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Review Article

Marine Macroalgae: Exploring a New Wave of Wound Healing

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Abstract

A wound can be defined as damage to tissue organs accompanied by the destruction of the integrity of the skin and mucous membrane. Wound healing is a complex process and requires the involvements of specialized cells and growth factors such as platelets, macrophages, fibroblasts, epithelial cells, the action of protein and glycoprotein cytokines, chemokines, and some other growth factors. Also, some basic mechanisms such as anti-infection, antioxidant, anti-inflammation play a pivotal role in the wound healing mechanism. For healing wound properly, there is a wide range of materials are useful nowadays but the new strategy is dealing with the use of new generation wound dressing materials for effective treatment. In current technology, researchers are developing regenerative medicines for effective wound recovery such as an effective drug delivery system, formulation, natural polymer-based biodegradable, and biocompatible drug dressing materials, etc. Normally, tissue engineer deals with some biological viable active ingredients in wound healing treatments. Many researchers suggested that the marine algae-derived noteworthy ingredients such as algal polysaccharides, alkaloids, phenolic compounds, essential oils, tannins, saponins, etc. helpful for enhancing wound recovery. The present review study highlights the role of marine macroalgae in wound repair mechanism as well as also revealed its role in antimicrobial, antioxidant, and anti-inflammatory effects which mitigates the wound healing process.

Keywords: Marine Algae; Wound Healing; Antiinflammation; Antimicrobial; Phycocompounds

Introduction

Wound arises due to several agents that induce injury or stress. Many alterations disrupt the mechanism of wound healing such as infection, diseases, and medications, etc. that damage and prolong the repair process. Wound healing is a repairing mechanism that tries to maintain normal anatomical structure and function which is regulated by multiple growth factors and cytokines. Wound healing is a process of recovering the normal form and function of injured tissues or skin layers. This wound healing activity is triggered by anti-inflammatory, antioxidant, antimicrobial, and procollagen synthesis. There are many natural phycocompounds such as alkaloids, tannins, saponins, flavonoids, phenolic compounds that played their role in the above mechanisms [1].

At present, drugs from natural sources are playing a pioneering role because of their potency, high efficacy, and less toxicity. Due to the presence of bioactive compounds in natural resources, it can be widely used in wound healing treatment. Many scientists studied natural compounds for effective wound healing treatments by regulating growth factors, the release of cytokines at wound sites, by evaluating its antioxidant, anti-inflammatory, antibacterial, antifungal, as well as procollagen synthesis activity, etc [2]. revealed the pharmacological importance of marine natural products isolated from different marine organisms [3].

Seaweed or marine algae are considered one of the most important marine resources of the world and being used as human and animal feed and raw material for many industries. Due to the presence of biologically active substances, marine algae are used as an attractive source of skincare [4]. Marine algae contain a broad range of phycocompounds such as carbohydrates, proteins, amino acids, lipids, fatty acids, important metabolites, polyphenols, alkaloids, essential oils, tannins, flavonoids, mycosporin amino acids (MAAs), hormones, pigments, minerals, and elements, etc. Pati., *et al.* (2016) suggested the importance and applications of seaweed in human welfare [5]. Due to the presence of such bioactive constituents, it can be applicable in a wide variety of applications such as the food and dairy industry, textile and polymer industry, cosmeceuticals, as well as in medicine and pharmaceuticals as a therapeutic agent, etc [6,7]. Among all the applications, widely useful in skin cosmetic benefits such as skin whitening effect, ant browning reaction, UV protection, skin moisturizer, anti-aging reaction, anti-wrinkle, etc. It is also applicable in many pharmaceutical applications' antimicrobial treatments, tissue engineering, drug delivery approach, wound healing, biomaterial and biopolymer productions, food supplements, etc [8]. By focusing on previous studies, Bilal and Iqbal, (2019) reported the importance of marine seaweed polysaccharide in the modern biomedical sector. They also revealed significant values of phycocompounds in modulating drug delivery and tissue engineering systems [9]. Silva., *et al*. (2012) focused on the biomedical applications of marine algae-derived sulfated polymers in the development of an innovative system for tissue engineering and drug delivery approaches [10]. For the first time, Kelman., *et al*. (2012) found the significant antioxidant activity of the carotenoid fucoxanthin from Hawaiian Marine algae *Turbinaria ornate* [11]. Padmakumar and Ayyakkannu, (1997) screened marine algae extracts for antibacterial and antifungal activities in different seasons from the Southern Coasts of India [12]. According to them, the class Rhodophyceae showed the highest antibacterial activity (80%) followed by the Chlorophyceae (62.5%) and the Phaeophyceae (61.9%) whereas antifungal activity also revealed as red algae (37%)>brown algae (33.3%) >green algae (8.3%). JY Jun., *et al*. (2018) reported a fucoidan (sulfated polysaccharide) from *Fucus vesiculosus* revealed significant antimicrobial activities against the bacteria that cause dental plaque and some food pathogens [13].

Hence, a study on Wound healing treatment by marine algae and its components was carried out by many researchers. Some of them focused on important components of marine algae for the effective treatment of healing wounds. Whereas, the present study highlights a review of the applicability of marine algae in wound healing. Mainly, this study reviewed the role of marine algae in this healing process by regulating different biological activities such as antimicrobial, antiinflammation, and antioxidant activity.

Role of marine algae in wound repairing mechanism

Besides, many researchers worked on targets of marine algae and their mechanism for effective wound healing. Includes, methanolic extract of brown algae *Sargassum wightii* has significant anti-inflammatory, antipyretic, and wound healing properties [14]. Syarina., *et al*. (2015) concluded that blue-green algae may have a potential biomedical application to treat various chronic wounds, especially in diabetes mellitus patients. They studied sample extracts by using *in vitro* scratch assay on human dermal fibroblast cells (HDF) [15]. Madkour., *et al*. (2013) showed that the selected experimental medicinal extract mixture (EMEM) beneficial for wound healing treatment in the diabetic rat model. The effective extract promoted wound contraction, reduced wound closure time, and induced proliferation of fibroblast as well as angiogenesis and re-epithelialization [16]. Senthil and Murugan, (2013) reported potential wound-healing and hepatoprotective properties of *Gracillaria crassa* whereas anti-ulcer activity was revealed by *Laurencia papillosa* for further pharmaceutical applications [17]. The study of aqueous extract from twenty-three different seaweed species extracts might be a potential therapeutic agent for skin wound healing activity by different mechanisms [18]. Whereas, an effective positive impact of spirulina crude protein (SPCP) on the viability of human dermal fibroblast cell line (CCD-986sk cells) studied [19].

Importance of Phycocompounds in the wound healing process

Ibrahim., *et al*. (2018) reviewed *in vitro*, *in vivo*, and clinical studies of wound healing properties of selected natural products and the mechanisms involved [20]. They suggested marine algae can be explored as a potential medicinal, health care, or pharmaceutically active compound due to the rich source of functional ingredients. Liu., *et al*. (2018) reviewed the application of chitosan-based hydrogel as a wound dressing and drug delivery system in the wound healing treatment. They suggested chitosan as an ideal material due to its bioactive, biodegradable, biocompatible, non-toxic, antimicrobial, and bioadhesive properties [21]. Potential and biological capacities of marine algal-derived carbohydrate beneficial for skin health which was reported [22]. They reported many beneficial activities of carbohydrates such as antioxidants, ant melanogenic, and anti-aging properties. Park., *et al*. (2017) reported fucoidan with low molecular weight can be applied to promote wound healing that is studied by the full-thickness dermal excision rat model [23]. Fucoidan is useful owing to its anti-inflammatory, antioxidant activities and reduces lipid peroxidation. Premarathna., *et al*. (2020) screened aqueous extracts of twenty-three different seaweed species in Sri Lanka with *in vitro* and *in vivo* assays [24]. In which, extracts of *Sargassum illicifolium* (SW23) showed significant wound healing activity in mice group III [25]. Bechir., *et al*. (2014) reported the beneficial effect of collagenic gels containing 10% *Ceramium rubrum* in the treatment of Recurrent Aphthous Stomatitis. This research suggested that this biosource can be used to reduce the healing time and recurrence of the condition [26]. Due to the prominent anti-inflammatory, antibacterial, and antiinoceptives effects of brown seaweed *Padina gymnospora*, Balianoa., *et al*. (2016)

suggested, this methanolic extract can be used for the natural wound-care product [27]. Premarathnaa., *et al*. (2018) analyzed aqueous extracts of *Sargassum illicifolium* for Wound healing properties by an in-vitro method. They reported cell proliferation and migration were significant with no cytotoxicity on the L929 cell line in their findings [28]. Fard., *et al*. (2011) evaluated the wound healing properties of *Eucheuma cottonii* extracts in Sprague-Dawley rats. They found an enhancement in epithelization and tissue granulation in ethanolic extracts. This also contains several antioxidant compounds that responsible to accelerate wound healing activity [29]. The antimicrobial, anti-inflammatory, and antioxidant activities of algal-derived phycoconstituents might be among the contributing factors that proved a significant role in the wound healing process by improving collagen synthesis, wound contraction, white bed score, and reduces the microbial load.

Antimicrobial potential of marine macroalgae

In response to different environmental stresses, seaweeds or marine algae produce metabolites and these metabolites are useful as an antimicrobial component on viruses, protozoa, fungi, as well as on bacteria. Many researchers screened many marine algae for antimicrobial compounds as well as their antimicrobial activities from various sea coasts by using different types of solvent extracts [30-32]. Marine organisms are a rich source of metabolites among all, marine algae are known to produce bioactive compounds such as primary and secondary metabolites. The efficacy of different algae-derived components, their mode of action, applications as antibiotics, disinfectants, as well as inhibitors of food pathogens and spoilage bacteria, etc. reviewed [33]. Eom SH., *et al*. (2012) suggested bioactive compound namely phlorotannins expresses antimicrobial effects and can be used as an antimicrobial agent [34]. Pérez., *et al*. (2016) reviewed on antimicrobial action of compounds from different marine seaweeds. They reported major compound as well as antimicrobial activities and their significant applications in the medication sector. These algae-derived compounds belong to the polysaccharide, fatty acid, phlorotannin, pigments, lectins, alkaloids, terpenes, and halogenated compounds [35]. Seaweed produces metabolites aiding in the protection against different environmental stresses. Boujaber., *et al*. (2015) explored the antimicrobial effect of two marine algae *Gelidium sesquipedale* and *Laminaria ochroleuca* collected from the coast of El Jadida-Morocco. They found that the methanolic extract of selected algae showed a significant antimicrobial effect on selected bacterial test strains [36]. El Shafay SM., *et al*. (2015) studied an antimicrobial activity of diethyl ether, methanol, ethanol, and chloroform extracts of red algae namely *Ceramium rubrum* (Rhodophyta), *Sargassum vulgare*, *Sargassum fusiforme*, and *Padina pavonia* (Phaeophyta) against multidrug-resistant bacteria. They suggested the presence of phycocompounds such as phenols, terpene, indoles, fatty acids, and volatile hydrocarbons are responsible for such activity [37]. Pandithurai., *et al*. (2015) found the methanol extract of marine brown alga *Spatoglossum asperum* showed highly effective antibacterial activity (84.94%) of various solvent extracts of marine brown alga *Spatoglossum asperum* on various bacterial pathogens [38]. Vimala and Poonghuzhali, (2017) evaluated an *in vitro* antimicrobial activity of solvent extracts of the marine brown alga, *Hydroclathrus clathratus* (*C. Agardh*) M. Howe from the Gulf of Mannar against human bacterial and fungal pathogens [39]. A comparative study on the antimicrobial activity of methanolic extract of seaweeds was performed [40]. They found *Sargassum swartzii, Jania rubens,* and *Stoechospermum marginatum* showed a broad spectrum of antibacterial activity against all the test pathogens. Christabell., *et al*. (2011) found *Ulva fasciata*, *Gracilaria corticata, Sargassum wightii* and *Padina tetrastromatica* showed significantly higher activity against 70% of the isolated bacterial test cultures. Generally, it was higher in gram-negative bacteria [41].

Anti-inflammatory response by marine macroalgae

Inflammation has prime importance in body homeostasis such as microbial infections, tissue stress, and damages. Sometimes, excessive and uncontrolled inflammation can lead to creating some pathogenic conditions as well as tissue toxicity. As much literature revealed marine algae are considered as a potential source of anti-inflammatory agents by mediating different factors involved in the inflammation process. Marine algae possess many important phycocompounds such as amino acids, polyphenolic compounds, terpenoids, flavonoids, fucoxanthin, fatty acids, and their derivatives, lipids, and carbohydrates, etc. which involved in the inflammatory response. Giriwono., *et al*. (2019) reviewed the importance of seaweed and its potential impact as a source of anti-inflammatory substances [42]. Ananthi., *et al*. (2011) checked the aqueous extract of marine brown alga *Turbinaria ornate* (ATO) (Turner) J. Agardh showed significant free radical scavenging and anti-inflammatory activity by ABTS method [43]. Oh., *et al*. (2016) revealed significant anti-inflammatory and antidiabetic effects of brown seaweed *Laminaria Japonica* (LJ) in a high-fat diet (HFD)-induced obese mouse. This study showed the applicability of seaweed in various health benefits [44]. Out of Nine fucoidans from brown seaweeds, *Laminaria saccharina*, *L. digitata*, *Fucus serratus*, *F. distichus*, and *F. vesiculosus* strongly revealed its effect in tumor metastasis by studying its anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities. This comparative study was performed by Cumashi., *et al*. (2007) [45]. Due to these benefits, it can be applied to the development of potential medication in thrombosis, inflammation, and tumor progression. Neelakandan and Venkatesan, (2016) evaluated an antinociceptive and anti-inflammatory effect purified components sulfated polysaccharide fractions from *Sargassum wightii* and *Halophila ovalis* in male Wistar rats [46]. Sanjeewa., *et al*. (2019) explored potential applicability in the industrial formulation of *Ecklonia cava* (Laminariales) and *Sargassum horneri* (Fucales) by using in combination in 8:2 ratio. They found that both algae synergistically inhibit the lipopolysaccharide-induced inflammation via blocking NF-κB and MAPK pathways [47]. Polyphenol is an important phycocomponent that played a significant role in the antioxidant and anti-inflammatory response. YU Yuan., *et al*. (2019) studied the anti-oxidant and anti-inflammatory activities of ultrasonicassistant extracted polyphenol-rich compounds from *Sargassum muticum* [48]. Lee., *et al*. (2013) suggested that marine algal biomaterials played important role in potential biological effects such as anti-oxidative, anti-inflammatory, and anti-cancer properties [49]. The therapeutic potential of red seaweed *Dichotoma riaobtusata* is considered a good source in the treatment of peripheral pain or/and inflammatory conditions that screened by using various tests such as analgesis activity, Mouse-ear oedema test, and Writhing test [50]. Radhika., *et al*. (2013) studied the anti-inflammatory activities of four seaweeds namely *Padina tertastomatica, Sargassum wightii, Gracilaria edulis,* and *Caulerpa racemose* collected from the Tuticorin coast, South India. They found good anti-inflammatory effects in the carrageenan [51]. Likewise, the significant anti-inflammatory activity of Methanolic Extract of *Gracilaria corticata* J. Ag. (Red Seaweed) was studied [52]. This studied alga sample was collected from the sea coast of Tamilnadu, India. Chalini., *et al*. (2017) found the highest percentage (95.55%) of anti-inflammatory activity in 250 μg/ml of *G. edulis* aqueous extracts. They found the highest result in *G. edulis* (Mandapam) whereas the lowest in *G. corticate var. cylindrica* (Tuticorin) [53]. Ripol A., *et al*. (2018) showed green seaweed *Ulva prolifera* from fish pond aquaculture to be a potential source of bioactive compounds by checking its bioaccessibility and anti-inflammatory activity [54].

The beneficial role of marine macroalgae in antioxidant activity

Regulation of wound oxidative stress and wound healing acceleration controlled by a variety of antioxidants. Various research studies were carried out on the role of algae-derived phycocompounds in antioxidant activity and its mechanism. Marinho., *et al*. (2018) suggested seaweed *Saccharina latissima* as a good source of antioxidants [55]. Ilknur and Turker, (2018) found a high amount of phenolic, flavonoid, and carotenoid in an aqueous extract of brown algae *Cystoseira barbata* which was collected from Çanakkale, Turkey. This alga also showed significant Antioxidant activity [56]. Heo SJ., *et al*. (2003) analyzed different enzymatic extracts of brown seaweeds for antioxidant activity. This assay in terms of lipid peroxidase inhibition revealed that the highest inhibition in Ultraflo and Alcalase extracts of *Ecklonia cava* and Neutrase extracts of *Scytosiphon lomentaria* [57]. Chakraborty., *et al*. (2017) reported significant hydroxyl radicle scavenging effect and was effective in stabilization of 2,2′-azino-bis-3-ethyl benzothiazoline-6-sulfonic acid (1.23 mg/mL) and 1,1-diphenyl-2-picryl-hydrazine (DPPH)radicals (0.48 mg/mL) [58]. Farasat., *et al*. (2013) studied that the good amount of phenolic and flavonoid content from edible Green Seaweeds which were collected from the Northern Coasts of the Persian Gulf revealed a positive correlation with radicle scavenging (DPPH) activity [59].

Ebrahimzadeh., *et al*. (2018) reported significant antioxidant activity of ethyl acetate extracts of two marine algae, *Nannochloropsis oculata,* and *Gracilaria gracilis* by using *in vitro* methods such as DPPH free radicle scavenging capacity, nitric oxide activity, iron chelation, and reducing power activity [60]. Barros-Gomes., *et al*. (2018) evaluated the antioxidant activity and protective action of red seaweed *Gracilaria birdiae* by *in vivo* study. They found this alga showed protective action on mice from CCl_4 induced damage as well as reduce weight and potential antioxidant activity in the aqueous extract [61]. Seaweeds from Kunakeshwar along the West Coast Maharashtra explored for antioxidant activity by Mole and Sabale, (2013). They found a good effect in the methanolic extract of *Enteromorpha intestinalis* and ethanolic extract of *Dictyota dichotoma* [62]. Vijayavel., *et al*. (2007) checked the minimum concentration of the extract exhibited a maximum of about 85% free radicle scavenging activity in albino rats. They suggested selected alga Chlorella vulgaris showed chemopreventive effect as well as lipid peroxidation during naphthalene intoxication [63].

Conclusion

This study offers various opportunities for developing the medical sector as well as exploring new bioactive compounds for pharmaceutical evaluation. However, in the future one, another benefit of this study is to study the mechanism of inhibition, as well as some more predictive studies, should be applicable in drug formulations. Currently, the development of new generation materials for wound healing and its dress is in demand. Tissue engineering tools and techniques are focusing on biocompatible material that can use as a remedy without harming an animal's body. A study about mechanisms of wound healing improves our potentiality to cure wounds at a faster rate by characterizing different phycocompounds from marine algae and their target effect in the cascade of wound repair. Many researchers suggested polysaccharide-based material can be applicable for wound treatment due to its prominent gelling ability, hydrophobicity, natural rigidity make it a perfect biomaterial for bioprinting of tissues and organs. Some future demands will be the formulation of hydrogels, 3D Porous scaffold, nanofibers, etc. Newer dressing investigation helpful to know the environment, the color of dressing, and alert to patient or person via smartphone as well as stem cell therapy in use and further development.

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