

Antioxidative and Regenerative Potential of Sea Cucumber: Focus on Bioactive Compounds and Exosome-Based Strategies for Combating Skin Oxidative Stress

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Abstract: Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, has a profound effect on skin health. This imbalance contributes to skin damage, premature aging, and the development of various dermatological conditions by modulating key signaling pathways with pro-inflammatory or antioxidant effects, such as NF- κ B, JAK/STAT, Nrf2, MAPK/AP1, and SIRT1/FOXO. So, the application of antioxidant compounds, particularly those derived from natural sources, is essential for protecting the skin against ROS-induced damage. Sea cucumber, a marine invertebrate known for its remarkable regenerative capacity, contains bioactive compounds, including phenolics, proteins, and polysaccharides, which exhibit antioxidative and anti-inflammatory properties. These bioactive components may offer protective effects against oxidative stress within the skin. Therefore, this study will first evaluate the potential of sea cucumber-derived bioactive compounds in mitigating oxidative stress by examining their ability to counteract ROS-induced cellular damage caused by ROS and their potential role in promoting skin repair and regeneration. The review will also discuss the underlying mechanisms, including key signaling pathways, and explore the therapeutic potential of sea cucumber-derived exosomes as a novel strategy to treating oxidative stress-related skin disorders. Finally, a comparison is made between the efficacy of the sea cucumber crud extract with its derived exosome in treating oxidative stress-induced skin damage.

Keywords: skin, oxidative stress, sea cucumber, exosome

Introduction

The skin, like other organs of the body, undergoes gradual changes over time. However, unlike other organs, skin is constantly exposed to harmful environmental factors that can cause cellular and molecular damage.¹ Oxidative stress is identified as one of the major causes of cellular damage, which occurs due to an imbalance between free radicals and antioxidant factors. This imbalance can impair the skin regeneration process and cause aging as well as various skin diseases.¹ Both internal and external factors contribute to the production of ROS in the skin.² Regarding the internal pathway, cellular metabolism in the mitochondria is the main source of the ROS production via respiratory chain reactions through ROS-producing enzymes such as NADPH oxidases, cytochrome P450 enzymes, etc.^{3,4} In the case of external factors, redox imbalance is caused by environmental factors including the pollution, ultraviolet (UV) radiation, and even poor diet that can reduce the antioxidant potential in the body.¹ Therefore, due to the destructive impacts of oxidative damage on skin health, various therapeutic methods have always been used to reduce or eliminate its effects.^{5,6} In this case, the use of compounds with antioxidant activity, including those derived from natural sources, is of great interest.

Sea cucumbers, marine invertebrates, have considerable regenerative potential, which makes them a good source of bioactive factors with anti-inflammatory, antioxidant and skin regeneration abilities.^{7,8} The most important bioactive compounds in sea cucumbers include polysaccharides, proteins, phenolic compounds, carotenoids, and saponins. All of these compounds have strong antioxidant properties.⁷ The phenolic compounds, including flavonoids and phenolic acids, as the most abundant agents in this marine invertebrate, show extraordinary antioxidant properties.^{9,10} The antioxidant effect of hydrolyzed proteins and their peptides has also been demonstrated, which depends on their amino acids composition and sequence as well as the molecular weight of the peptides (molecular weight ≤ 20 kDa is desirable).¹¹ Moreover, the antioxidant activity of sea cucumber polysaccharides such as fucosylated chondroitin sulfate has been indicated.^{12,13} However, the activity of these bioactive compounds depends on the species of sea cucumber, the part of the body they are extracted from as well as the processing method used.⁷ According to the beneficial effect of the sea cucumber bioactive molecules, recently, various studies have been conducted on the advantages of the extracellular vesicles (EVs) derived from this invertebrate.¹⁴

EVs, including exosomes, are nanoscale vesicles secreted by the cells and play an important role in intercellular communication and different biological processes.¹⁵

Exosomes are nano-vesicles (30–150 nm) secreted by different cell types which have raised as important mediators of cellular cross-talk in skin physiology and pathology.¹⁶ They contain diverse cargo of proteins, lipids, and nucleic acids, enabling them to regulate various biological processes related to skin health.¹⁶ In wound healing, exosomes can increase cell proliferation and migration (fibroblast and keratinocytes), angiogenesis, collagen synthesis, thereby enhancing tissue regeneration and decreasing inflammation.^{17,18} About skin aging, exosomes play crucial roles in the increasing of the collagen and elastin production, harnessing matrix metalloproteinases (MMPs), and reducing oxidative stress, caused the skin elasticity improvement and reduced wrinkle formation.¹⁹ In pigmentation disorders, including vitiligo and melasma, exosomes can control melanin synthesis via microRNAs and proteins that influence the MITF–tyrosinase pathway; and suppressing hyperpigmentation.²⁰ Furthermore, in inflammatory skin diseases like atopic dermatitis²¹ and psoriasis,²² exosomes can modulate immune responses by regulating the Th17/Treg ratios and suppressing pro-inflammatory signaling pathways like JAK/signal transducer and activator of transcription (STAT) and nuclear factor-kappa B (NF- κ B), thereby decreasing inflammation and promoting skin repair.²³ In addition to their biological roles, exosomes are being explored as diagnosis and prognosis biomarkers, as well as natural nanocarriers for therapeutic and cosmetic applications due to their good biocompatibility and targeted delivery potential.²⁴

Exosomes derived from sea cucumber have also shown favorable results in terms of antioxidant and anti-inflammatory activity.²⁵ Exosomes can be isolated from different part of the sea cucumber such as intestine and respiratory organs but the body wall is a more common source for isolation of these vesicles.²⁵ Exosome derived from sea cucumber can comprise bioactive compounds such as peptides, collagens and other molecules with antioxidant ability and they can provide their antioxidant properties by decreasing the glutathione depletion, reducing the mitophagy and mitochondrial superoxide levels.^{14,25,26} Nevertheless, exosome content and activity can vary based on the tissue from that they are derived. The antioxidant and anti-inflammatory properties of sea cucumber bioactive compounds and their derived exosomes make this marine invertebrate a noteworthy candidates for pharmaceutical and cosmetic applications.^{27,28} So, this article focuses on the antioxidative and anti-inflammatory effects of sea cucumber-derived exosome and bioactive factors by comparing their potential to enhance skin regeneration.

Oxidative Stress Effect on the Skin Health

The skin is the largest organ of the body, which serves as a protective barrier against the external environmental factors. Oxidative stress is a process that occurs due to the imbalance of the redox homeostasis in the skin following the internal or external events.¹ It can significantly affect skin health, leading to premature aging, inflammation, and different skin disorders.²⁹ This imbalance can disrupt skin cells and skin elasticity by damage to the collagen, elastin and other essential components, resulting in wrinkles, and other obvious signs of skin aging.³⁰

As previously mentioned, redox homeostasis disruption results in high ROS production in the cell. Cellular ROS production is attributed to the organelles including the mitochondria,⁴ endoplasmic reticulum (ER),³¹ and peroxisomes³² with their own antioxidant system to protect cells from oxidative damage.

Mitochondria are considered the main cellular structure in the production of ROS. Briefly during the oxidative phosphorylation process, electron leakage from the electron transport chain can reduce the oxygen and produce the superoxide species ($O_2^{\bullet-}$). Hydrogen peroxide (H_2O_2) as another type of ROS, is created from superoxide via superoxide dismutase (SOD) enzyme.³³ ER is the other organelle involved in the ROS production in the cells which have a critical role in the protein folding as well as Ca^{2+} homeostasis. ER dysfunction results in ER stress and ROS release. This phenomenon eventually causes the activation of apoptosis and autophagy pathways.³¹ The role of peroxisomes in ROS production is also dependent on the mitochondria and ER activity in the cell, so their dysfunction results in H_2O_2 production and release into the cell.³² It should be noted that organelles damage and ROS production in the cells can occur due to various factors such as environmental toxins, drugs, and aging. In addition to the internal factors, exogenous stimuli, such as UV radiation of skin cells, pollution and other environmental chemicals and infectious agents can cause ROS production and accumulation in the skin cells.^{34–36} In the physiological conditions, the low level of the ROS in the cells is essential for some of the cellular functions such as cell growth and proliferation. Thus, this favorable ROS level is maintained in the cells via the balance between oxidant and antioxidant factors.³⁷ Two important enzymes with antioxidative activity are catalase and glutathione (GSH) that are present in the mitochondria, protect the integrity of this organelle and clean the cells from the ROS species.³⁸ However, in the pathological condition (imbalance of the redox condition), the overall ROS accumulation in the cell can notably affect proteins, DNA, and lipids leading to cellular damage (Figure 1).³⁹

Excessive ROS can also induce the proinflammatory cytokines production by direct effect on some important signaling pathways including NF- κ B, nuclear factor erythroid 2-related factor 2 (Nrf2), JAK/ STAT, Sirtuin 1 (SIRT1)/ FOXO, and MAPK/AP1. These signaling pathways play important role in activating or inhibiting the expression of genes involved in cell survival and inflammatory responses (Figure 2).⁴⁰

Increased levels of ROS in skin cell activate the MAPK signaling pathway which in turn leads to the activation of other downstream transcription factors including AP1.⁴¹ The exact redox control of the AP1 activity is important for maintenance of the cellular homeostasis and aberrant activation of this transcription factor can disrupt cellular homeostasis and ultimately lead to secretion of proinflammatory cytokines.⁴²

The NF- κ B, a family of transcription factors with a crucial impact on the expression of various genes involved in cell growth, proliferation, immune and inflammatory response.⁴³ At low levels, ROS can initiate the NF- κ B activity and its

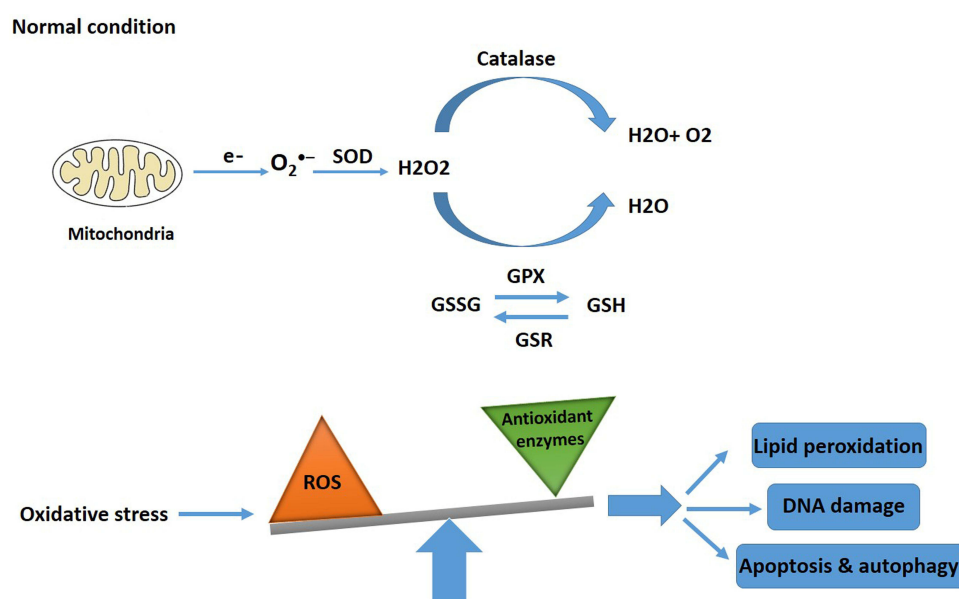


Figure 1 Redox homeostasis in the normal condition.

Notes: Redox homeostasis in the normal condition is established through the antioxidant enzymes in the cells such as SOD and GPX. However, in the oxidative stress state in the cells, imbalance of the ROS and antioxidant enzymes result in the cell damaged.

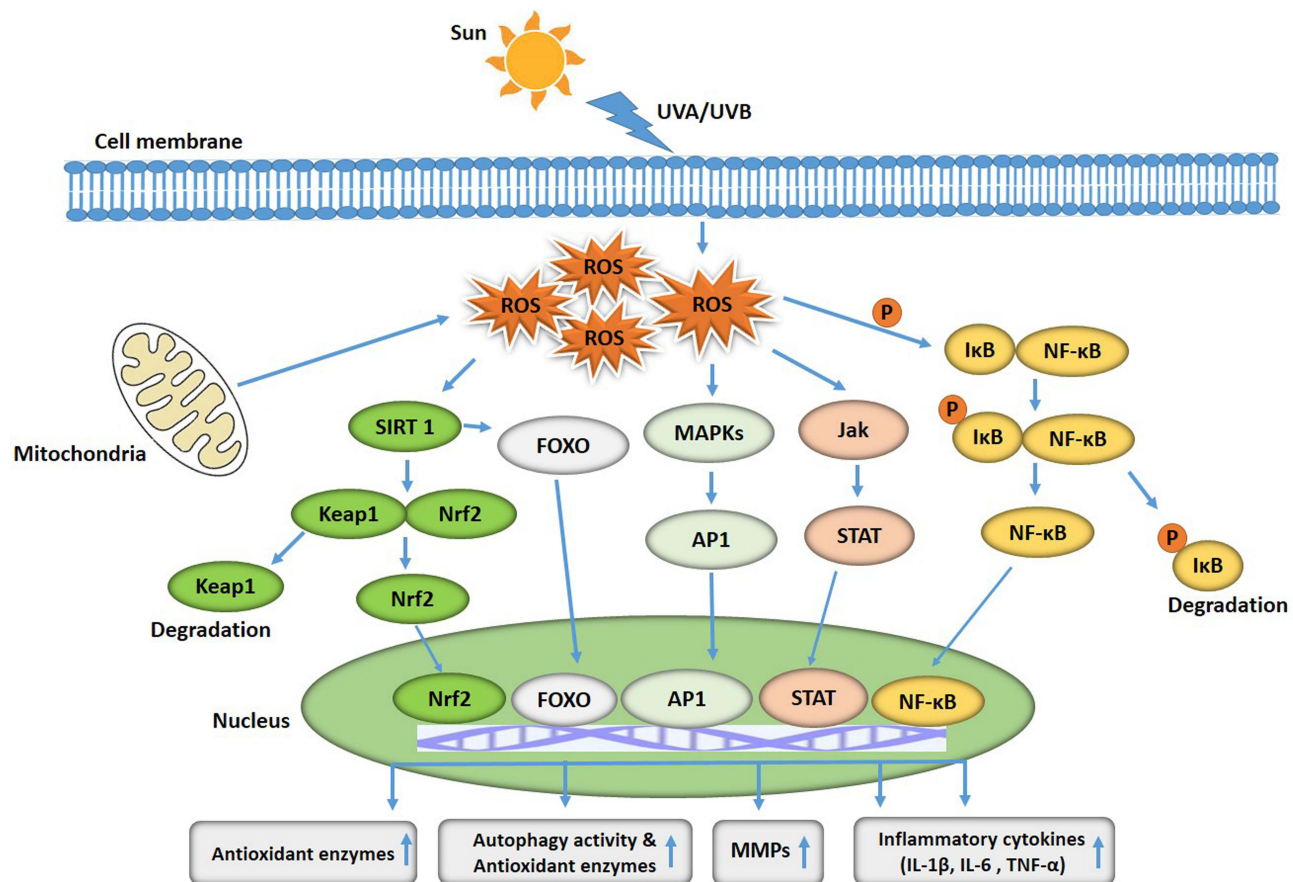


Figure 2 Cell signaling pathways activated by ROS in the skin cells.

Notes: Different cell signaling pathways are activated through the ROS such as NF- κ B, JAK/STAT, SIRT1/FOXO, and MAPK/API.

translocation to the nucleus.⁴⁴ ROS trigger the NF- κ B signaling pathway via I κ B phosphorylation by IKK (indicated by P) and subsequent degradation through the ubiquitin-proteasome system.⁴⁵ However, in the high concentration of the ROS, the IKK regulation is disrupted and resulting in sustained NF- κ B activation and inflammatory responses in the skin.⁴⁵ According to the previous studies activation of the AP-1 and NF- κ B can lead to the dermal destruction through increased of MMPs expression and degradation of different protein components in the ECM subsequently.⁴⁶ The continuous activity of MMPs can severely damage skin collagen and lead to the production of large amounts of abnormal elastic fibers, which can result in the cellular damage and aging of the skin. In addition, skin cell senescence can occur through the inflammatory factors secretion in the skin cells.⁴⁷

The Nrf2 and SIRT1 are other key signaling pathways that involved in the cellular protection against oxidative stress and inflammatory reactions. Their cooperation via reciprocal regulation play an important role in cellular hemostasis.⁴⁸ SIRT1 is a deacetylase that regulates different cellular process such as oxidant-antioxidant balance. Nrf2 is among the various signaling molecules that their activity can be affected by SIRT1. In the normal condition, Nrf2 interaction with Keap1 (Nrf2 inhibitor) caused its inactivation and prevents its translocation into the cell nucleus.^{49,50} But when the cell is exposed to oxidative stress, Nrf2 is transferred into the nucleus and activated the expression of the antioxidative and anti-inflammatory factors in the cells. This process is regulated by SIRT1 molecules. Thus, SIRT1's effect on the Nrf2 signaling pathway can directly modulate Nrf2 via deacetylation and its dissociation from the Keap1 or indirect by reduced expression of the Keap1 in the cell.⁵¹

The SIRT1/FOXO is another signaling pathway that is activated by oxidative stress in the cell and its activity may help in preventing or treating the inflammation and senescence effect on skin cells.⁵¹ FOXO is an autophagy-regulating factor that is regulated by deacetylation with SIRT1. FOXO activity can protect skin cells from oxidative damaged

through two mechanisms. At first it can eliminate the oxidative damaged macromolecules via autophagy process activation. Second, it can activate antioxidant enzymes such as CAT and SOD transcription factor.^{52,53} JAK/STAT signaling pathway is also among the important signaling pathway that is activated in the oxidative stress in the cell.⁴⁷ In the physiological condition, this signaling pathway is involved in the skin development and its barrier function in the body. However, its dysregulation in cellular stress such as ROS elevation in the cell, result in the autoimmune and inflammatory skin diseases such as atopic dermatitis and psoriasis.^{54,55}

Therefore, given the importance of skin health and the negative effects of oxidative stress on this organ through dysregulation of signaling pathways, redox hemostasis in the skin by eliminating excessive ROS in the skin cells is important.⁴⁰

In recent studies, the use of antioxidants and bioactive compounds derived from natural sources are considered, because of their stability, biocompatibility and bioavailability. Many bioactive antioxidants have been recognized between different natural sources, such as plants, fungi, and animal. Among them marine creatures such as sea cucumber with diverse effects and high efficiency in various therapeutic fields are of interest.⁵⁶

Sea Cucumber: A Source of Bioactive Compounds

Sea cucumbers are marine invertebrates commonly used in cosmetics products and traditional medicine. There are about 100 species of sea cucumbers with varied diets and habitats, which affect the bioactive compounds extracted from them. Traditionally, these invertebrates have been used to treat rheumatoid arthritis, joint pain, wound injuries, and asthma has been demonstrated.⁵⁷ Furthermore, different products are made from various parts of their body, most of which are dry tablets prepared from the body wall, whole sea cucumbers derived liquid extract and extract obtained from their skin.⁵⁸ Generally, sea cucumber possess a high amount of proteins (approximately 40–60%) and low level of lipids (10%) that are more unsaturated. The presence of minerals including Zn^{2+} , Fe^{2+} , Ca^{2+} and Mg^{2+} , vitamins such as B1, B2, A as well as carbohydrates in these organisms has also been shown.¹⁰

In addition, sea cucumbers contain different bioactive compounds, such as phenols, triterpene glycosides (saponins), proteins (collagen and peptides), and polysaccharides (fucosylated chondroitin sulfate), with potential antioxidant, anti-inflammatory, anticancer, anti-diabetic and antimicrobial activities. However, biological activities mainly depend on the species, chemical structures, molecular weights, and testing methods.⁵⁸

Sea Cucumber Antioxidant and Anti-Inflammatory Effect

As previously mentioned, the antioxidant effect of sea cucumbers is related to the presence of various bioactive compounds including phenolics, protein hydrolysates and peptides as well as polysaccharides and etc. These compounds eliminate free radicals in the body and reduce oxidative stress as well as inflammatory damages (Table 1).⁵⁸

Phenolic compounds, including phenolic acids and flavonoids, are secondary metabolites that have one or more aromatic rings and hydroxyl groups.⁶⁹ It has been indicated that the different parts of the sea cucumber body including the body wall, viscera and its tentacles contain high amount of phenolic compounds with strong antioxidant activity.⁷⁰

Phenolic antioxidants act by scavenging free radicals from the cells, suppressing singlet and triplet oxygen, or breaking down peroxides. They can neutralize ROS by donating a hydrogen atom or electron to them.⁷¹

Various in vitro and in vivo studies have assessed the potential health benefits of phenolic compounds derived from the sea cucumber.⁷ For example, the protective effect of the flavonoid extracted from these invertebrates has been shown by inhibiting DNA damage by hydroxyl and peroxy-radicals. According to Hossain et al, the antioxidant effects of sea cucumber phenolics are based on the nature of phenolic compounds and the part of body which they are derived.⁶³ Furthermore, anti-inflammatory effects of these compounds have been demonstrated through its inhibitory effect on the pro-inflammatory cytokines production in the cells.⁷² Therefore, it can be concluded that the phenolics compounds can have anti-aging effect.

Protein hydrolysates and peptides are other bioactive compounds with antioxidant effect. Lin et al's study showed the anti-aging effect of sea cucumber hydrolysates, which was related to the peptides with low-molecular-weight (<3 kDa).⁷³ As stated by their results, the anti-aging mechanism of sea cucumber peptides is attributed to the decrease of acetylcholinesterase activity and increased SOD as well as GSH-Px activities, and inhibition of lipid and protein oxidation.⁷³ Furthermore, it has been indicated that antioxidant peptides can exhibit their antioxidant activity through scavenging the hydroxyl and superoxide radical.⁷⁴

Table 1 The Antioxidant and Anti-Inflammatory Potential of Sea Cucumber Bioactive Compounds

Bioactive Compound	Type	Antioxidant Effect	Anti-inflammatory Effect	References
Triterpene glycosides (saponins)	Secondary metabolite	Scavenge free radicals, enhance antioxidant enzyme activity (SOD, CAT, GPx)	Inhibit pro-inflammatory cytokines (TNF- α , IL-6), suppress NF- κ B and COX-2 pathways	[57,59,60]
Sulfated polysaccharides (fucosylated chondroitin sulfate, Fucoidan like- compounds)	Polysaccharides	Reduce oxidative stress by scavenging ROS, increase cellular antioxidant capacity	Block leukocyte infiltration, downregulate iNOS, reduce expression of inflammatory mediators	[7,61,62]
Phenolic compounds (Flavonoids, phenolic acids)	Polyphenols	Strong radical scavengers (DPPH, ABTS assays), prevent lipid peroxidation	Modulate inflammatory signaling, inhibit COX and LOX enzymes	[7,63]
Proteins (collagen and peptides)	Proteins	Improve oxidative balance, act as free radical scavengers	Reduce inflammation markers, protect tissues against inflammatory damage	[57,64,65]
Cerberosides (glycosphingolipides)	Lipids	Moderate antioxidant properties, membrane stabilization	Suppress pro-inflammatory cytokines, contribute to immunomodulation	[57,59,66]
Omega 3 fatty acids (DHA, EPA)	Poly unsaturated fatty acid	Prevent lipid peroxidation, support antioxidant defenses	Well-known anti-inflammatory effect via resolvins/protectins, inhibit eicosanoid synthesis	[66,67]
Carotenoids (e.g. Astaxanthin in some species)	Pigments	Strong antioxidant capacity, quench singlet oxygen	Reduce inflammatory signaling, protect against inflammatory tissue damage	[7,68]

Abbreviations: ABTS:2, 2'-azino-bis(3-ethylbenzothiazoline)-6-sulphonic acid; CAT, Catalase; COX-2, Cyclooxygenase-2; DHA, Docosahexaenoic Acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EPA, Eicosapentaenoic Acid; GPx, Glutathione peroxidase; IL-6, Interleukin-6; iNOS, Inducible nitric oxide synthase; LOX: Lysyl Oxidase; NF- κ B, Nuclear factor- κ B; SOD, Super oxide dismutase; TNF- α , Tumor necrosis factor- α .

Zhu et al⁷⁵ reported the antioxidant activity of the collagen derived from the body wall of sea cucumber and shown that this protein was more active in elimination of hydroxyl radicals than vitamin C. Likewise, gelatin hydrolysate also showed the antioxidant activity against superoxide and hydroxyl radicals and inhibitory activity against melanin synthesis, tyrosinase enzyme, and melanogenesis.^{75,76}

Moreover, it has been indicated that sea cucumber extract containing peptides can facilitate skin cell migration and wound healing under oxidative stress. They can regulate the expression of proteins involved in ribosomal pathways, glycolysis and those related to protein processing in the ER, which may help protect DNA and cellular organelles (eg mitochondria and the ER), in skin cells with oxidative stress.⁵⁶

About sea cucumber derived polysaccharides, it has been demonstrated that the body wall of these invertebrates, is a good source of polysaccharides.¹² The antioxidant activity of the polysaccharides strongly depends on their chain conformation as well as sulfate and carboxyl groups.^{12,77} In particular, sulfate and carboxyl groups are nucleophilic functional groups of the polysaccharides which can chelate metal ions such as Fe²⁺ and Cu²⁺ and scavenge the hydroxyl radical. Furthermore, the superoxide radical elimination may occur via sulfate groups because of their electron-donating substituents in a saccharide.⁷⁸ Moreover, the ability of polysaccharides to increase the activity of antioxidant enzymes such as catalase and SOD has been observed.⁷⁹

The anti-inflammatory effect of the sea cucumber extract has also been investigated. So that, it has been demonstrated that the glycosaminoglycan-rich fraction of these invertebrates can decrease proinflammatory protein levels such as NF- κ B which is closely linked to the AP-1, tumor necrosis factor alpha (TNF α), interleukin-6 (IL6), IL10, IL-11 and STAT3.⁸⁰ The sea cucumber peptides also have anti-inflammatory effects through modulating the JAK-STAT signaling pathway that can be modulated by AP-1.^{81,82}

Furthermore, antioxidant and anti-inflammatory effect of the sea cucumber proteins has been shown via their inhibitory impact on the Keap1 and iNOS as two important factors involved in inflammatory and oxidative stress pathways in the cells.⁸

Despite these studies, attention has recently shifted toward EVs derived from these marine organisms and their regenerative, anti-inflammatory, as well as antioxidant effects have attracted the attention of researchers.

EVs are membrane-bound particles with heterogeneous size and cargo and play an important role in intercellular communication. EVs are categorized into different subtypes, including exosomes, microvesicles, and apoptotic bodies, each with distinct biogenesis and release mechanisms. Among the different subtypes of EVs exosomes are more used as the diagnostic and therapeutic tools.

Antioxidant and Anti-Inflammatory Effects of Sea Cucumber Derived Exosome

Exosome Biogenesis

Exosomes are small membrane bound EVs (30–150 nm) containing various structures including, the nucleic acids (RNA, DNA, mRNA), proteins and lipids.⁸³ These small vesicles act as a natural delivery system with potential to transport the cellular products. Exosomes biogenesis is a complex process which include the sorting of the cargo, formation and maturation of the multivesicular endosomes (MVB), MVBs transport fusion with the plasma membrane.⁸⁴ Briefly, after endocytosis and internalization of the extracellular materials into the cells, the early endosomes are made from these endocytic vesicles. Thereafter, early endosomes are matured and late endosomes or MVB are formed. During this maturation process, inward invagination of the endosomal membrane caused the intraluminal vesicles (ILVs) formation. Finally, MVBs can either fuse with lysosome and degraded or fuse with plasma membrane to release ILVs, the so-called exosomes⁸⁴ (Figure 3).

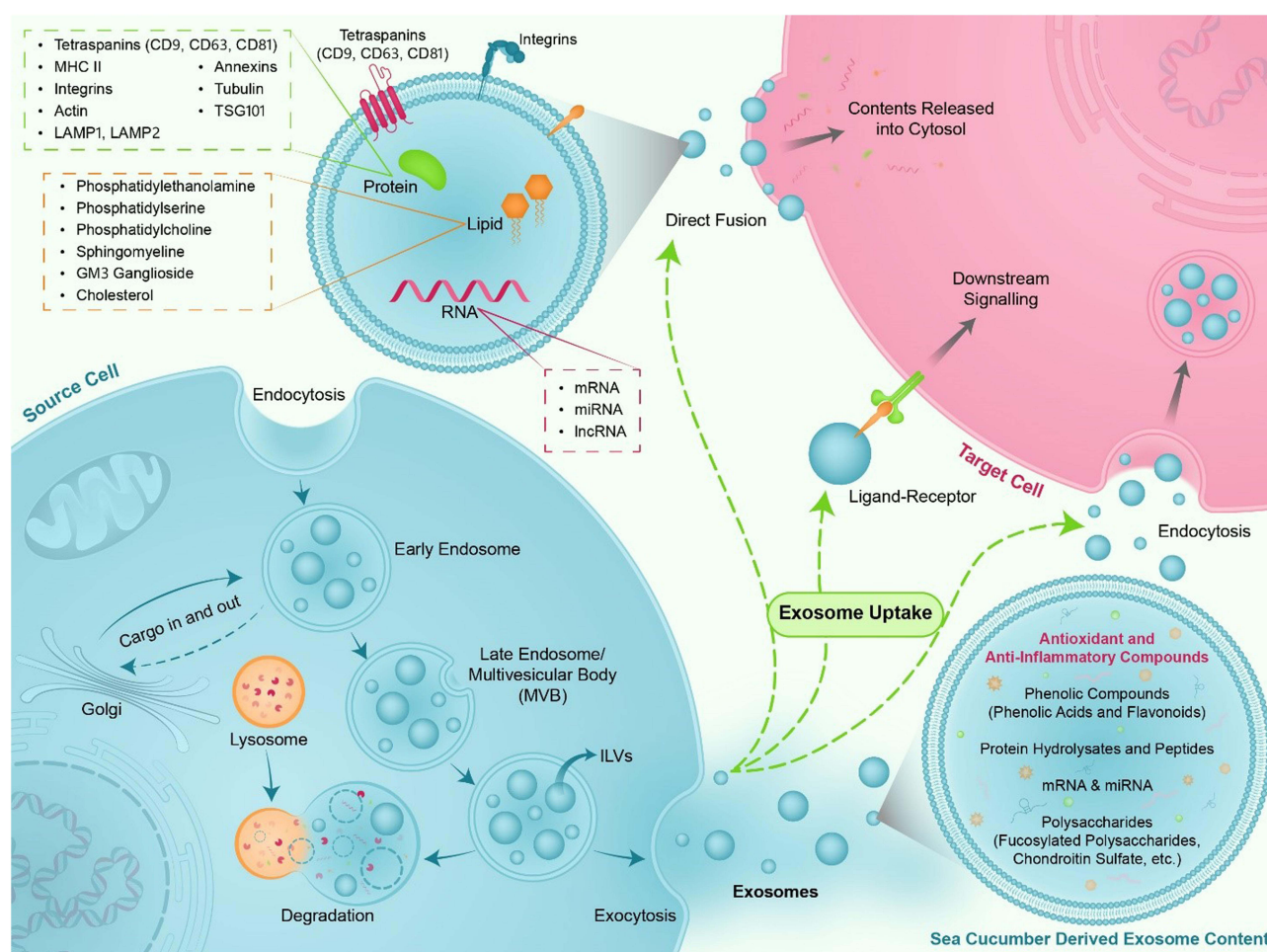


Figure 3 Exosome biogenesis.

Notes: MVBs are formed from early endosome maturation, which MVBs can either fuse with lysosome and degraded or fuse with plasma membrane to release exosomes. Sea cucumber-derived exosomes can carry the antioxidant and anti-inflammatory compounds and transfer them to the target cells.

MVBs have dynamic communication with other organelles in the cells such as ER, mitochondria, trans-Golgi network (TGN), RNA granule and micronuclei, so their cargoes can include various macromolecules including the RNAs, DNAs, proteins or lipids.⁸⁴

After releasing the exosomes into the intercellular spaces, they can move toward the target cells and affect them via some specific mechanisms. Briefly, they can fuse with target cell membrane and release their specific content into the cytosol, or interact with the specific cell surface binding proteins to activate or suppress the signaling pathways in the target cells. Furthermore, exosomes can enter into the specific target cells via endocytosis process and affect their function via releasing their target to modulating the gene expression in the cells⁸⁴ (Figure 3).

The Source of the Sea Cucumber Exosome

According to the literature, EVs and also exosomes can be isolated from different part of the sea cucumber body including the digestive tract (intestine), gonads (reproductive organs), and respiratory tree (branchial trees) as well as body wall.²⁵ However, body wall is the main source of the anti-inflammatory and antioxidant compounds which are naturally secreted or stored in its cells, making it a strong candidate for exosome isolation enriched in bioactive cargo related to these events.¹⁴ For example, methanol extract of the sea cucumber body wall showed a decreased expression of the pro-inflammatory cytokines (TNF- α and IL-1 β) in a rat model of the inflammation.⁸⁵ Furthermore, body wall preparation extract from this invertebrate can suppress the inflammatory factors including the TNF- α , IL-6, NF- κ B, cyclooxygenase-2 (COX-2) and iNOS in the ear inflammation model of the mouse.⁸⁶

Antioxidative and Anti-Inflammatory Effects of the Sea Cucumber Derived Exosomes

Sea cucumber-derived EVs and exosomes can carry proteins and miRNAs that suppress inflammatory cytokines production and enhance expression of anti-inflammatory genes (eg, I κ B α , SOCS-3).²⁵ Moreover, sea cucumber exosomes likely exert antioxidant effects by loading regulatory molecules (proteins hydrolysis, phenolic compound, etc) during their biogenesis. These processes involve MVBs formation and selective sorting mechanisms that incorporate anti-inflammatory and antioxidant cargos into exosomes before their release¹⁴ (Figure 3).

For example, studies suggest that exosomes from sea cucumber can comprise the bioactive compounds with anti-inflammatory, antioxidant, and regenerative characteristics to promote skin regeneration.²⁵ Research has shown that sea cucumber exosomes can suppress the gene expression of the pro-inflammatory factors such as TNF- α , IL-1 β , IL-6, MCP-1, iNOS, and NF- κ B and promote the gene expression of anti-inflammatory factors including the I κ B and suppressor of cytokine signaling proteins-3 (SOCS-3) in the animal model of atopic dermatitis.⁸⁷

Oxidative stress can damage DNA and mitochondria, leading to cellular dysfunction. The effect of sea cucumber-derived exosome on DNA replication and repair following damage has been demonstrated. So that, these effects of exosomes have been attributed to the microRNAs contained within them. Moreover, immunity regulation through key miRNAs such as miR-92_1, miR-2005, and miR-2006 in the sea-cucumber exosomes was observed.⁸⁸

Sea cucumber-derived exosomes can likely eliminate the free radicals and decrease ROS in the cells through some peptide and polysaccharides with antioxidant effect within them. So, due to the various content of exosomes, sea cucumber-derived exosomes may also be used in cosmetic process to improve skin elasticity, texture and health after damage.

Sea Cucumber Derived Extract or EVs (Exosomes) for Skin Damage Therapy?

Sea cucumber extract and exosomes derived from this invertebrate differed from each other in number of specific features that can effect on their therapeutic potential (Table 2).

Exosomes reveal high specificity in their content and targeting in comparison to whole cell or organ extracts. Exosomes, specific cargoes (RNA, DNA, Proteins and lipids), are selectively packaged and released. This selectivity allows exosomes to act as targeted messengers, interacting with specific cells and influencing their behavior in a more focused manner than cell condition media or organ extracts.⁸⁹ For example, about anti-inflammatory effects, studies indicated that crude extracts contain a mixture of various compounds such as anti-inflammatory and inflammatory cytokines as well as other growth factors that can have broader, less targeted effects and potentially induce both pro-inflammatory and anti-inflammatory responses. However, during the exosome biogenesis, anti-inflammatory factors such

Table 2 Comparison of the Features of Sea Cucumber Derived Exosomes and Extracts

Feature	Sea Cucumber Exosomes	Sea Cucumber Extracts
Nature	Nano-sized extracellular vesicles, (membrane bound with proteins, RNAs and bioactive cargo)	Crude/fractionated chemical mixture (saponins, polysaccharides, phenolics, peptides)
Antioxidant mechanism	Indirect: activate endogenous antioxidant enzymes (eg. SOD, catalase, Nrf2/HO-1 pathway), reduce ROS generation, protect mitochondria	Direct: free radical scavenging (DPPH, ABTS, superoxide, hydroxyl radicals), metal chelation
Specificity	Targeted delivery into recipient cells; intercellular communication	Non-specific; systemic effects via chemical compounds
Stability	High stability (lipid bilayer protects cargo; withstands circulation)	Less stable; composition varies by extraction method and solvent and dependent on the storage method
Potential use	Nanomedicine, skincare delivery systems (drug delivery), regenerative effects	Dietary antioxidants, topical antioxidant extracts

Abbreviations: ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline)-6-sulphonic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl HO-1, Hemoxygenase 1; Nrf2, Nuclear factor erythroid 2; SOD, Super oxide dismutase.

as IL-10, IL-19, TGF- β and anti-inflammatory miRNAs (eg, miR-146a, miR-145-5p) specifically packaged into this vesicles and can target the specific target cell for regulating the inflammation in the controlled manner.⁹⁰

In addition to the specificity of the exosomes cargo, it has been indicated that the stability of the bioactive compounds in this lipid bilayer structures is greater than their presence in cell or organ extracts. In this regard it has been shown that the quantity of the miRNAs in exosomes is higher than that in the parent cells or cells extract which means the miRNAs are protected in these nano-vesicles and can maintain in the stable form for transferred to the target cells and genes expression modulation.⁹¹

About the therapeutic effect of the crud extract, it can be used as the dietary antioxidants or topical antioxidant extracts. However, extracts may not penetrate the skin barrier effectively; topical formulations may require encapsulation or nanocarriers for real efficacy.⁹²

So, due to the stability of the exosomes content, their therapeutic potential can be higher than crud extract with different unstable compositions. Furthermore, exosomes are considered as the nanocarrier in the drug delivery system for their high selectivity in delivering the cargo to target which represent them as the best cellular-free system for therapy between the therapeutic approaches.^{93,94} The above applies to all exosomes, including those derived from sea cucumbers.

Concluding Remarks and Future Directions

Imbalance of redox hemostasis in skin cells results in oxidative damage which can affect the skin health. Therefore, when oxidative factors (ROS) exceed antioxidants in cells, the use of synthetic or natural antioxidants becomes important.² However, due to the potential carcinogenicity and toxicity of some synthetic antioxidants, researchers have shown great interest in natural antioxidants.⁷³ Sea cucumbers are a marine invertebrate rich in bioactive compounds with antioxidant, anti-inflammatory, and regenerative properties.^{7,56} Furthermore, sea cucumber-extract and their derived exosomes, with their potent antioxidative and regenerative properties, can represent a promising avenue for developing novel therapies to combat oxidative stress and promote skin regeneration.^{14,87} However, the use of these exosomes presents several challenges and further research is required to fully elucidate their mechanisms of action and optimize exosome delivery and therapeutic efficacy. For example, it is essential to develop standardized methods for isolating and characterizing sea cucumber-derived exosomes for consistent results. Moreover, exploring the various delivery methods (eg injections, topical application) could enhance therapeutic efficacy.

Today, various strategies are used to isolate and deliver exosomes, each with its own strengths and weaknesses. The most used but low-purity method is differential ultracentrifugation; however, density-gradient ultracentrifugation is the other way that improves purity at the cost of time and throughput. Chromatography offers mild, reproducible separation way while ultrafiltration scalable concentration despite membrane-related damages. By polymer precipitation method, exosome with high yield is obtained but this way suffers from co-precipitated contaminants.⁹⁵ Newer microfluidic systems (viscoelastic, acoustic, and immuno-microchips) provide high-purity separation from low sample volumes.⁹⁶

Furthermore, EV subpopulations with special resolution can be isolated by advanced asymmetric-flow field-flow fractionation (AF4) method particularly when combined with density gradients.⁹⁷ About exosome delivery for therapeutic purposes, their cargo can be placed endogenously through engineering donor cells to package RNAs or proteins,⁹⁸ or exogenously by other methods such as passive incubation, sonication, freeze–thaw cycling, electroporation, extrusion or by using membrane-permeabilizing agents such as saponin, each balancing loading efficiency and vesicle integrity.⁹⁹ Other methods such as hybrid vesicles made of liposome and exosome, exosome loading using ultrasound, and their surface engineering using targeting peptides or antibodies can improve in vivo biodistribution and specificity of these nano-vesicles.¹⁰⁰

The diverse habitats and diets of sea cucumber species is the other challenge that may result in exosomes with differing compositions and effects. Therefore, isolating exosomes from various species and analyzing their contents may facilitate their optimal therapeutic application. Finally, because using the sea cucumbers (extract and exosomes) are in the very early stage in dermatology and almost all published work is in vitro (cell models) or proof-of-concept animal studies; the human clinical trials are also needed to elucidate their exact therapeutic effect in the skin damage.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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