Review Article

Wound healing by functional compounds of Echinodermata, Spirulina and chitin products: A review

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Received: August2020 **Accepted:** October 2020

Abstract

Wound healing in humans and animals, occurs with a completely complex and advanced mechanism of stages: inflammation, proliferation, repair and regeneration. So far, many health and financial costs have been incurred in human society due to a lack of timely repairs. Therefore, in modern knowledge to heal all kinds of wounds, reduce repair time and prevent infection, much consideration is paid to the use of natural treatment methods and the use of biological science. In the meantime, seas have opened up a wide range of natural medicines for us. If new pharmacological findings show positive results from aquatic effects such as sea cucumber, sea urchin, starfish, algae and their products such as alginate and chitosan, they can be introduced as antibacterial, anti-coagulant, anti-inflammatory, anti-diabetic, anti-parasitic, anti-viral, anti-protozoan and anti-fungal compounds. In these products, many repair factors have been proven such as prevention of wounds from infections caused by bacterial, fungal and viral microorganisms, ease of use of the product, cheapness and availability, the ability to clean secretions and protect the skin, prevent the growth of granular tissue and repair fast without allergenic reactions. According to studies, Sea-derived products may increase pro-inflammatory factors and inhibit inflammatory factors, thereby enhancing wound healing. These factors increase the production of cytokines in wound sites. By increasing the command of phagocytic cells, cytokines cleanse the wound and prevent infection. In addition, stimulation of keratinocyte migration to wound edges, proliferation and differentiation of fibroblasts, and regulation of extracellular matrix proteins are mediated by the release of extra cytokines and growth factors.

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Keywords: Wound healing, Functional compounds, Echinodermata, Spirulina, Chitin

[DOR: 20.1001.1.2345315.2020.6.2.5.5]
[DOI: 10.52547/ijaah.6.2.23]

[DOR: 20.1001.1.2345315.2020.6.2.5.5]

[DOI: 10.52547/ijaah.6.2.23]

Introduction

Skin and skin wounds

The skin has three layers, the epidermis, dermis and hypodermis. The most superficial layer of the skin named the epidermis, which protects the human body against the environment. This layer is composed of different layers. The deepest layer of the epidermis calls the basal layer. This layer generation skin cells, which is why it is also called the germ layer. Langerhans cells, which are responsible for skin immunity, Tyrosinase, and melanocyte, which are responsible for producing melanin pigments and regulating skin color, are all located in the epidermis. (Geerligs *et al.,* 2011). The dermis layer has a superficial papillary part and a deeper reticular part. The dermis is placed between the epidermis and the hypodermis. The sensory receptors of the skin, hair follicles, apocrine glands, sebaceous glands, sweat glands, blood vessels and lymph are all in this layer. The hypodermis is the layer of adipose tissue between the dermis and the muscle layer. The thickness of this layer varies according to age, gender, race and nutrition. The hypodermis is structurally and functionally integrated with the dermis through the nerve and vascular net and along with the dermal appendages, such as the hair and the nerve endings (Geerligs, 2009).

When a wound occurs, depending on the extent of damage to different layers of skin and the type of wound, there are processes to repair these layers. The steps to improve skin layers can be summarized in five steps: After the coagulation and inflammation stages, the epithelialization and migration stage is the third stage, which includes the proliferation of basal cells and the migration of epithelial cells in the fibrin bridge inside the clot and as long as the individual cells are surrounded by similar cells, proliferation continues and then migration stops. (Ross *et al.,* 1970) Reproduction involves covering the wound with endothelial cells. At this stage, after four days, a new tissue called granulation tissue is formed. It takes about two weeks to complete this step (Zahedi *et al.,* 2010).

Types of wounds

Wounds are disorders of the functional structure of the skin and the soft tissue beneath it, which disrupts the integrity of the skin to protect against dehydration, bleeding, and the entry of germs. Skin lesions are caused by a variety of causes including physical, chemical and biological damage and according to the method and duration of repair; they are divided into two types, chronic and acute. Acute wounds such as cuts and burns usually involve the epidermis and dermis and heal completely in 8 to 12 weeks. However, chronic wounds for instance venous or arterial foot ulcers, diabetic foot ulcers and pressure ulcers usually related to physiological disorders caused by the cessation or slowing of wound healing and their repair time is more than twelve weeks (Ghaderi and Afshar, 2014).

Wound healing steps

Wound healing is a dynamic process including complex interactions between molecular, cellular, physiological, and biochemical activities that cause the regeneration and replacement of injured connective tissue at the wound site (Velnar *et al.,* 2009). Acute

[DOR: 20.1001.1.2345315.2020.6.2.5.5]

[DOI: 10.52547/ijaah.6.2.23]

wounds have four stages of healing, which are summarized as follows:

1- Homeostasis and coagulation phase:

The first step in wound healing is the homeostasis phase. The homeostasis and coagulation phase begins immediately after wounding. After skin damage, capillaries cause homeostasis by wound contraction within 5 to 10 minutes and platelet aggregation leads to coagulation cascade and secretion of cytokines and essential growth factors. Meanwhile, the fibrin matrix in the form of a temporary scaffold leads to wound stabilization (Gonzalez *et al.,* 2016).

2- Inflammatory phase:

The next stage of wound healing is the inflammatory or delayed phase of inflammation, which begins shortly after the coagulation and homeostasis phase. During different stages of this phase, vascular permeability and cell absorbed increase and mononuclear leukocytes accumulate and macrophages enter (Doillon *et al.,* 1985, Velnar *et al.,* 2009).

3- Epithelialization phase:

The third stage, as the epithelialization or migration phase, involves the proliferation of basal cells and the migration of epithelial cells within the fibrin bridge within the clot. This proliferation continues until individual cells are surrounded by similar cells and then migration stops (Ross *et al.,* 1970).

4- Fibroplasia phase and tissue differentiation:

The fourth stage is the stage of fibroplasia, which begins a few days after the wound. Fibroblast proliferation, underlying material accumulation, and collagen production occur at this stage (Doillon *et al.,* 1985), and in the final stage, tissue differentiation occurs, in which collagen regeneration, wound shrinkage, and re-pigmentation occur. Chronic ulcers usually stop in the inflammatory phase and do not progress in wound healing, but acute ulcers progress through all stages in a scheduled manner over four weeks. It is clear that the speed of wound healing depends on numerous factors, including blood flow to the area, wound size, oldness and health of the patient, the presence of foreign objects and microorganisms, as well as the patient's nutritional status and medication (Darby and Hewitson, 2007; Velnar *et al.,* 2009).

Wound healing products gained from aquatic organisms and their products

The effects of primary and secondary metabolites of many substances of natural origin, both plant and animal, have been discovered and exploited today (Kanani *et al.,* 2014; Sahraei *et al.,* 2019; Ebntorab *et al.,* 2020). However, despite the existence of unique species of marine life in our waters, fewer studies have been done in this area. Today, science has proven that phycocyanins, carotenoids, selenium and gamma-linoleic acid, seaweed, have strong antioxidant effects and have significant radical scavenging potential (Țigu *et al.,* 2016). In addition, to adapt to environmental conditions, different compounds are produced from some marine organisms,

[DOR: 20.1001.1.2345315.2020.6.2.5.5]

[DOI: 10.52547/ijaah.6.2.23]

such as echinoderms, called saponins (Kamyab *et al.,* 2020). Saponins, as secondary metabolites, have all the antioxidant, repair and anti-inflammatory properties with minimal side effects (Rinaudo *et al.,* 2006). The properties of several types of aquatic animals and their products are listed in next sections.

Chitin and chitosan

Chitosan is a biopolymer that has been widely used due to its low cost as well as biological properties for example biodegradability, antibacterial and health safety. Chitosan is a cationic polysaccharide gotten from the alkaline deacetylation process of chitin. The main sources of chitosan production are the cell wall of fungi and the outer skin of crustaceans. The major biochemical actions of chitin and chitosan in wound healing include stimulation of fibroblasts, motivation of polymorphonuclears, production of cytokines, assistance in the synthesis of type IV collagen and migration of giant cells. Chitosan activates various repair phases, polymorphonuclear cells, vascular endothelial cells and fibroblasts. Previous research has shown that chitin and chitosan have a positive effect on the migration of endothelial cells and fibroblasts and are effective in wound healing (Peck, 2011).

Many researchers have studied the strong and natural antibacterial properties of chitosan, which has positively charged polysaccharide (Rinaudo *et al.,* 2006; Yang *et al.,* 2019; Li *et al.,* 2019) and this biopolymer and its family compounds have been introduced as a substance with bactericidal properties. While it has shown very little toxicity to cells, it has also reduced the growth of antibiotic-resistant bacteria in dry and wet conditions (Lee *et al.,* 2009; Liu *et al.,* 2004; Vallapa *et al.,* 2011). This product can also act as a blood-clotting agent and relieve inflammatory pain. Positively charged chitosan can also be connected to other negatively charged substances such as alginate (alginate is currently being studied as a stem cell retainer in biotechnology) (Rinaudo *et al.,* 2006). Chitosan is an effective granulation accelerator in wound healing due to a better function as a bioactive wound dressing compared to other conventional wound dressings. (Boateng *et al.,* 2008) Like other restorative drugs, changes in the surface properties of chitosan particles are intended to facilitate movement in tissue and blood and increase its effectiveness. Due to the high flexibility of chitosan, this substance can be easily used as a carrier for proteins, enzymes and other micro factors. Chitosan is easily completed with compounds such as hyaluronic acid and chondroitin sulfate. Research has shown that chitosan acts as a matrix metalloproteinase inhibitor (MMP) and acts on skin fibroblasts. The minor the molecular weight of chitosan, the greater the inhibition of matrix metalloproteinase, so as the level of chitosan particles decreases, the wound healing rate increases (Park *et al.,* 2004).

Echinoderms

Sea cucumbers are one of the most significant species of echinoderms and belong to the Holothuridea. Approximately 1,400 living species of this genus have been identified (Pawson *et al.,* 2007). Anticancer, anticoagulant,

[DOR: 20.1001.1.2345315.2020.6.2.5.5]

[DOI: 10.52547/ijaah.6.2.23]

antihypertensive, anti-inflammatory, antimicrobial, antifungal, antiviral, antioxidant, anti-atherosclerotic, anti-tumor and accelerate wound healing are some of the known biological activities in sea cucumbers. Studies have shown that the presence of substances such as saponins, chondroitin sulfate, glucose aminoglycans, sulfate polysaccharides, glycoproteins, glycosphingolipids and essential fatty acids in sea cucumbers are the source of such biological properties (Bordbar *et al.,* 2011). Sea cucumbers produce compounds called saponins to adapt to environmental conditions to eliminate risk factors and factors such as oxidants and cellular destroyers in tissues (Klita *et al.,* 1995). Some properties of Saponins include hemolytic, anti-tumor, anti-bacterial, anti-inflammatory, anti-viral, ichthyotoxic, cytostatic and anti-neoplastic (Kerr *et al.,* 1995). Anti-angioedema has also been identified from sea cucumber. (Tian *et al.,* 2005) More studies have published that sea cucumber extracts can have inhibitory and deadly effects against some gram-positive and gram-negative bacteria (Rumpold *et al.,* 2013). Sea cucumber extract has been specified as a potential antimicrobial agent in several studies and the antifungal activity of their methanolic extracts has also been studied (Abraham *et al.,* 2002). Sea Cucumber body walls contain stronger antibacterial extracts. In general, echinoderms can be studied as an ecological natural source for discovering new antibiotic compounds and preventing open wound infection (Haug *et al.,* 2002). Today, we are trying to replace industrial antioxidants with natural types, among which sea cucumber is one of the appropriate choices. Studies on sea cucumber extracts have shown that, these compounds, in addition to strong antioxidant properties, also have antiviral, anti-tumor, anti-cancer effects, and in the pharmaceutical industry of some countries are effective in treating skin cancer (James, 2001). According to recent research by scientists, connective tissues of the skin, body membrane and endocrine glands of cucumber tubules contain polysaccharide compounds that have a great effect on improving inflammatory diseases, ossification, prevention of tissue aging and disease and atherosclerosis. In addition, its mucopolysaccharide has a high anti-cancer effect (Zhao *et al.,* 2007). It has also been documented in several studies that cucumber tissues lesions can be used as potent sources for dealing with inflammation (Collin *et al.,* 1998; Collin *et al.,* 2004) Extracts produced with alcoholic solvents have reduced cyclooxygenase activity in inflamed tissues. Therefore, these extracts can be considered as a novel marine source as an anti-inflammatory drug in wound healing (Herencia *et al.,* 1998). Zeng and his colleagues examined the antioxidant activity of sea cucumbers and found that the internal tissues of dried sea cucumber samples had more antioxidant activity than fresh samples (Zeng *et al.,* 2007). In another study by Chenghui, ethyl acetate extracts of Atlantic cucumber were found to have higher antioxidant activity than aqueous extracts from viscera. (Chenghui *et al.,* 2007) The antioxidant properties of fresh and dried sea cucumber with and minus internal organs have also been investigated by Zhong *et al*. The Sea cucumber examined showed the ability to completely curb free radicals, so that according to experiments, it was able to eliminate the harms of free radicals. Rehydrated dried samples (re-added), particularly those with internal organs, had greater antioxidant activity than their newer counterparts. . Conferring to the findings of this study, there is a weak correlation between the radical discharge capacity and the total phenolic content of sea cucumber, which indicates that in addition to the main components, other components of sea cucumber can also contribute to the antioxidant activity of this marine organism. (Zhong *et al.,* 2007) in 2000, Villasin *et al*. Detected the antifungal activity of triterpene glucosides of marmoratosides type A, B and 17_alpha_hydroxy impationside A and 25asetoxbivittoside D, along with two other glycosides of terpene impatienside A and bivittoside D in sea cucumber. The structures of triterpene glycosides were identified by spectroscopic data and biochemical methods and two-dimensional NMR. The antifungal activity of type A and B marmarathosides impatinside A and biotoside D has been proven against A. Niger and C. Albicans fungal strains (Villasin *et al.,* 2000).

Spirulina

From ancient times the plants have been used as a medicine to speed up the healing process of wounds. But there has been no scientific evidence about the effectiveness of plants and the knowledge of the compounds and how it works. Some herbs can be formulated with simple methods for any skin damage, whether cut or burn, to be able to use them as the best and easiest candidate in natural remedies In addition; these plants are effective natural and healing substances against endocrine syndromes and other diseases (Arulselvan *et al.,* 2014). Today, algae have become very widespread due to their excellent performance as medicine (Barrow and Shahidi, 2007) Studies have shown that Spirulina algae extract, in addition to helping increase the survival of fibroblasts at the wound site, strengthens the antioxidant mechanism of fibroblasts, controls the oxidative stress process and helps to repair and heals wounds (Jung *et al.,* 2016). Spirulina is a vascular, blue-green algae produced in many high-pH alkaline lakes. This algae contains about 70% protein and contains 18 of the 22 non-essential amino acids and all essential amino acids, make it a unique algal with complete protein (Somchit *et al.,* 2007). Numerous studies have confirmed that various components of spirulina, such as phycocyanin, carotenoids, selenium and gammalinolenic fatty acid, have antioxidant effects and have significant radical scavenging potential. As a result, spirulina can have an effective factor for wound healing and treatment of diseases caused by oxidative stress, inflammation, allergies, viruses, immune system diseases, liver diseases and cancers (Shetty *et al.,* 2006). Research on spirulina by the World Health Organization and various scientists around the world has confirmed the fact that spirulina is a mixture of different compounds that no other substance alone contains all of them. Spirulina protein is higher than all other foods and contains all the micronutrients in the wound healing process (Ciferri *et al.,* 1983; Chronakis *et al.,* 2000).

Table 1. Introduction of some species of sea cucumber and their wound healing effects

Sea cucumber species	Properties	Description
Stichopus chloronotus	Speed in wound healing	In one study, the effect of 0.1%, 0.5% and 1% aqueous extract concentrations on the wound was investigated by wounding in Balb Si mice. The rate of wound healing and its pathological changes in the 10-day process were studied by taking pathological samples in the first, third, sixth and eighth days. Result: The dose was 0.5 / the most optimal dose and had a high wound healing rate (Mazliadiyana *et al.,* 2017).
Stichopus *chloronotus*	Antioxidant activity	One study found that the aqueous extract of this sea cucumber had a higher content of unsaturated fatty acids (PUFA) and (DHA) and a completely superior antioxidant activity (approximately 80%) compared to this sea cucumber organic extracts (Althunibat *et al.,* 2009).
Sthicopus hermanii	More effective wound healing in drug release in hydrogel dressings	In one study, dressing wound burns with S.hermanii sea cucumber with hydrogel was investigated. As a result of increased wound contraction on days 21 and 28 compared to days 7 and 14 of burn wounds, hydrogel dressing for delivery of "gamat" The skin acts as a reservoir with a continuous release that facilitates the healing process, especially in the final stage (Zohdi *et al.,* 2011).
Sthicopus hermanii	Increase in the number of lymphocytes at the wound site at the appropriate concentration of the extract	In one study, the effect of Stichopus hermanii extract that named golden sea cucumber on the number of lymphocytes during the healing development of traumatic ulcers of the oral mucosa of rat mice in Indonesia was investigated. This type of sea cucumber contains glycosaminoglycans, heparin sulfate and chondroitin sulfate, which can have a positive effect on the wound healing process and speed up the traumatic, wound healing process by increasing the number of lymphocytes. Golden sea cucumber extract has been used by a freeze-dried method with three doses of 0.20%, 0.40% and 0.80%. Results: In the pathological examination of wounds, 0.40% sea cucumber extract showed the highest lymphocyte count and the lowest white blood cell count was related to the control group. (Arundina *et al.,* 2015)
Sthicopus hermanii	Regulation of anti-inflammatory genes	In a prospective observational study, this gel-based cucumber (Carbopol) was used topically in people with diabetic foot ulcers for 12 weeks. The results presented that there was a major difference in TNF-α levels between weeks 0 versus week 8, There was a difference in level of 0 vs. 10 and 0 vs. 12, respectively ($p = 0.005$, $p = 0.006$ and $p = 0.010$). The reason for this is that the saponin content of sea cucumber extract may break the production of TNF-α-induced lipopolysaccharide by NF-κB. NF-κB is a version of the factor that controls the transcription of many genes related to inflammation. El (Barky *et al.,* 2017) In addition, the main fatty acids in sea cucumber (EPA and DHA) can stimulate the production of resolutions and anti-inflammatory mediator proteins over the cyclooxygenase (COX-2) and lipoxygenase (5-LOX) pathways. Resoluin primarily inhibits IL-1β production, while protecting TNF and IL-1β (Calder, 2010).
S. horrens	Wound shrinkage in different phases according to the type of application	Topical use of S. horrens proved a significant effect on minor wounds on day 4 ($P < 0.001$), but on days 8, 12, 16 and 21 showed no significant change compared to negative controls ($P < 0.001$). > 0.05) This suggests that direct topical use of sea cucumber can cause wound contraction in the early stages of wound healing. In contrast, hydrogels containing sea cucumber, and the use of diverse species, may help to change the rate of wound contraction in different phases (Subramaniam *et al.,* 2013).
Stichopus badionotus	Antibacterial properties (effective in controlling *Staphylococcus aureus* infection)	Sea cucumber extract has the possible to become an alternative source of anti-MRSA drugs. Methicillin-resistant Staphylococcus aureus (MRSA) stands as one of the most important subspecies of Staphylococcus aureus and differs from other subspecies in that it is not effective in treating common antibiotics. This type of Staphylococcus aureus is resistant to beta-lactam antibiotics so that these antibiotics have no effect on the treatment of infections. Although bacteria are also present in healthy people, resistance to antibiotics can lead to severe infections and even death. The prevalence of MRSA is higher, especially in nosocomial

		infections, patient care centers, in patients with open wounds, in patients with prosthetic implants, and in patients with weakened immune systems (Mariana *et al.,* 2011).
Bohadschia mamorata, S. variegatus, S. badionotus	Antioxidant properties	Sea cucumber can scavenge free radicals. Excessive free radicals are related to the impaired wound healing. The antioxidant properties of these species have been attributed to their coelomic fluid and intracellular contents (Hawa *et al.,* 1999).
Holothuria scabra, Holothuria leucospilota, S. chloronotu	Antioxidant properties	High antioxidant activities against free linoleic acid radicals of these three species of sea cucumber were reported at 77.46%, 64.03% and 80.58%, respectively (Althunibat *et al.,* 2009).
Cucumaria frondosa	Antioxidant properties	The antioxidant activity of Atlantic cucumber has been related to its phenolic content, especially flavonoids that act in contradiction of the oxidative reaction (Mamelona *et al.,* 2007).
Cucumaria frondosa	Antibacterial properties	The walls and different parts of the body of Cucuari frondosa have been examined separately and have shown activity against gram-positive bacteria. Eggs of this species had relatively higher antibacterial properties than adults (Haug *et al.,* 2002).
Storopus choronotus	Better wound healing power at optimal dose compared to conventional drugs	The wound healing properties of this species of sea cucumber have been observed in the early stages of wound healing. Medium dose, ٪ 0.5 W / W of its aqueous extract with a mixture of emulsifying ointment, from the sixth day after wound formation, the highest ratio of wound reduction compared to other groups (including concentrations of 0.1%, 0. 1 ٪ and positive and negative controls). At the optimal dose of S. choronotus, the healing of small wounds was meaningfully better than the healing of wounds with the standard gold drug (flavin - yellow acridine with antiseptic properties) (Mazliadiyana *et al.,* 2017).
Actinopyga echinites, Actinopyga Militaristic, Holothuria atra, Holothuria scabra	Antibacterial and antifungal properties	Microbial agents are one of the most common factors preventing wound healing, and antibiotics are usually used to control them. On the other hand, pathogenic bacteria become resistant to antibiotics after a while Therefore, research is needed to discover resistant antibiotics. In the study of antibacterial and antifungal actions of alcoholic extracts of sea cucumber, these species have been studied. The extract of these organisms has antibacterial effects against infectious microorganisms (Al-Haj *et al.,* 2010).
Holothuria edulis, Stichopus horrens	Effect on cancer cells and cytotoxic properties	In a study, the effects of aqueous extracts of these two species on lung cancer cells and TE1 were investigated and the ability to collect radicals (DPPH) with IC 50 at 2.04 Mg / ml and 8.73 Mg / ml was investigated. Both extracts inhibited the oxidation of beta-carotene with the help of free radical linoleate with 79.62 and 46.66%, respectively. Sea cucumber *S. horrens* had the highest cytotoxic effect on both cancer cells. This effect was observed in IC50 of 15.5 and 4 Mg / ml, one-to-one (Althunibat *et al.,* 2013).
Holothuria holothurian	Cytotoxic properties	In a study, the cytotoxic effect of Holothuria sea cucumber extract on shrimp Was studied. In this study, the highest effect was related to methanolic extract of sea cucumber with IC50 equal to 50.5 Mg / ml and then sea cucumber with methanolic extract with IC50 equal to 70 Mg / ml (Mohammadizadeh *et al.,* 2013).
Holothuria scabra	Antifungal properties	One study showed a specific antifungal effect on the methanolic extract of *Holothuria scabra* from the respiratory tract of this creature as a barrier to Aspergillus niger 50 mm in diameter with a concentration of 18 µg / ml extract (Mohammadizadeh *et al.,* 2013).
Holothuria scabra	Antifungal properties	Studies have informed an antifungal compound from the sea cucumber *Holothuria scabra*, a substance called Herein. This combination of three triterpene glycosides, against 7-human pathogens; *Candida psedotropicalis, Cryptococcus neoformans, Candida albicans, Fonsecaea compeca, Microsporum Gypseum, Trichophyton rubrum* and *Aspergillus fumigatus*. Glycoside triterpenes called Scabraside A, Echinoside A and Holothuria A1 have been identified to have antifungal effects in the range of less than 16 and 1 µg / ml (Sun *et al.,* 2007; Xiong *et al.,* 2008).

[DOR: 20.1001.1.2345315.2020.6.2.5.5]

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Staurocucumis liouvillei	Antiviral properties and therapeutic properties in immunodeficiency disorders	Triterpene trisulphate glycosides liouvillosides A, B derived from this species have antiviral activity. According to the effects of bioassay activity, both glycosides had antiviral activity against genital virus type 1 (HIV_1). Sea cucumber chondroitin sulfate can also inhibit HIV activity and prevent its progression. It can be said that these marine invertebrates are a natural therapeutic agent in contrast to HIV disorders and acquired immunodeficiency syndrome (Zou *et al.,* 2005; Mourão *et al.,* 1998).

Table 2. Introduction of some species of starfish and sea urchins and their wound healing effects

Species	Properties	Description
Starfish **Asterias rubens**	Lysosomal effects, Hemolytic and Antibacterial	Several tissues of *A. rubens* showed similar lysozyme effects. The hemolytic activity has also been observed in almost all starfish species In particular; their body walls had stronger extracts. The wide variety of bioactivity among starfish extracts indicates that the species has different antimicrobial capabilities. Therefore, these sea urchins can categories as a sustainable biological source for the discovery of new antibiotic compounds (Haug *et al.,* 2002).
Sea urchin **Strongylocentrotus droebachiensis**	Lysosomal, antibacterial effects	The lysozyme effects and hemolytic activity, in particular, their body walls were stronger. They have different antimicrobial properties and can be considered as a stable source for the finding of new antibiotic combinations (Haug *et al.,* 2002).

Table 3. Introduction of wound healing effects of some type and extracts of Spirulina

Type	Properties	Description
Methanolic, ethanolic and aqueous extracts of Spirulina	Accelerated effects on wound healing and the effect on fibroblast cell proliferation	In one study, wound healing of methanolic, ethanolic, and aqueous extracts of Spirulina (50 µg / ml) was performed on human dermal fibroblast cells (HDF) in vitro. Among the extracts, aqueous Spirulina extract has been very effective in stimulating, proliferating and migrating HDF cells at certain concentrations. And the wound site within 24 hours after treatment with aqueous extract, showed an increase in wound closure. Methanolic and ethanol extracts have also presented a proliferative effect, but these extracts are weaker in fibroblast cell migration and wound closure than aqueous extracts. According to the phytochemical characteristics of Spirulina extracts analyzed via LC-MS / MS, Factors involved in accelerating wound healing contain: cinnamic acid, narigenin, kaempferol, temsirolimus phosphatidylserine isomeric derivatives & sulphoquinovosyl diacylglycerol. The findings of this study suggest that blue-green algae can have potential biomedical applications for the treatment of various kinds of wounds, even chronic wounds, such as chronic diabetic wounds or wounds infected with fungal infections (Syarina *et al.*, ٢015).
Spirulina Nano fiber dressing	Anti-inflammatory And antioxidant effect	In one study, a spirulina Nano fiber dressing (PCL) was produced by enhancing the antioxidant mechanism to heal skin wounds. The study found that skin regeneration is a multifaceted process that involves the proliferation and differentiation of cells, but sometimes there is an obstacle to complete skin repair, the top one being the overproduction of reactive oxygen species (ROS) due to infections or inflammation. ROS are tiny, unstable, reactive molecules that have ability oxidize proteins, lipids, and DNA. ROS are shaped by the incomplete reduction of an oxygen electron. ROS includes oxygen anions, free radicals including superoxide and hydroxyl radicals, and peroxides for example hydrogen peroxide (H_2O_2). Spirulina blue-green algae have antioxidant and anti-inflammatory properties, so they can be used to reduce the negative effect and pressure of ROS in the wound healing process. In this study, Nano fibers enriched with Spirulina-PCL extract as a skin wound dressing were evaluated for their antioxidant mechanism. This in vivo study showed that spirulina extract and its dressing, in addition to helping to increase the viability of fibroblasts at the wound site, Control the stress-induced oxidative enhancement (ROS) process by enhancing the antioxidant mechanism of fibroblasts And helps heal wounds (Jung *et al.,* 2016).

[DOR: 20.1001.1.2345315.2020.6.2.5.5]
[DOI: 10.52547/ijaah.6.2.23]

Table 4. Introduction of wound healing effects of some forms of chitin (crustacean shell)

Type	Properties	Description
Chitin, chitosan Chitin powder and chitin hydrogel	Increased lysozyme activity, accelerating wound healing effect	In one study, chitin and chitosan hydrogels were applied as wound dressings, which resulted in the sensitivity of chitin hydrogel to chitosan in lysozyme activity. Chitin, chitosan, chitin powder and chitin hydrogel were implanted in the incision. Among them, chitin powder was extra effective than chitin and chitosan as a wound- healing accelerator. Wounds treated with chitin hydrogel were totally epithelialized and the granular tissues were almost replaced by fibrosis and hair follicles. . Approximately 7 days after the initial wound was treated, the treated skin showed the top tensile strength and collagen fiber arrangement, which was quite similar to normal skin. Therefore, due to its ease of use and high effectiveness, chitin hydrogel is considered a suitable wound healing factor (Cho *et al.,* 1999).
Chitosan nanoparticles	Angiogenicity	In one study, the effect of angiogenesis of chitosan nanoparticles in the treatment of burn wounds on an adult male NMRI model was investigated. In this study, 42 mice were randomly separated into control and experimental groups. Under sterile conditions and anesthesia, a circular wound with a diameter of one centimeter and full thickness of the skin was placed on the back of each mouse. The day of surgery was considered day zero and from the first day all mice were treated topically with chitosan nanoparticle solution daily. Mice were killed with chloroform on days 28, 14, and 7 after daily treatment and wound samples were taken from each mouse. Histological studies have been performed on the relevant samples. The findings of this study and the analysis of statistical data show that the number of angiogenesis and the diameter of blood vessels improved meaningfully ($P < 0.001$) compared to the control group. According to the findings of this study, it can be said that chitosan nanoparticles have a positive effect on angiogenesis (Jabbari *et al.,* 2012).

Conclusion

Wound healing is situated one of the most important issues that science has always faced; Wounds from accidents, trauma, bullets, metabolic diseases and many more have all made this a major challenge in society. Today, many humans and animals suffer from a variety of acute and chronic wounds that affect society both spiritually and economically. Consequences of not healing wounds, pain and infection caused by it, leaving scars and expensive chemical drugs, are just a few of the problems in this category. On the other hand, due to the use of chemicals to eliminate these risk factors that lead to problems in humans and other organisms and due to the presence and increase of factors such as oxidants and cell destroyers in the tissues that cause them. They lead to cancer and tumor induction and non-healing of wounds. Drugs of bio-origin or biopharmaceuticals should be given serious attention.

The oceans have always been the habitat and source of natural products, and compounds found in marine organisms have been a power source of nutrients for food, pigment, medicine, and medicine (Jha and Zi-rong, 2004).

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[DOR: 20.1001.1.2345315.2020.6.2.5.5]

[DOI: 10.52547/ijaah.6.2.23]

Currently, science has proven that phycocyanins, carotenoids, selenium and gamma-linolenic acid, spirulina, have strong antioxidant effects and have significant radical scavenging properties. Compounds are also produced from echinoderms to adapt to environmental conditions, called saponins. Saponins, as secondary metabolites of sea cucumber, bring us all the antioxidant, repair and anti-inflammatory properties with minimal side effects. Chitosan biopolymer is also known as a facilitator of wound healing by activating fibroblasts, activating polymorphonuclears, producing cytokines, helping to synthesize type IV collagen, and migrating macrophage cells. The best bio-carriers with the least sensitivity in today's wound-healing drugs. Due to the constant presence of relatively high levels of bacteria, echinoderms, viruses and pathogenic fungi have antimicrobial and wound healing mechanisms. For many years, these creatures have been traditionally used by the natives of East Asia without knowing the scientific reasons (Reich *et al.,* 2006). Because today in modern medicine in developed countries, for the optimal treatment of skin wounds, reducing the healing time and preventing their infection, much attention has been paid to the use of natural and biological treatment methods, It is necessary to identify the effects of the metabolites of native species as much as possible in order to achieve the highest effect and to make drugs of biological origin and self-sufficiency in this field.

Conflict of Interest

The authors declare that they have no conflict interest.

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