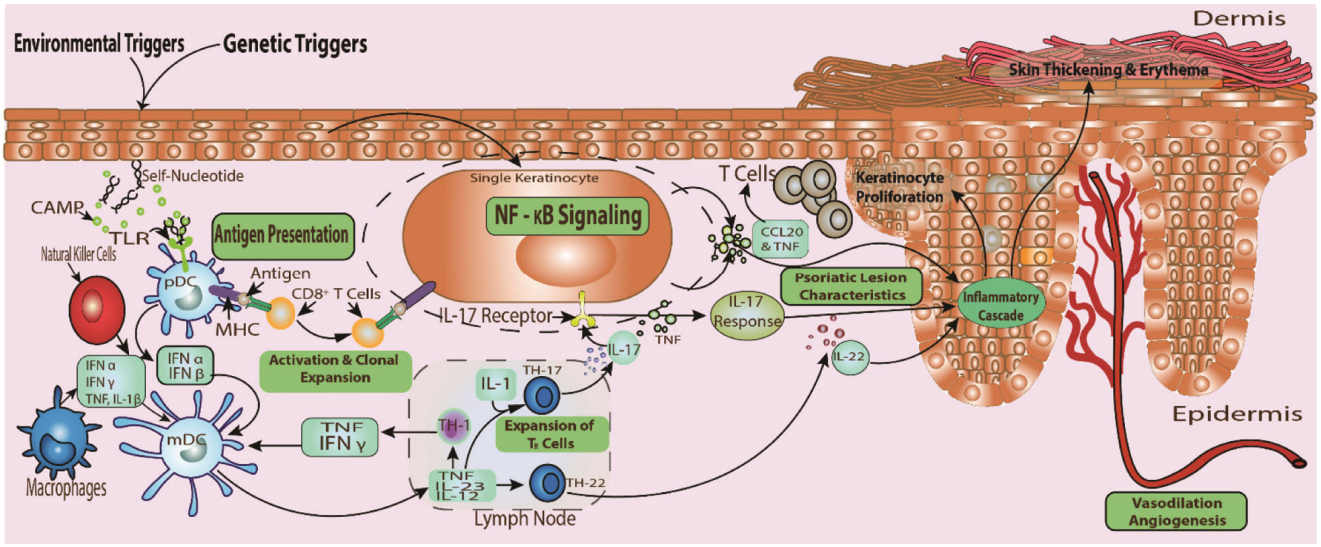

Fig 1 — Pathophysiology of psoriasis: keratinocyte perspective

Table 2 — Summary of conventional therapies used in psoriasis

Drug class	Name of the drug	Mechanism of action	References
Drugs that are administered topically			
Corticosteroids	Hydrocortisone Betamethasone Clobetasol Mometasone Triamcinolone	Suppression of histamine, phospholipase A2, prostaglandins and arachidonic acid.	12
Vitamin D analogues	Calcipotriene Calcitriol	Regulates growth and division of skin cells, activates keratinocyte differentiation and proliferation by binding to Vitamin D receptors.	
Retinoids	Tazarotene	Modulates epithelial tissue differentiation and proliferation.	13
Calcineurin inhibitors	Tacrolimus Pimecrolimus	Prevents the release of inflammatory mediators from mast cells, blocks calcineurin and inhibit T-cell activation via Th1 & Th2 suppression.	13
Miscellaneous	Coal tar Salicylic Acid Anthralin	Keratolytic, inhibits DNA synthesis and normalizes keratinocyte differentiation.	12
Phototherapy	Broadband & NB-UVB PUVA therapy	inhibits production of inflammatory cytokines and immunomodulatory properties.	11
Non-biologic systemic therapy for psoriasis			
Disease-modifying drugs OR Antimetabolites	Methotrexate	Inhibits dihydrofolate reductase which suppress the formation of thymidylate synthetase that involves in cellular replication.	14
Systemic retinoids	Acitretin	Targets retinoid receptors and inhibit the expression of pro-inflammatory mediators.	15
Immunosuppressants	Cyclosporine	Inhibits interleukin 2 and related T-lymphocytes	16
Phosphodiesterase (PDE) 4 inhibitors	Apremilast	Blocks PDE 4 and downregulating cyclic adenosine monophosphate, resulting in decreased inflammatory mediators and nitric oxide production.	15

(*Contd*.)

Table 2 — Summary of conventional therapies used in psoriasis

Drug class	Name of the drug	Mechanism of action	References
Biologics for psoriasis treatment			
TNF-α inhibitors	Infliximab Adalimumab Etanercept Certolizumab Golimumab	Inhibits TNF-α resulting in reduction of associated interleukins, leukocyte migration, activation of neutrophils and reduces epidermal thickness in plaque psoriasis.	[16]
IL-12/23 and related cytokines inhibitors	Ustekinumab Guselkumab Tildrakizumab Risankizumab	Binds to IL-12 and 23 related cytokines to block the action of natural killer cells and CD4+ T-cells, which reduces pro-inflammatory mediators.	[17]
IL-17 inhibitors	Ixekizumab Secukinumab Brodalumab Bimekizumab	Blocks IL 17 A receptors and related interleukins to decrease production of cytokines and chemokines.	[14]
Tyrosine kinase inhibitors or Janus Kinase inhibitors	Deucravacitinib	Inhibition of tyrosine-kinase 2, prevents transcriptional signalling pathways that interfere with cytokine production.	[18]

*This table summarizes the existing synthetic drugs that are used in psoriasis with their pharmacological activities in brief.

which are conditioned by the hostile and competitive oceanic environment, produce biochemical substances as adaptive strategies to withstand a variety of stresses. Various marine species include algae, invertebrates like tunicates, sponges, soft corals, sea whips, echinoderms like sea cucumbers, starfish, and bryozoans produce secondary metabolites to protect themselves from the host. These secondary metabolites usually contain biomolecules such as nucleic acids, lipids and polysaccharides that have several healing properties including anti-inflammatory, antioxidant, and anti-psoriatic activities[7]. These species can also be categorized into algae, sponges, crustaceans and coelenterates, and further subclassified as sea whips, soft corals and sea fans. The invertebrate phyla which comprise of tunicates, molluscs and echinoderms which includes sea hares, star fish, sea cucumbers and bryozoans. Marine fish species are a good source of gelatin and collagen, and these corals and crustaceans provide various groups of polysaccharides like chitosan, astaxanthin and chitin, indeed, can be used as potential pharmaceutical, nutraceutical and cosmeceutical agents[19].

Marine metabolites from sponges

In Table 3, Marine sponges have a strong capacity to withstand environmental stresses and to defend against harmful substances considering that they lack physical defense barriers and produce metabolites that are necessary for their chemical defense against predators. Many investigations are attempting to discover novel antioxidants, anti-inflammatory abilities, and other agents in which marine sponges are a rich source of biologically active compounds that are employed in pharmaceuticals. *Dysidea* sp., shows strong immunosuppressive properties by inhibiting IL-8 and the biomolecules derived from them are polyoxygenated sterols. Khaledi M. *et al.* 2020 conducted a study using *Dysidea avara,* a marine sponge, to classify different chemical compounds and to determine their efficacy in psoriasis. They concluded that *Dysidea avara* has proven to have immunosuppressive and anti-inflammatory activity against psoriasis[20]. Other compounds like manoalide, secomanoalide, *etc*., derived from the species of *Luffariella variabilis,* possesses anti-inflammatory activity by inhibition of phospholipase A_2 and antimicrobial activity by the disruption of quorum sensing, which is defined as cell-to-cell communication in bacteria that helps them to produce extracellular signalling molecules. Marine steroids are produced from sponges, which have potential activity when compared to conventional steroids. They also possess anti-inflammatory properties by suppressing the NF-κB pathways and various steps of inflammatory cascade. Solomonsterol A, an extract of *Theonella swinhoei* are pregnane X receptors (PXR) which shows steroidal action. In some cell line studies, sclerosteroids exerts inducible nitric oxide synthase (iNOS) and COX-2 pathway blockage and a spiny star *Marthasterias glacialis* has proven anti-inflammatory properties by

Table 3 — Summary of marine bioactive compounds and their pharmacological activities

Sl. No	Biological sources	Bioactive compounds/Metabolites	Pharmacological activity	References
		Marine sponges		
1	*Dysidea avara*	Avarol	Immunosuppressive/ anti-psoriatic activity & anti-inflammatory properties	20
	Luffariella variabilis	Manoalide	Inhibition of phospholipase A2	
		Secomanoalide	Antimicrobial properties by disruption of quorum-sensing	
	Theonella swinhoei	Solomonsterol A	Blocks pregnane X receptors to exert steroidal action	
	Marthasterias glacialis	Sclerosteroids	Blocks iNOS and COX-2 pathway and release of eicosanoids.	
	*Tridid*emnum *solidum*	Didemnins	Decreases production of leukocytes	
	Mycale sp.	Pateamine A	Reduces selective IL-2 production	
	Astropecten polyacanthus	Unknown	Inhibits various pro-inflammatory cytokines	
	Petrosa spongia nigra	Petrosaspongiolide M	Diminution of TNF-α and eicosanoids	
	Petrosia contignata	Contignasterol	Anti-allergic and anti-inflammatory properties by reducing IgE-mediated histamine release	
	Clathrialissosclera	Clathriol B	Modulates superoxide production and shows free-radical scavenging activity	
	Haliclona	Halipeptides	Better anti-inflammatory activity than naproxen and indomethacin	
	Petrosia	Petrocortynes	cytotoxic activity and anti-inflammatory properties by macrophages modulation, reducing TNF-α, phlogistic infiltration	
		Marine polysaccharides		
2	*Fucus vesiculosus*	Fucoidan	Shows anti-inflammatory, antioxidant and immunosuppressive activity by modulating NO production, suppression of NF-κB and various signaling pathways	23
		Fucoxanthin		
	Nostoc	Extracts from brown-green	Diminishes pro-inflammatory cytokines like	
	Phormidium	algae	TNF-α, IL-6, COX-2, iNOS and IL-1β in cell-line studies	
	Chlorella stigmatophora	Unknown	Anti-inflammatory abilities in carrageenan-induced rat paw edema studies.	
	Phaeodactylumtricornutum			
	Arthrospira platensis	Spirulina	Antioxidant properties by blocking NO production, iNOS action, synthesis of PGE2 and reduces TNF-α, IL-1 and COX-2 expression	
		Astaxanthin		
		Fucoxanthin		
		Marine Seaweeds		
3	*Arthrospira platensis Chlorella pyrenoidosa, Rhodella maculata, Porphyridium cruentum*	Phycobiliproteins	Acts as antioxidant by inhibiting the free radicals in the surface proteins	30
	Aphanizomenon flos-aquae	Klamath	Anti-inflammatory properties	
	Sargassum siliquastrum, F.	Fucoidan	reducing oxidative stress induced by UVB	
	Vesiculosis and *serratus, Ulva*	Fucoxanthin	radiation and antibacterial properties against	
	Lactuca		various strains	
	Laminariaci chori codes, Fucus evanescens Laminaria japonica	Fucoidan	Interferes with TLRs and cause activation of NF-κB and other related signaling pathways in an *in vitro* study	
	Gelidiella acerosa	Polyphenolic compound	reveals ROS scavenging activity, decrease DNA damage	
	Ishige okamurae	Diphlorethohydroxycarmalol	Decreases fine dust mediated inflammation due to air pollutants	
		Marine proteins		
4	*Cyanobacteria*	Phycobiliproteins	antioxidant properties, anticancer and immunomodulatory activity	23
	Echinoderms	Mycosporine like amino acids	Anti-photoaging action	
	Chlorella and *D. salina*	Proteins	Nutraceuticals	
	Various marine bacterial sp.	Cyclomarins, Salinamides	potent anti-inflammatory activity, compared to hydrocortisone	

(Contd.)

Table 3 — Summary of marine bioactive compounds and their pharmacological activities

Sl. No	Biological sources	Bioactive compounds/Metabolites	Pharmacological activity	References
		Sesquiterpenoids and diterpenes from marine		
5	*Pseudopterogorgia elisabethae*	Tricyclic diterpene	shows analgesic and anti-inflammatory action by blocking eicosanoid and phospholipase A_2biosynthesis.	28
	Eisenia bicyclis *H. fusiformis* *E. kurome* *Ecklonia cava*	Pseudopterosin Phlorotannin Phloroglucinol	photoprotective agent to prevent UVB induced skin damage than ascorbic acid and α-tocopherol	
	Lemnalia cervicornis	Lemnalol	Neutrophil-mediated inflammation	
	Rumphella antipathies	Sesquiterpene and diterpenes	decrease superoxide, elastase release of neutrophils and anion production at cellular levels	
	Streptomyces sp.	Strepsesquitriol	suppressed TNF-α synthesis in RAW264.7 macrophage cells	
	Sinularia lochmodes	Diterpenes compounds	prevents augmentation of COX-2 in RAW264.7 cells	
	Lemnalia flava	Flavalin A	Anti-inflammatory properties	
	Briareum excavatum	Excavatolide B	mRNA expression of iNOS and COX pathways in macrophages	
	Lobophytum crassum	lobocrasols A and B	inhibitory effect on NF-κB and TNF-α expressions	
		Marine alkaloids		
6	Marine bryozoans	Convoluntamydine A	Decreases leukocyte migration or COX-2, iNOS, prostaglandin E_2, TNF-α and IL-6 in RAW 264.7 cells	28
	Eurotium sp.	Neoechinulin A and B	Anti-inflammatory properties in cell line studies	
	Acanthella aurantiaca & Axinella verrucosa	Hymenialdisine	Specific inhibition of NF-κB	
	Chaetomium globosum	Alkaloid derivatives	downregulate the expression of CD14, mRNA expression of cytokines and NF-κB/p38 pathways	
		Marine Cyanobacteria		
7	*Lyngbya majuscula*	Microcolin A Malyngamides	Immunosuppressive and anti-inflammatory activity by decreasing NO production	24
	Cyanobacterial species	Syctonemin	blocks protein kinase Cβ activity in concentration dependent levels and downregulates neovascularization	
	Pigments from blue-green algae	Phycocyanin	shows anti-inflammatory and antioxidant properties by inhibition of prostaglandin E_2, phospholipase A_2 and histamine release which is like that of ibuprofen and indomethacin	
	Oscillatoria and *planktothrix*	Cyanobacterial lipopolysaccharides	shows TLR4 receptor antagonism	
		Miscellaneous marine compounds		
8	*Laurencia claviformis*	Pacifenol	shows anti-inflammatory activity by blocking phospholipase A2, thromboxane and leukotrienes	23
	Aplysia californica	Prepacifenol		
	Stypopodium flabelliforme	Epitaondiol Stypotriol triacetate Isoepitaondiol	Blocks phospholipase A2, thromboxane B2 and leukotrienes B4 and interferes arachidonic acid pathway/ shows free radical scavenging activity	24
	Fish oils Omega-3 fatty acids Omega 6 fatty acids	docosahexaenoic acid (DHA) eicosapentaenoic acid (EPA)	suppress the chemotaxis of leukocytes, diminishes production of eicosanoids, prevents inhibition of adhesion molecules	32

*This table explains the existing compounds extracted from marine sources with various anti-inflammatory potentials that could be explored in psoriasis as a novel alternative approach

NF-κB signalling pathway suppression from releasing eicosenoic acid and eicosadienoic acid. Didemnins, under the class of depsipeptide, are isolated from the tunicates of Caribbean *Tridemnum solidum* exhibits numerous biological activities such as immunosuppression by blocking the activation of lymphocytes[21]. Pateamine A from *Mycale* sp. inhibits IL-2 production selectively, which further causes secondary immune response. A starfish *Astropecten polyacanthus* inhibits various pro-inflammatory cytokines that are involved in inflammatory pathways, and it is more effective than conventional steroids, stated in a clinical study. Caledonian marine sponge *Petrosa spongia nigra* possess biomolecules such as Petrosaspongiolide M, significantly blocks chronic inflammation by diminution of TNF- α production and eicosanoids, stated in a pre-clinical study. They also decrease DNA binding capacity to NF-κB. Contignasterol, a polyoxygenated steroid extracted from *Petrosia contignata* of Papua New Guinea shows anti-inflammatory and anti-allergic properties by inhibition of IgE mediated histamine release[22]. Clathriol B, a marine steroid that modulates superoxide production and alleviates inflammation and promotes radical scavenging activity. Halipeptides a cyclic depsipeptide, from the marine sponge *Haliclona,* shows better results of anti-inflammatory properties than the synthetic drugs like naproxen and indomethacin. Petrocortynes are polyacetylenic alcohols and lipidic compounds from *Petrosia* collected from Korean coast reveals cytotoxic activity and anti-inflammatory properties by modulation of macrophages, reducing TNF-α and cell migration of phlogistic infiltration. These contribute to their immunopathology mechanisms in autoimmune diseases and various acute and chronic inflammatory diseases[22].

Marine metabolites from Seaweeds

Among all marine derived organisms, seaweed facilitates easy adaptation to various kinds of hostile environments. Since they have abundant levels of amino acids, enzymes, fatty acids, fibers, lipids, minerals, pigments, proteins, polyphenolic compounds, sugars, terpenoids and vitamins, they are mostly incorporated as an added value of nutrients, health and aesthetic medicine. Indeed, these are divided into two; microalgae and macroalgae which possess several biomolecules or secondary metabolites that exhibit activities including antioxidant, anti-inflammatory, anticancer, antivirals *etc*. Some species of microalgae, *i.e*., Spirulina (*Arthrospira platensis*)*, Chlorella pyrenoidosa, Rhodella maculata, Porphyridium cruentum* have enormous amounts of phycobiliproteins that acts as an antioxidant by inhibiting the free radicals in the surface proteins. Klamath seaweed and *Aphanizomenon flos* algae show anti-inflammatory activity. In general, macroalgae are classified as Phaeophyta, Rhodophyta and Chlorophyta which refers to brown algae, red algae and green algae respectively. Fucoidan and fucoxanthin from *Sargassum siliquastrum, Fucus vesiculo sis, Fucus serratus,* Xanthophylls from *Fucus evanescens* and *Ulva Lactuca* (Sea lettuce) possess antioxidant properties by reducing oxidative stress induced by UVB radiation, and antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *B. cereus* and *Klebsiella pneumoniae*. The same biomolecule fucoidans from brown seaweed *Laminaria cichoriodes, Fucus evanescens* and *Laminaria japonica* possess immunomodulatory activities by interfering with TLRs and cause activation of NF-κB and other related signalling pathways, stated in an *in vitro* study[23]. *Gelidiella acerosa,* which is a Rhodophyta from Indian Ocean, is a polyphenolic compound that reveals ROS scavenging activity and decreases DNA damage and have been experimented for Alzheimer disease. Another species of Phaeophyceae *Ishige okamurae* derives compounds like diphlorethohydroxycarmalol which have reduced fine-dust mediated inflammation caused due to various air pollutants and downregulates IL-6 production. Furthermore, these extracts of seaweed are also used in regenerative medicine and tissue engineering for their prominent activities like anti-inflammatory, anticancer and immunomodulatory action[23].

Marine metabolites from Cyanobacteria

In general, cyanobacteria are prokaryotic blue-green algae that possess anti-inflammatory and immunomodulatory properties due to their robust host-defense mechanisms. As a result, they produce various biomolecules such as carotenoids which have shown anti-inflammatory activity and slow disease progression of psoriasis by blocking nitric oxide production and inhibit pro-inflammatory markers like IL-6, TNF-α, COX-2, iNOS, and IL-1β in cell line studies on RAW 264.7 macrophages and NF-κB pathway in carrageenan-induced rat paw edema study. When tested for their antioxidant properties they act as free

radical scavengers[22]. In addition, the underlying pathophysiological mechanism of psoriasis and other skin disorders are the resistance to apoptosis of keratinocytes, cyanobacteria derived compounds have antiproliferative effects by modulating cell cycle, p53 induction and caspase cascade. This could exert tremendous advantages over psoriasis in balancing the abnormal rapid skin cell turnover. Extracts of cyanobacteria that possess anti-inflammatory activity can be derived either from lipids or polysaccharides. For instance, a lipopeptide Microcolin A and malyngamides from the source *Lyngbya majuscula* of filamentous cyanobacteria, reveals immunosuppressive and anti-inflammatory activity by balancing the NO production and several biomarkers involved in inflammatory cascade. Scytonemin, an alkaloid from cyanobacteria has anti-proliferative, antioxidant and anti-inflammatory properties, which blocks protein kinase Cβ activity in concentration dependent levels and downregulates neovascularization. Phycocyanin shows anti-inflammatory and antioxidant properties by inhibition of prostaglandin E_2, phospholipase A_2 and histamine release which is similar to that of ibuprofen and indomethacin mechanism. It also reduces β-glucuronidase levels in animal study, which is a used as a diagnostic marker for determining autoimmune diseases. Cyanobacterial lipopolysaccharides derived from *Oscillatoria* and *Planktothrix* shows TLR4 receptor antagonism and reveals protective anti-inflammatory properties.

Other essential metabolites from marine sources

Marine polysaccharides

With tremendous properties such as hydration due to their higher affinity in water retention, antioxidant, antimicrobial, and anti-inflammatory activities, polysaccharides are most desirable to use as a cosmetic ingredient. These can be derived from various marine organisms, mainly from species like Chondrus, Gigartina and Kappaphycus. In industry, currently, there are two main categories of polysaccharides: Sulphated and non-sulphated. Examples of sulphated are carrageenans, fucoidans, galactans, laminarins, and ulvan whereas the non-sulphated polysaccharides are agars and alginates. Sulphated polysaccharides are negatively charged and have enormous beneficial properties towards the harmony of biodegradability and biocompatibility. The sulfate content present in marine polysaccharides is crucial in stimulating macrophages and ameliorates cell surface protein interactions. Thus, subsequently it states that most of the polysaccharides are derived from marine algae[23]. Fucoidan, being the most overrated compound that is derived from edible seaweed *F. vesiculosus,* has many therapeutic benefits that can have the potential to cure the root causes of inflammatory diseases. They possess antioxidant properties by preventing the generation of superoxide anions, hydroxy radicals, hydrogen peroxides and decreasing lipid peroxidation. They also act as immunomodulators by interfering with innate immunity, modulating nitric oxide production, and decrease inflammation. Some recent studies have portrayed that fucoidan and fucoxanthin shows anti-inflammatory abilities by suppressing NF-κB through JNK, p38, MAPK, ERK and AKT pathways. Other species such as *Chlorella stigmatophora and Phaeodactylum tricornutum* show anti-inflammatory properties in some studies with carrageenan-induced paw edema. A variety of extracts from blue-green algae like *Nostoc* and *Phormidium* diminishes proinflammatory cytokines such as TNF-α, IL-1β, IL-6, COX-2 and iNOS in cell-line studies with RAW 264.7 cells. Polysaccharides derived from *Arthrospira platensis (*Spirulina) have significant immunomodulatory properties. Astaxanthin, fucoxanthin and certain marine carotenoids possess effective antioxidant results than the synthetic and terrestrial ones. They decrease the NO production, iNOS action, synthesis of PGE2 and prevent inflammation by interrupting inflammatory cytokines such as TNF-α, IL-1 and COX-2 expression, thus eliminating reactive oxygen species[24].

Marine proteinsand peptides

Marine proteins have the beneficial properties of scavenging reactive oxygen species (ROS) and minimizing lipid peroxidation. These agents have a combination of properties that can heal psoriatic lesions. Since the disease is totally concerned with skin barrier functions, marine peptides can aid with balance in transepidermal water loss and give strength and support to the skin by enhancing components like ceramides that ameliorate skin hydration[25]. Specific marine peptides have antibacterial properties that might promote skin health and protect psoriatic lesions from developing secondary infections. Marine collagen, as an alternative to the collagen that is produced by bovine, has similar beneficial effects in maintaining the skin texture and repair process. These are derived from fish, cnidaria, porifera, Echinodermata and mollusc organisms. However, further research is required to investigate their

physiochemical properties. Phycobiliproteins, which are abundant in cyanobacteria, possess antioxidant properties, anticancer and immunomodulatory activity. These properties are associated with several variations in the side chains of amino acid moieties. Phycobiliproteins have beneficial effects including prevention of free radical scavenging and lipid peroxidation. In a study, peptides from pacificoyster (*Crassostrea gigas*) reveal significantly higher and better antioxidant properties than synthetic α- tocopherol. Some biomolecules like Mycosporine like amino acid (MAA) possess anti-photoaging action[26]. High protein concentrations are revealed in seaweeds including Spirulina, *Chlorella* and *Dunaliella salina* and they are prominent as nutraceuticals. Marine lectins show anti-inflammatory activity due to the presence of host defense peptides like antimicrobial peptides. Epinecidin-1 and Chrysophsin-1 have the capacity to suppress Th2 cells in adaptive immune response and inhibit various inflammatory cytokines. Cyclomarins are cyclic heptapeptides, derived from marine bacteria, actinomycete of *Streptomyces* sp., in the coasts of California. They are classified as cyclomarin A, B and C in which A and C have the most dynamic anti-inflammatory action proved in various preclinical studies, in comparison to hydrocortisone. Salinamides contain five peptides of A, B, C, D and E isolated from the same marine bacteria species, showing anti-inflammatory properties[26].

Terpenoids: Sesquiterpenoids and diterpenes

These are aromatic hydrocarbon molecules that are abundant in plants that possess artificial flavors and aromas. According to a study, marine terpenes like sargafuran show effective bactericide properties compared to clindamycin, demonstrating their vigorous antimicrobial activity. Their minimal inhibitory concentration determines the extent of their bacteriostatic or bactericidal action. Sesquiterpenes have antifungal properties in addition to their ability to combat marine bacteria and both gram-positive and gram-negative bacteria. They have anti-inflammatory properties by inhibiting the nitric oxide generation triggered by lipopolysaccharide. The tricyclic diterpene glycoside from the source of Caribbean Sea whip named *Pseudopterogorgia elisabethae* from the family Gorgoniidae, shows analgesic and anti-inflammatory action by blocking eicosanoid and phospholipase A_2biosynthesis. Pseudopterosin extracts have already been investigated for prevention of skin irritation caused by exposure to sunlight and chemicals and in market used as an additive to a cosmetic product *Resilience by Estée Lauder*. A non-sulfated glycosaminoglycan hyaluronic acid, which is depolymerized by the enzyme hyaluronidase, is present prominently in extracellular spaces of connective tissues. This enzyme contributes to inflammation, migration of tumor cells and in allergic responses. Phlorotannins derived from several marine biological sources have been a significant downregulates the effect of hyaluronidase. Examples of such phlorotannins are some polyphenolic compounds from *Eisenia bicyclis, Hizikia fusiformis, Eckloniakurome* and *Ecklonia cava* are phloroglucinol metabolites such as eckol, dieckol and phlorofucofuroeckol A, which have better photoprotective agent to prevent UVB induced skin damage than ascorbic acid and α-tocopherol. They also possess antioxidant effects against free radicals like hydrogen peroxide induced cellular damage and phospholipid peroxidation. Lemnalol, which is derived from *Lemnalia cervicornis,* a soft coral from Taiwan, inhibits acute neutrophil mediated inflammation. Anti-inflammatory activity of Taiwan gorgonian coral, *Rumphella antipathies* has the potential to decrease superoxide, elastase release of neutrophils and anion production at cellular levels. Strepsesquitriol derived from *Streptomyces* sp., suppressed TNF-α synthesis in RAW264.7 macrophage cells. *Sinularia lochmodes* have beneficial sesquiterpenoids derived from soft corals of Taiwan prevents augmentation of COX-2 in RAW264.7 cells. Another soft coral from Taiwan, *Lemnalia flava* gives a biomolecule called flavalin A resulting in anti-inflammatory activity in cell-line studies. Diterpenes in soft corals generally produce secondary metabolites with effective anti-inflammatory properties. These are sometimes grouped under NF-κB pathway inhibitors. Excavatolide B, cultured from *Briareum excavatum* modulates mRNA expression of iNOS and COX pathways in macrophages. Methanolic extract of lobocrasols A and B extracted from *Lobophytum crassum* from Vietnam revealed inhibitory effect on NF-κB and TNF-α expressions[27].

Marine alkaloids

Marine organisms like tunicates, sponges, algae, sea anemones and molluscs have alkaloids that show anti-inflammatory and antioxidant activities. These are recently used in cosmeceuticals, like skin moisturizers and sunscreens. It is proven that they have properties like anti-photooxidative stress and decreasing UV induced damage. Most of the biological activity is due to the presence of piperazine molecules in the marine alkaloid. These are available in marine

fungi, which are considered as salient source of marine-derived piperazine alkaloids with properties such as anti-proliferative, cytotoxicity, anti-inflammatory, antioxidant, antimicrobial, and enzyme inhibition. Alkaloids are generally cyclic compounds that might exert various properties. Convoluntamydine A, an oxindole alkaloid derived from marine bryozoans reveals their action by targeting several steps involved in inflammatory cascade. These can be either leukocyte migration or COX-2, iNOS, prostaglandin E_2, TNF-α and IL-6 in RAW 264.7 cells. Neoechinulin A and B, sourced from marine fungus *Eurotium* sp., which is diketopiperazine type indole alkaloids exert *in vitro* anti-inflammatory activity. *Chaetomium globosum* from endophytic fungus might downregulate the expression of CD14, mRNA expression of cytokines and NF-κB/p38 pathways. Alkaloids derived from marine sponges including *Acanthella aurantiaca* and *Axinella verrucosa* specifically inhibits NF-κB. One of them are hymenialdisine, which suppresses activation of NF-κB and IL-2, IL-8 and TNF-α production. Hence, they possess all beneficial activities, this can be used for the potential development of drug for the treatment for various diseases[28].

Miscellaneous biomolecules from marine

Most conventional anti-inflammatory drugs are COX inhibitors. From this aspect, certain marine natural products recently reveal to possess antioxidant and the potential to target COX and NF-κB pathways. Pacifenol and its precursor prepacifenol which are terpenoids derived from marine algae *Laurencia claviformis* belongs to the family Rhodomelaceae, shows anti-inflammatory activity by blocking phospholipase A2, which is the rate-limiting step of cyclooxygenase pathway. They also downregulate the response of leukotriene B4 and thromboxane B2 production. Both pacifenol and prepacifenol are also found in marine invertebrates like mollusc *Aplysia californica.* Epitaondiol, a terpenoid from seaweeds *Stypopodium flabelliforme* possess anti-inflammatory effects by inhibiting eicosanoids leukotriene B4 and thromboxane B2 and phospholipase A2 which further prevents the formation of arachidonic acid in COX pathway. Isoepitaondiol shows free radical scavenging properties which are similar to ascorbic acid. Stypotriol triacetate, a polycyclic meroditerpenoid which is also found in the same seaweed *S. flabelliforme* has a similar COX pathways inhibition activity along with blocking elastase release. Thus, they can be used as a possible potent cure for psoriatic and rheumatoid arthritis[31].

Polyunsaturated fatty acids (PUFAs) are generally obtained from marine sources, especially fish oils. These include omega (ω) 3 and omega 6 fatty acids. Recent studies stated that these fatty acids have proven anti-inflammatory properties and have the potential to modulate and suppress various inflammatory cascades. Some clinical studies have demonstrated that incorporating certain quantities of ω-fatty acids in the diet has a beneficial impact if the patient suffers from any inflammatory diseases. Moreover, eicosanoids like docosahexaenoic acid, eicosapentaenoic acid (DHA and EPA) and arachidonic acid (AA) from omega 3 and omega 6 fatty acids respectively show anti-inflammatory and pro-inflammatory immune active properties. Some researchers elucidated that these fatty acids might suppress the chemotaxis of leukocytes, diminish the production of eicosanoids such as leukotrienes and prostaglandins as well prevent inhibition of adhesion molecules and reduce the synthesis of inflammatory cytokines which are essential for initiating inflammatory processes[29].

Benefits and novelty of marine natural products over existing conventional drugs

Marine natural products have promising benefits when compared with existing synthetic molecules because they are derived naturally from marine which makes them unique characteristics like less toxicity and less side-effects. Typically, marine species that flourish in harsh environments often generate metabolites with potent survival mechanisms, which have resistance to various enzymatic degradation and denaturation processes, and to meticulously strive to produce host-defense mechanisms. These evolutionary changes prove that marine-derived natural products have more potential advantages over terrestrial compounds and existing synthetic drugs[5].

The presence of unique structural properties paves the way for the discovery of novel therapeutic pathways and mechanisms of action. This can exhibit effective results, particularly in patients who have developed resistance with limited response to current conventional drugs. In addition, these critical aspects such as its unique structural properties, biodiversity, and unexplored biological activities illustrate the novelty of the marine-based drug approach. To date, terrestrial natural resources have been well exploited in all standpoints of research including autoinflammatory diseases. Thus, exploring marine natural products might be the novelty of this approach

because it has the potential to unveil new therapeutic agents that might contribute to advancing the treatment of psoriasis and other inflammatory-related autoimmune disorders[5].

Conclusion

In conclusion, bioactive substances that originate from marine sources have drawn interest because of their potential anti-psoriatic properties. In recent literature, marine organisms such as marine algae and sponges have proved to have various biomolecules such as polysaccharides, terpenoids, alkaloids, peptides, *etc*., that can heal various inflammatory diseases. Interestingly, these seaweeds also have nutritional advantages which can be implemented as oral nutraceuticals to alleviate disease symptoms. Therefore, the future directions for marine bioactive research will witness crafting them into innovative technologies such as nanomedicine, personalized medicine, and multi-omics strategies to enhance and explore their potential as an anti-psoriatic and against other autoimmune disorders. The biggest challenge that will be faced during these developments will be related to procuring marine natural compounds, ensuring a streamline uniform supply, while maintaining the fragile marine ecological balance. In this context, advanced mariculture, aquaculture and marine biotechnology will play an indispensable role. Thus, incorporating natural products from the marine could significantly reduce all the problem statements in existing treatments and provide a novel therapeutic approach for treating psoriasis.

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Conflict of interest

All authors declare no conflict of interest.

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