

Omega-3 Fatty Acids: A Review on Molecular Mechanism as Regenerative Medicine

Hamsaveni L, Priyadarshini D, Amrutha K, Poornima KR, Chandan K*,
Syed Sagheer Ahmed, Jayanth BM

Department of Pharmacology, Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, India

Received October 4, 2024; Revised October 24, 2025; Accepted December 27, 2025

Cite This Paper in the Following Citation Styles

(a): [1] Hamsaveni L, Priyadarshini D, Amrutha K, Poornima KR, Chandan K, Syed Sagheer Ahmed, Jayanth BM, "Omega-3 Fatty Acids: A Review on Molecular Mechanism as Regenerative Medicine," *Advances in Pharmacology and Pharmacy*, Vol. 14, No. 1, pp. 27 - 37, 2026. DOI: 10.13189/app.2026.140103.

(b): Hamsaveni L, Priyadarshini D, Amrutha K, Poornima KR, Chandan K, Syed Sagheer Ahmed, Jayanth BM (2026). *Omega-3 Fatty Acids: A Review on Molecular Mechanism as Regenerative Medicine*. *Advances in Pharmacology and Pharmacy*, 14(1), 27 - 37. DOI: 10.13189/app.2026.140103.

Copyright©2026 by authors, all rights reserved. Authors agree that this article remains permanently open access under the terms of the Creative Commons Attribution License 4.0 International License

Abstract Tissue regeneration is a complicated physiological process which is necessary to preserve skin's integrity after injury. Severe health problems can result from impaired wound healing, which is frequently linked to problems including diabetes and vascular disorders. ω -3 Polyunsaturated fatty acids (PUFAs), which include EPA and DHA, have become more recognized for their capacity to enhance wound healing and tissue regeneration. ω -3 fatty acids are used as regenerative medicine through various molecular mechanisms. Because of their anti-inflammatory and immunomodulatory characteristics, ω -3 PUFAs, especially EPA and DHA, have the potential to significantly improve tissue regeneration and wound healing. They enhance tissue quality, lessen scarring, and encourage the production of collagen. To improve dosage, administration techniques, and their effectiveness for various wound types, further research is necessary. This illustrates the potential benefits of using ω -3 PUFAs as an adjuvant for wound care. Current research on the processes by which ω -3 PUFAs affect different activities is summarized in this review. Key studies indicate that ω -3 PUFAs work through anti-inflammatory and immunomodulatory mechanisms, supporting more efficient and effective wound healing. They stimulate collagen synthesis, minimize scarring, and improve overall tissue quality. Despite promising evidence, additional investigation is required to ascertain the best dosage, the best ways to administer them, and the extent to which they are beneficial for different kinds of wounds. The analysis

finds that ω -3 PUFAs have substantial promise for therapeutic use in wound management, providing a supplementary approach to existing treatments. Future studies should focus on improving treatment protocols.

Keywords Tissue Regeneration, Omega-3 Fatty Acids, Inflammation, Wound Healing

1. Introduction

Wound healing is an essential physiological process that helps to retain skin integrity following trauma, whether inflicted by accident or deliberate action. Typical wound healing consists of three sequential but overlapping phases: hemostasis or inflammation, proliferative phase, and remodeling phase [1]. Wound healing is a unique mechanism that provides evolutionary benefits. Restoring the barrier function to prevent further injury or infection appears to be one of the key causes of skin wound healing [2]. The economy and public health are significantly impacted by several kinds of problems that can arise from impaired wound healing or tissue regeneration, including immunological disorders, serious burns, and chronic ulcers [3]. Any element that hinders or lessens the healing process of wounds can lead to major health issues; for example, smoking cigarettes has been linked to a lower capacity for regeneration [4]. Additionally, poorer wound healing is

linked to aging and a significant contributing component to this process is poor angiogenesis [5]. The rate and process of wound healing are significantly influenced by conditions such as metabolic disorders like diabetes and vascular illnesses. Wounds like ulcers and chronic refractory sores can be difficult to heal, and their prolonged care may lead to even more complications [6]. Understanding why these wounds don't heal properly is crucial, as millions of people around the world are affected by it. This issue is particularly common among those suffering from conditions like diabetes, vascular disease, or those who are more than 60 years of age [7].

Regenerative medicine is a multidisciplinary field that involves principles from both engineering and biological sciences to regenerate damaged tissues and organs. The FDA, or Food and Drug Administration, issued approval for several regenerative therapies, including those designed for orthopedic applications and wound healing [8]. In recent years, stem cell therapies such as bone marrow and adipose-derived mesenchymal stem cells (ADMSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and pluripotent stem cells (PSCs) have been explored for their skin repair actions [9].

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been proven to promote tissue regeneration in many systems. These fatty acids play a crucial function in inflammatory regulation, and in skeletal muscle, they have been related to enhanced recovery and regeneration. By managing the body's inflammatory responses, omega-3 polyunsaturated fatty acids (PUFAs) may help muscles heal more effectively [10]. Additionally, omega-3 fatty acids are appropriate therapeutic agents for neurological illnesses because of their neuroprotective, anti-inflammatory, and antioxidant qualities [11]. In addition, PUFAs protect skeletal muscle cells from lipotoxicity and aid in muscle growth and regeneration; docosapentaenoic acid (DPA) demonstrates the greatest protective effects [12]. ω -3 PUFAs have gained greater recognition in recent times due to their numerous health benefits and ability to reduce the risk of disease. Docosapentaenoic acid (DPA), EPA, stearidonic acid (SDA), α -linolenic acid (ALA), and DHA are the polyunsaturated fatty acids that make up the ω -3 group. These fatty acids (FAs), or parts of them, are mostly found in marine, algal, and single-cell sources in addition to plants. Linoleic acid is found in a variety of plant-based products and seeds, including sunflower, corn, and soybean oils. Flaxseed, chia seeds, walnuts, and echium seed are well-known sources of alpha-lipoic acid (ALA) [13]. It has been shown that these ω -3 fatty acids are important for the process of wound healing or tissue regeneration, as well as for lowering the occurrence of wound-related infections [14]. This review emphasizes the anti-inflammatory, tissue-regenerative, and antioxidant effects of omega-3 fatty acids, exploring their potential therapeutic applications in improving wound healing outcomes and

preventing infections, particularly in individuals with chronic conditions like diabetes and vascular diseases.

1.1. Biochemical Properties of ω -3 Fatty Acids

The chemical species of ω -3 fatty acids, EPA and DHA, differ in their degree of unsaturation and length of carbon backbones, but their functional groups are similar. EPA has 20 carbon atoms and 5 double bonds, while DHA has a longer chain of 22 carbon atoms and 6 double bonds (22:6). Diphytanoylphosphatidylcholine synthetic lipid bilayer membranes' permeability is likely enhanced by DHA's increased degree of unsaturation, resulting in an increase in conductance and proton selectivity [15]. Lipid mediators are impacted by EPA and DHA, which promote wound healing. Studies have demonstrated that wounds treated with acellular fish skin grafts (FSG) have significantly greater levels of EPA and DHA-derived lipid mediators, which influence the early stages of wound healing [16].

These mediators include 18-HEPE (18-hydroxyeicosapentaenoic acid) and 17-HDHA (17-hydroxy Docosahexaenoic Acid). It has been shown that bioactive lipid mediators such as 18-HEPE and 17-HDHA can promote wound healing in a number of ways. Because 18-HEPE is derived from EPA, it contains anti-inflammatory properties that may help lower inflammation while wounds heal. On the other hand, 17-HDHA, which is derived from DHA, promotes tissue regeneration and lowers inflammation to help heal wounds. These lipid mediators improve tissue repair, control the inflammatory stage of wound healing, and modify immunological responses, all of which enhance the healing process. Both 18-HEPE and 17-HDHA can successfully improve wound healing, especially in diabetics, since they upregulate X-box binding protein 1 (XBP1) and inositol-requiring enzyme type 1 (IRE-1) [17]. Additionally, during the wound healing process, its anti-inflammatory, tissue-regenerative, and immune-modulating properties aid in lowering inflammatory reactions, accelerating healing, and minimizing the formation of scars [18].

1.2. Mechanisms of ω -3 Fatty Acids in Tissue Regeneration

DHA and EPA aid in lowering inflammation while wounds heal. Due to their competition with arachidonic acid, they have anti-inflammatory properties. In addition to activating G-protein coupled receptor 120 to inhibit inflammation, EPA and DHA also activate PPAR γ , which raises the anti-inflammatory hormone adiponectin. NF- κ B pathways reduce pro-inflammatory markers like interleukin-6 and tumor necrosis factor alpha, while raising anti-inflammatory markers like interleukin-10 and transforming growth factor beta [19]. EPA has a significant role in tissue regeneration by controlling cytokines in inflammatory pathways [20]. Furthermore, EPA can

enhance the activity of lipid mediators including protectins and resolvins, which aid in tissue repair and inflammation reduction [21]. Specialized pro-resolving mediators called protectins and resolvins, which are derived from polyunsaturated fatty acids, are essential to the processes involved in wound healing. Maresins are one type of protectin that helps to decrease the generation of compounds that cause inflammation, encourage the uptake of cells that have undergone death, and lessen the infiltration of polymorphonuclear leukocytes [22]. Resolvins, including RvE1 and RvD1, may work through mitogen-activated protein kinase and G protein-coupled receptors pathways to stimulate the growth and synthesis of DNA in intestinal epithelial cells. This aids in the healing of damaged epithelium and lowers inflammation [23].

One of the ω -3 fatty acids, DHA, is particularly crucial for controlling membrane fluidity, which is required for tissue regeneration and cellular function [10],[24]. DHA's ability to alter the shape and fluidity of membranes, which is crucial for cellular responses to external signals, has a substantial impact on the local and systemic inflammatory responses to damage, which in turn are essential in supporting their regeneration. Ultimately, the ability of ω -3 fatty acids, especially DHA, to modulate membranes is critical for improving tissue regeneration and cellular function.

ω -3 PUFAs or n-3 PUFAs, have also been shown for antioxidant effects that support the healing processes of wounds. Research indicates that n-3 polyunsaturated fatty acids (PUFAs) help mitigate oxidative stress by increasing the activity of antioxidant enzymes like glutathione peroxidase and catalase and reducing malondialdehyde levels [25]. In order to stabilize n-3 PUFAs for potential use in skin care and wound healing, formulations including antioxidants like tocopherol and ascorbic acid have been developed [26]. Therefore, the processes that promote wound healing benefit considerably from the antioxidant properties of ω -3 fatty acids.

2. Interaction of Various Omega-3 Fatty Acids with Transcriptional Cascades of the Cell

2.1. PPAR (Peroxisome Proliferator-Activated Receptor) Pathway

PPAR is divided into three isoforms: PPAR α , PPAR β/δ , and PPAR γ . Upon activation by ligands, these nuclear receptors function as transcription factors. Endogenous ligands for eicosanoid metabolites such as prostacyclin and 15-hydroxyeicosatetraenoic acid (15-HETE) including polyunsaturated fatty acids, can activate PPAR β/δ which regulates the fundamental processes involved in wound healing and regeneration.

To preserve, repair, and regenerate tissue, a number of processes need to be strictly controlled. These include apoptosis (resulting from factors like increased oxygen demand or deprivation), stem cell proliferation and/or differentiation to generate lost cell types, and extracellular matrix remodelling and breakdown. Healing and regeneration are dependent on hypoxia-induced signalling, pro-angiogenic factor release, and metabolic alterations, as has been shown by research on natural regeneration in model species including zebrafish, newts, and Murphy Roths Large (MRL) mice.

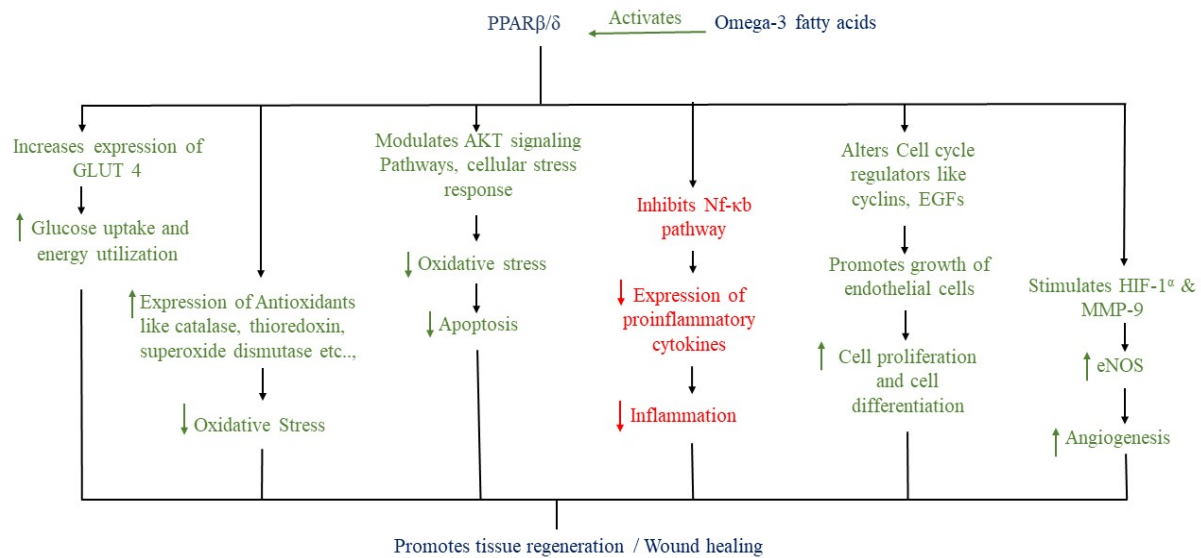
PPAR β/δ Activation: When activated, PPAR β/δ triggers a series of events that promote tissue regeneration. PPAR β/δ interacts with specific genes involved in various aspects of regeneration, including altering energy metabolism by promoting the gene expression involved in glycolysis, a vital metabolic route that activates Glut4 to provide energy for cell survival and proliferation. This process indirectly improves the uptake of glucose or energy in injured tissues, which is crucial for regeneration.

PPAR β/δ stimulates genes for antioxidant enzymes such as catalase, superoxide dismutase, and thioredoxin, which protect cells from reactive oxygen species during tissue damage or inflammation.

PPAR β/δ 's role in apoptosis is complex and context-dependent. It generally acts to inhibit apoptosis through several mechanisms, including the modulation of survival signalling pathways, protein interactions, and cellular stress responses. However, its effects can vary depending on the type of cell, the presence of specific ligands, and other environmental factors. By altering certain signalling pathways, such as the Akt signalling pathway, and upregulating the expression of proteins like 14-3-3 α protein, which suppresses the expression of pro-apoptotic proteins, PPAR β/δ can prevent the apoptosis pathway. It can also prevent oxidative stress-induced apoptosis by upregulating the expression of antioxidants.

PPAR β/δ initially promotes inflammation to recruit immune cells necessary for tissue repair. However, it later inhibits inflammation to prevent excessive damage. PPAR β/δ prevents inflammation by inhibiting NF- κ B pathway and lowering pro-inflammatory cytokines and adhesion molecules. It also reduces fibrosis by inhibiting fibroblast and myofibroblast proliferation and collagen production, allowing for smoother tissue healing. PPAR β/δ promotes tissue healing by regulating inflammation and fibrosis, resulting in optimal repair and regeneration.

PPAR β/δ promotes the proliferation of endothelial progenitor cells, cardiomyocytes, and cancer cells while inhibiting vascular smooth muscle cells and keratinocytes by modifying cell cycle regulators (e.g., cyclins), growth factors (e.g., HB-EGF), and signalling pathways (e.g., Akt, Wnt/ β -catenin). PPAR β/δ also promotes differentiation by shifting metabolism from glycolysis to fatty acid oxidation. It controls genes like Edg-2, promotes differentiation in various cell types and influences Wnt signalling for osteoblast differentiation.



PPAR β/δ is involved in different processes of regeneration where it activates glycolysis, oxidative stress, apoptosis, cell proliferation and differentiation, angiogenesis but inhibits inflammation. Green represents activation, Red represents inhibition

Figure 1. Mechanism of action of PPAR pathway

PPAR β/δ promotes angiogenesis by enhancing endothelial cell function and progenitor cell activity. It stimulates new vessel formation through pathways like HIF-1 α (Hypoxia-inducible factor-1 α) and MMP-9 (Matrix metalloproteinase 9), crucial for tissue repair and regeneration. It also activates endothelial nitric oxide synthase (eNOS), supporting healthy vascular function and preventing complications like thrombosis and atherosclerosis, which is depicted in Figure 1 [27].

2.2. NF- κ B (Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells) Pathway

NF- κ B pathway affects a variety of cellular functions in various tissues and is essential to tissue regeneration. In certain cellular environments and in relation to tissue damage, NF- κ B can either promote or hinder regeneration. In order to attract inflammatory mediators that aid in tissue regeneration, the NF- κ B pathway must first be activated. However, over activating of this pathway can make the situation worse [28]. Thus, ω -3 fatty acids, which have been shown to suppress the NF- κ B pathway, could be a highly effective strategy to stop tissue damage-related inflammation from getting worse [29].

In case of chronic liver disease, the NF- κ B -inducing kinase (NIK) pathway is active, inhibiting hepatocyte replication and liver regeneration. Deleting NIK or its mediator, IKK α (Inhibitory Kappa B Kinase α), leads to increased hepatocyte proliferation after damage, suggesting that NIK is a negative regulator of liver regeneration [28]. The abnormal stimulation of NIK in liver disorders impairs cell cycle progression by blocking JAK2/STAT3 (janus kinase 2 /signal transducer and activator of transcription 3) pathway, which is required for

hepatocyte proliferation [30].

In skeletal muscle, NF- κ B activity in pericytes regulates myogenic differentiation as well as muscle precursor cell proliferation. Elevated NF- κ B activity reduces differentiation while increasing MPC proliferation, emphasizing its complicated involvement in muscle regeneration [31]. Mesenchymal stromal cells' (MSCs') mechanocompetence during cartilage regeneration is similarly impacted by NF- κ B signalling. The synthesis of extracellular matrix components is increased when NF- κ B is inhibited, suggesting that careful control of NF- κ B activity is essential for successful cartilage healing [32].

Numerous inflammatory disorders are impacted by the NF- κ B pathway, which has been shown to be inhibited by ω -3 fatty acids, particularly DHA. DHA prevents lymphocytes from activating NF- κ B, which lowers inflammation and increases chemotherapy sensitivity in patients with chronic lymphocytic leukemia [29]. Furthermore, DHA inhibits NF- κ B translocation to limit inflammasome activation, which lowers macrophage production of IL-1 β , which is depicted in Figure 2 [33]. In addition, long-chain n-3 PUFAs, which are independent of PPAR γ , influence dendritic cell function by reducing NF- κ B activation, which adds to their anti-inflammatory qualities [34]. While ω -3 fatty acids often block the NF- κ B pathway to promote anti-inflammatory responses, their effects can differ based on the kind of fatty acid and the particular setting [35].

2.3. mTOR (Mechanistic Target of Rapamycin) Signalling Pathway

The serine or threonine protein kinase mTOR is critical for cell survival, growth, and metabolism. It serves as the

catalytic subunit for two distinct protein complexes: mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). mTOR, Raptor, and mLST8 make up mTORC1, whereas DEPTOR, mSin1, and Protor1/2 make up mTORC2 [36]. Numerous biological activities, including wound healing, depend on the mTOR system, specifically the PI3K or AKT or mTOR signalling pathway. The three main wound healing stages are: inflammation, proliferation, and remodelling. The inflammatory phase begins right after damage, when immune cells are dispatched to the wound site to clean up debris and fight infection. During this stage, the PI3K/AKT pathway is extremely active, driving the early repair steps. During the ensuing proliferation phase, fibroblast cells enter the wound site and create new extracellular matrix components. AKT promotes the survival and proliferation of these cells, allowing wound to heal with new tissue. In the last remodelling phase, the newly produced tissue is recognised and strengthened, with collagen fibers straightened and unnecessary cells eliminated via apoptosis. AKT prevents excessive apoptosis by suppressing pro-apoptotic proteins like BAD and BAX (Bcl-2-associated death protein and Bcl-2-associated X protein), which promote cell survival. Furthermore, mTORC1, which is triggered by AKT, regulates protein synthesis, which is required for cell proliferation and cell growth, especially during the proliferation phase. mTOR also stimulates angiogenesis and collagen formation, giving the wound blood flow and structural support, which is depicted in Figure 3 [37].

ω -3 fatty acids have shown to increase mTOR activation, which is required for cellular processes involved in wound repair [38]. When mixed into hydrogels, ω -3 fatty acids greatly improve wound healing by moderating

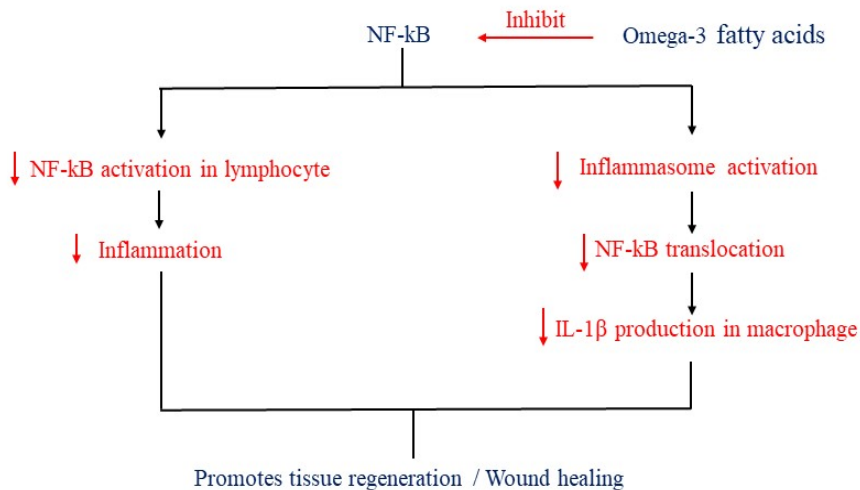
inflammatory responses and boosting cell migration, both of which are intimately tied to mTOR pathway activation [39]. The interaction of omega-3 fatty acids and mTOR signalling offers a viable avenue for developing enhanced wound care techniques, particularly for chronic wounds [40].

2.4. SPMs (Specialized Pro-resolving Mediators)

PUFAs represent the source of lipid compounds, as specialized pro-resolving mediators (SPMs), which are essential for controlling body's inflammatory reactions. Through particular cellular and molecular pathways, they actively support the resolution of excessive inflammation and aid in its prevention, this facilitating tissue regeneration [41],[42].

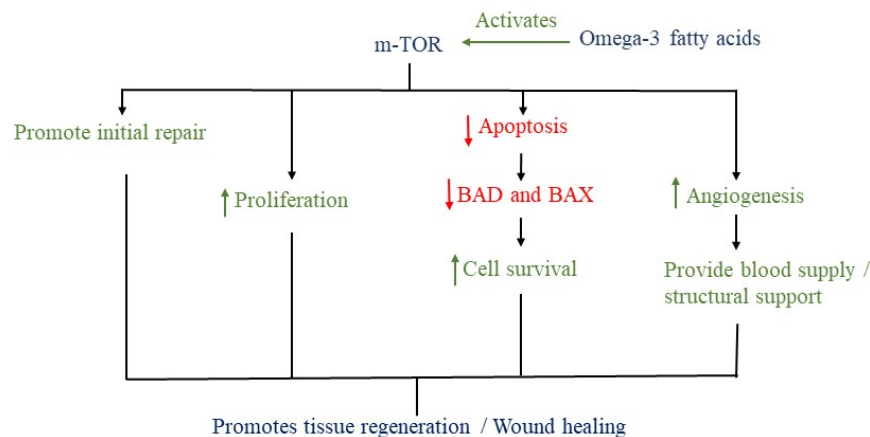
By lowering the production of pro-inflammatory mediators and improving the removal of apoptotic cells, SPMs assist in the resolution of inflammation. Additionally, they aid in tissue regeneration by encouraging stem cells to proliferate, differentiate, and migrate to damaged areas. Furthermore, SPMs affect the function of important immune cells like T cells and macrophages, which modulate the immune response and foster optimal healing and regeneration.

Certain stem cells, particularly human periodontal ligament stem cells (hPDLSCs), can create SPMs as part of their natural pro-resolving activity. Several animal studies have connected its production to higher cell survival, reduced organ damage, improved bacterial clearance, and quicker inflammation resolution [43].



NF-kB pathway is inhibited by omega-3 fatty acids which ultimately inhibits inflammation and inflammasome activation and promotes tissue regeneration. Red represents inhibition

Figure 2. Mechanism of action of NF-kB pathway



m-TOR pathway is activated by omega-3 fatty acids which promotes initial repair and proliferation also promotes angiogenesis but inhibits apoptosis and enhances cell survival promotes tissue regeneration. Green represents activation, Red represents inhibition.

Figure 3. Mechanism of action of m-TOR pathway

Moreover, SPMs increase the transition and proliferation of skin cells like keratinocytes by activating signalling pathways like ERK (extracellular signal-regulated kinase), which is especially advantageous in demanding situations like diabetic wound environments. SPMs help to speed up the healing process and restore the damaged skin's normal function and appearance by preventing fibrosis and scarring. Adipose tissue-derived secretomes enhanced with stem cell monolayers (SPMs) have also shown regenerative capabilities through neurite outgrowth, and certain SPMs, such as pigment epithelium-derived factor (PEDF), promote fibroblast migration to wounded tissues, hence facilitating efficient tissue regeneration.

All things considered, SPMs play a significant role in reducing inflammation and encouraging effective tissue regeneration, which underscores their potential therapeutic uses in improving wound healing and injury recovery. SPMs provide a number of benefits for applications including wound healing: Scaffolds can offer a native extracellular matrix-like microenvironment to further enhance tissue repair; they can be easily manufactured and formulated into various delivery systems, such as scaffolds, for sustained release of proteins to support tissue regeneration; and they can be packaged and transported more easily than cells.

In a number of wound healing situations, such as diabetic ulcers and chronic wounds, SPMs are showing promise as therapeutic agents for reducing inflammation and speeding up tissue regeneration [44].

3. Clinical Applications and Evidence

3.1. Cardiovascular Tissue Regeneration

ω -3 fatty acids, notably EPA and DHA, are crucial for heart tissue regeneration and protection, particularly after myocardial infarction (MI). Clinical research has

demonstrated that these fatty acids improve the regenerative potential of heart cells produced from embryonic stem cells. When cardiac tissues are preincubated with EPA, DHA, and ascorbic acid, oxidative stress is significantly reduced, cell viability improves, and fibrosis decreases, indicating a protective effect against cellular damage in hostile settings [44].

Furthermore, ω -3 fatty acids alter cardiac remodelling, increase endothelial function, and have anti-inflammatory properties—all of which are critical mechanisms that enhance heart failure prevention and recovery following MI. Because of these characteristics, ω -3 fatty acids show great promise as a therapeutic agent for improving the regeneration of cardiovascular tissue. Their potential role in clinical methods aimed at improving outcomes for patients with heart disease is highlighted by their capacity to preserve and repair heart tissues, reduce inflammation, and support overall cardiac function [45].

3.2. Neural Regeneration

Nervous system regeneration is the process of repairing or replacing nerve cells that have been destroyed by injury or disease. While lower creatures have strong neural regenerative potential, humans and other higher organisms have limited nerve cell regeneration capacity, making it difficult to treat nervous system injuries and disorders [46].

ω -3 PUFAs stimulate brain regeneration via a variety of biochemical pathways. Many studies revealed that ω -3 PUFAs inhibit cortisol-induced neurogenesis and promote apoptosis in hippocampus tissues [47]. Additionally, research has linked ω -3 supplementation to enhanced nerve regeneration in diabetic distal-symmetric polyneuropathy patients, as seen by longer corneal nerves [48]. Overall, these results point to ω -3 PUFAs as a feasible treatment approach for brain and nerve regeneration since they control many molecular pathways to provide neuroprotective and regenerative advantages.

3.3. Impact on Neurogenesis and Brain Plasticity

The processes of neurogenesis and brain plasticity are fundamental ability of the brain to alter, restructure, as well as react to events and external obstacles. Learning, environmental stimuli, and hereditary variables all have an impact on brain plasticity, the brain's capacity to change both structurally and functionally throughout life. Plasticity and neurogenesis are intimately related, especially in learning and the healing process following an injury. The plasticity of the brain steadily decreases with age, resulting in a more fixed allocation of neuronal resources to particular processes [49].

PUFAs with ω -3 content have a major impact on brain plasticity and neurogenesis. Studies emphasize the importance of dietary n-3 PUFAs for neurodevelopment, demonstrating that deficiency in a mother can significantly impact the expression of important neurogenesis alleles in her progeny [50].

Furthermore, it has been proven that ω -3 PUFAs, like EPA and DHA, offer protection against cortisol-induced reductions in hippocampus neurogenesis. In general, neurogenesis, synaptic plasticity, and cognitive performance are all positively impacted by ω -3 PUFAs, which are fundamental for development and function of brain [51].

3.4. Musculoskeletal Tissue Repair

The musculoskeletal system, gives the body's internal organs the necessary structural support, load-bearing ability, and protection. Significant discomfort, weakness, and even loss of function can result from injuries and wear and tear on this system over time [52]. The advantages of ω -3 PUFAs (n-3 PUFAs), such as DHA, EPA and DPA, for musculoskeletal repair and regeneration have been promising.

Skeletal muscle cells benefit from the protection that n-3 PUFAs provide against lipotoxicity, as well as from increased muscle development and repair [53].

Furthermore, consumption of ω -3 has been linked to a decrease in indicators of exercise-induced muscle injury, including creatine kinase, lactate dehydrogenase, and myoglobin, suggesting that it may become useful as a rehabilitation aid for musculoskeletal problems [54].

Additionally, some of the research has reported that the anti-inflammatory properties of ω -3 fatty acids lessen inflammation and discomfort in those with osteoarthritis, highlighting the possibility of using this nutrient as an intervention for a wide variety of musculoskeletal disorders [55].

3.5. Bone and Muscle Healing

The process of repairing bones is sophisticated and involves a variety of cells, growth factors, and signalling

molecules. It consists of a series of sequential events that are controlled in both time and space, including angiogenesis, remodelling, stem cell recruitment to the site of damage, and differentiation into particular tissue types. Because of its close closeness to bone and extensive circulatory network, muscle tissue is essential for the healing of fractures. In addition to supporting structure and blood flow, muscles can produce progenitor cells that are capable of developing into bone-forming cells, particularly in cases when the periosteum is injured [56].

Among the ω -3 PUFAs, EPA and DHA particularly have shown promising results in bone and muscle regeneration. Research mentions that these fatty acids may benefit the bone mineral density (BMD) of both adults and children. They have a significant impact on bone health. Research has shown that menaquinone-7 (MK-7) and ω -3 fatty acids can prevent bone problems including aortic vascular calcification, lower osteoclast activation, and increase sarcopenia-related indicators. These outcomes help to avoid vascular calcification, sarcopenia, and osteopenia [57].

This suggests that they could be useful supplements to improve musculoskeletal health in general and bone and muscle healing in particular.

3.6. Skin Wound Healing

The aim of tissue regeneration and repair is to heal damaged tissue using a variety of molecular and cellular processes. Three main phases of these processes are identified: the exudative phase, which is marked by inflammation and fluid accumulation; the proliferative phase, which involves tissue growth and cellular proliferation; and the extracellular matrix remodeling phase, which integrates blood cells, parenchymal cells, and various soluble mediators to finalize tissue repair [58].

EPA and DHA in particular, are ω -3 fatty acids that help heal skin wounds by reducing inflammatory reactions and encouraging tissue repair. Studies have indicated that EPA-rich oils might change the skin's fatty acid composition, which may enhance tissue quality and wound closure [59].

Research on rats has indicated that improved skin wound healing is facilitated by an increased ratio of ω -3 to ω -6 PUFAs. Omega-3 fatty acids have demonstrated to have the potential to efficiently stimulate tissue repair and speed the healing process for a range of skin injuries due to their improved collagen organization and lower oxidative stress [60].

4. Current Research and Future Directions

Many recent studies have been conducted on ω -3 fatty acids as a regenerative medicine, and some of them are listed below.

In regenerative medicine, ω -3 fatty acids show promise in many settings. As per the studies conducted by Sepehr Zamani *et al.* on July 24, 2024, hydrogels that incorporate these fatty acids have demonstrated significant improvement in wound healing, with over 91% improvement in wound closure observed in rat models. This suggests that the hydrogels may be useful as topical treatments for skin regeneration [39]. According to research done by Parisa Shabani *et al.* on May 1, 2019, EPA and DHA in particular, have been proven to have protective effects in cardiac applications on cardiac cells obtained from embryonic stem cells, improving cell viability, decreasing fibrosis in myocardial infarction models and enhancing cardiovascular regeneration [45].

ω -3 fatty acids provide a great deal of potential for novel therapeutic approaches in regenerative medicine, like nanotechnology, hydrogel system, stem cell therapy, genetic profiling, regenerative medicines for chronic diseases, tissue engineering (Scaffold development) etc., from neuroregeneration and cardiovascular health to enhanced wound care. Researchers and medical professionals can create novel medicines that target acute injuries as well as chronic conditions, enhancing patient outcomes and quality of life, by utilizing ω -3 fatty acids.

Although they show great promise for regenerative medicine, several challenges need to be addressed before they can be effectively used as a therapy. These include enhancing stability and bioavailability, establishing a defined dosage, understanding complicated mechanisms, overcoming obstacles in the way of clinical translation, and handling practical and financial concerns. Addressing these limitations through some research and innovation will be important in producing effective and broadly available ω -3 based medicines.

5. Conclusions

This review mainly focuses on the important role of ω -3 polyunsaturated fatty acids, specifically EPA and DHA, in wound healing and tissue regeneration. The evidence supports its anti-inflammatory, immunomodulatory, and pro-regenerative capabilities, through some molecular pathways which all lead to better healing outcomes. ω -3 PUFAs have been proven to have the capacity to speed up wound closure while also increasing the quality of regenerated tissue. Their incorporation into clinical practice, particularly in the setting of chronic wounds and post-surgical healing, could provide a promising complement or alternative to traditional treatments. However, further research is needed to improve dosage, delivery routes, and completely understand their mechanisms of action in a variety of therapeutic scenarios. Overall, omega-3 PUFAs are an important addition to the treatment weapons for wound healing as well as tissue regeneration.

Acknowledgements

The authors acknowledge the support of Faculty of Pharmacy, Sri Adichunchanagiri College of Pharmacy.

REFERENCES

- [1] Wang PH., Huang BS., Horng HC., Yeh CC., Chen YJ, "Wound healing," *Journal of the Chinese Medical Association*, vol. 81, no. 2, pp. 94–101, 2018. DOI: 10.1016/j.jcma.2017.11.002.
- [2] Sorg H., Tilkorn DJ., Hager S., Hauser J., Mirastschijski U, "Skin Wound Healing: An Update on the Current Knowledge and Concepts," *European Surgical Research*, vol. 58, no.1–2, pp. 81–94, 2017. DOI: 10.1159/000454919.
- [3] Yang F., Bai X., Dai X., Li Y "The Biological Processes During Wound Healing," *Regenerative Medicine*, vol. 16, no. 4, pp. 373–90, 2021. DOI: 10.2217/RME-2020-0066.
- [4] Alvarez M., Chávez MN., Miranda M., Aedo G., Allende ML., Egaña JT, "A Novel In Vivo Model to Study Impaired Tissue Regeneration Mediated by Cigarette Smoke," *Scientific Reports*, vol. 8, no. 1, pp. 10926, 2018. DOI: 10.1038/S41598-018-28687-1.
- [5] Örling J., Kosonen K., Villman J., Reichard M., Paatero I, "Impaired fin regeneration and angiogenesis in aged zebrafish and turquoise killifish," *Biology Open*, vol. 12, no. 4, 2023. DOI: 10.1242/bio.059622.
- [6] Yufeng., Jiang., Xiaobing., Fu., Shuliang., Lu., Yiwen., Niu., Qi., Wang., Ting., Xie., Wei., Dong., Chiyu., Jia., Rungong., Yang., Yao., Lu., Jialiang., Zhu, "Tissue Repair and Regeneration Disorders: Repair and Regeneration of Chronic Refractory Wounds", In: *Regenerative Medicine in China*. Singapore: Springer Singapore, pp. 139–78, 2021. DOI: 10.1007/978-981-16-1182-7_5.
- [7] Eming SA., Martin P., Tomic-Canic M, "Wound repair and regeneration: Mechanisms, signaling, and translation", *Science Translational Medicine*, vol. 6, no. 265, 2014. DOI: 10.1126/SCITRANSLMED.3009337
- [8] Mao AS., Mooney DJ, "Regenerative medicine: Current therapies and future directions," *Proceedings of the National Academy of Sciences*, vol. 112, no. 47, pp. 14452–14459, 2015. DOI: 10.1073/pnas.1508520112.
- [9] Sharma P., Kumar A., Dey AD, "Cellular Therapeutics for Chronic Wound Healing: Future for Regenerative Medicine," *Current Drug Targets*, vol. 23, no. 16, pp. 1489–1504, 2022. DOI: 10.2174/138945012309220623144620.
- [10] Jannas-Vela S., Espinosa A., Candia AA., Flores-Opazo M., Peñailillo L., Valenzuela, "The Role of Omega-3 Polyunsaturated Fatty Acids and Their Lipid Mediators on Skeletal Muscle Regeneration: A Narrative Review," *Nutrients*, vol. 15, no. 4, pp. 871, 2023. DOI: 10.3390/nu15040871.
- [11] Chitre NM., Moniri NH., Murnane KS, "Omega-3 Fatty Acids as Druggable Therapeutics for Neurodegenerative Disorders," *CNS Neurol Disorder Drug Targets*, vol. 18, no. 10, pp. 735–749, 2020. DOI: 10.2174/1871527318666191

- 114093749.
- [12] Tachtsis B., Whitfield J., Hawley JA., Hoffman NJ, "Omega-3 Polyunsaturated Fatty Acids Mitigate Palmitate-Induced Impairments in Skeletal Muscle Cell Viability and Differentiation," *Frontiers in Physiology*, vol. 11, pp. 563, 2020. DOI: 10.3389/fphys.2020.00563.
- [13] Shahidi F AP, "Omega-3 polyunsaturated fatty acids and their health benefits," *The Annual Review of Food Science and Technology*, vol. 9, pp. 345–81, 2018. DOI: 10.1146/annurev-food-111317-095850.
- [14] Alexander JW., Supp DM, "Role of Arginine and Omega-3 Fatty Acids in Wound Healing and Infection," *Advances in Wound Care (New Rochelle)*, vol. 3, no. 11, pp. 682–90, 2014. DOI: 10.1089/wound.2013.0469.
- [15] Ma Y., Lindsey ML., Halade G V, "DHA derivatives of fish oil as dietary supplements: a nutrition-based drug discovery approach for therapies to prevent metabolic cardiotoxicity," *Expert Opinion on Drug Discovery*, vol. 7, no. 8, pp. 711–721, 2012. DOI: 10.1517/17460441.2012.694862.
- [16] Kotronoulas A., de Lomana ALG., Karvelsson ST., Heijink M., Stone II R., Giera M., et al, "Lipid mediator profiles of burn wound healing: Acellular cod fish skin grafts promote the formation of EPA and DHA derived lipid mediators following seven days of treatment," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 175, pp. 102358, 2021. DOI: 10.1016/J.PLEFA.2021.102355.
- [17] Ishihara T., Yoshida M., Arita M, "Omega-3 fatty acid-derived mediators that control inflammation and tissue homeostasis," *International immunology*, vol. 31, no. 9, pp. 559-567, 2019. DOI: 10.1093/intimm/dxz001.
- [18] Weylandt KH., Chiu CY., Gomolka B., Waechter SF., Wiedenmann B, "Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvins and protectin formation," *Prostaglandins & Other Lipid Mediators*, vol. 97, no. 3-4, pp. 73-82, 2012. DOI: 10.1016/j.prostaglandins.2012.01.005.
- [19] Komprda T, "Effect of n-3 long-chain polyunsaturated fatty acids on wound healing using animal models – a review," *Acta Veterinaria Brunensis*, vol. 87, no. 4, pp. 309–320, 2018. DOI: 10.2754/AVB201887040309.
- [20] Saini A., Sharples AP., Al-Shanti N., Stewart CE, "Omega-3 fatty acid EPA improves regenerative capacity of mouse skeletal muscle cells exposed to saturated fat and inflammation," *Biogerontology*, vol. 18, no. 1, pp. 109–129, 2017. DOI: 10.1007/S10522-016-9667-3.
- [21] Kang JX., Weylandt KH, "Modulation of Inflammatory Cytokines by Omega-3 Fatty Acids," In: *Lipids in Health and Disease*. Dordrecht: Springer Netherlands, vol. 49, pp. 133-143, 2008. DOI: 10.1007/978-1-4020-8831-5_5.
- [22] Gil Á., Fontana L, "Protectins, resolvins and maresins," In: *Encyclopedia of Human Nutrition*, Elsevier, pp. 209-214, 2023. DOI: 10.1016/b978-0-12-821848-8.00179-7.
- [23] Stornuolo CE., Pequera M., Vilariño A., Moreno JJ, "Specialized pro-resolvin mediators induce cell growth and improve wound repair in intestinal epithelial Caco-2 cell cultures," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 187, pp. 102520, 2022. DOI: 10.1016/j.plefa.2022.102520.
- [24] Augusta., Santis., Giuseppe., Vitiello., Marie-Sousai., Appavou., Ernesto., Scoppola., Giovanna., Fragneto., Lester., C., Barnsley., Luke., A., Clifton., Maria, Francesca, Ottaviani., Luigi., Paduano., Irene., Russo., Krauss., Gerardino., D'Errico, "Not just a fluidifying effect: omega-3 phospholipids induce formation of non-lamellar structures in biomembranes," *Soft Matter*, vol. 16, no. 46, pp. 10425–10438, 2020. DOI: 10.1039/D0SM01549K.
- [25] Fanxing., Meng., Jiayi., Qiu., Houjie., Chen., Xiaojun., Shi., Meifang., Yin., Zhu., Meishu., Guang., Yang, "Dietary supplementation with N-3 polyunsaturated fatty acid-enriched fish oil promotes wound healing after ultraviolet B-induced sunburn in mice," *Food Science & Nutrition Research*, vol. 9, no. 7, pp. 3693–3700, 2021. DOI: 10.1002/FSN3.2330.
- [26] Wei., Zhuang., Guo., Wang., Li., Li., Guoqiang., Lin., Zhenyu., Deng, "Omega-3 Polyunsaturated Fatty Acids Reduce Vascular Endothelial Growth Factor Production and Suppress Endothelial Wound Repair," *Journal of Cardiovascular Translational Research*, vol. 6, no. 2, pp. 287–293, 2013. DOI: 10.1007/S12265-012-9409-0.
- [27] Magadam A., Engel FB, "PPAR β / δ : Linking Metabolism to Regeneration", *International Journal of Molecular Sciences*, vol. 19, no. 7, 2018. DOI: 10.3390/ijms19072013.
- [28] Yi., Xiong., Adriana., Souza., Torsoni., Adriana., Souza., Torsoni., Feihua., Wu., Feihua., Wu., Hong., Shen., Yan., Liu., Xiao., Zhong., Mark., J., Canet., Yatrik., M., Shah., M., Bishr., Omary., Yong., Liu., Liangyou., Rui, "Hepatic NF-kB-inducing kinase (NIK) suppresses mouse liver regeneration in acute and chronic liver diseases," *Life Sciences*, vol. 7, 2018. DOI: 10.7554/ELIFE.34152.
- [29] Johannes., F., Fahrman., Oscar., Ballester., Gabriela., Ballester., Theodore., R., Witte., Alexander., J., Salazar., Benjamin., Kordusky., Kelsey, G, "Inhibition of Nuclear Factor Kappa B activation in Early-Stage Chronic Lymphocytic Leukemia by Omega-3 Fatty Acids," *Cancer Investigation Journal*, vol. 31, no. 1, pp. 24–38, 2013. DOI: 10.3109/07357907.2012.743553.
- [30] Yi., Xiong., Adriana., Souza., Torsoni., Feihua., Wu., Hong., Shen., Yan., Liu., Mark., J., Canet., Yatrik., M., Shah., Bishr., M., Omary., Yong, Liu., Liangyou, Rui, "Hepatic NF-kB-inducing Kinase (NIK) Suppresses Liver Regeneration in Chronic Liver Disease," *Frontiers in Cellular and Infection Microbiology*, pp. 238717, 2017. DOI: 10.1101/238717.
- [31] Robert., D., Hyldahl., Lawrence., M., Schwartz., Priscilla., M., Clarkson, "NF-KB activity functions in primary pericytes in a cell- and non-cell-autonomous manner to affect myotube formation," *Muscle & Nerve*, vol. 47, no. 4, pp. 522-531, 2013. DOI: 10.1002/MUS.23640.
- [32] Janine., Lückgen., Elisabeth., Raqué., Tobias., Reiner., Solvig., Diederichs., Wiltrud., Richter, "NF κ B inhibition to lift the mechano-competence of mesenchymal stromal cell-derived neocartilage toward articular chondrocyte levels," *Stem Cell Research & Therapy*, vol. 13, no. 1, 2022. DOI: 10.1186/s13287-022-02843-x.
- [33] Yolanda., Williams-Bey., Cedric., Boularan., Ali., Vural., Ning-Na., Huang., Il-Young., Hwang., Chong., Shan-Shi., John., H., Kehrl, "Omega-3 free fatty acids suppress macrophage inflammasome activation by inhibiting NF-kB activation and enhancing autophagy," *PLOS ONE*, vol. 9,

- no. 6, 2014. DOI: 10.1371/JOURNAL.PONE.0097957.
- [34] Eve., Draper., Clare., M., Reynolds., Mary., Canavan., Kingston., H., G., Mills., Christine., E., Loscher., Helen., M., Roche, "Omega-3 fatty acids attenuate dendritic cell function via NF- κ B independent of PPAR γ ," *Journal of Nutritional Biochemistry*, vol. 22, no. 8, pp. 784-790, 2011. DOI: 10.1016/J.JNUTBIO.2010.06.009.
- [35] Mishra A., Chaudhary A., Sethi S, "Oxidized omega-3 fatty acids inhibit NF-kappaB activation via a PPARalpha-dependent pathway," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 9, pp. 1621-1627, 2004. DOI: 10.1161/01.ATV.0000137191.02577.86.
- [36] Saxton RA., Sabatini DM, "mTOR Signaling in Growth, Metabolism, and Disease," *Cell*, vol. 168, no. 6, pp. 960-976, 2017. DOI: 10.1016/j.cell.2017.02.004.
- [37] Jere SW., Houreld NN., Abrahamse H, "Role of the PI3K/AKT (mTOR and GSK3 β) signalling pathway and photobiomodulation in diabetic wound healing," *Cytokine & Growth Factor Reviews*, vol. 50, pp. 52-59, 2019. DOI: 10.1016/j.cytogfr.2019.03.001.
- [38] Rogerio., M., Castilho., Cristiane., H., Squarize., Jorge, S., Gutkind, "Exploiting PI3K/mTOR signaling to accelerate epithelial wound healing," *Oral Diseases*, vol. 19, no. 6, pp. 551-558, 2013. DOI: 10.1111/ODI.12070.
- [39] Sepehr., Zamani., Nariman., Rezaei., Kolarijani., Mahdi., Naeji., Ahmad., Vaez., Hasan., Maghsoodifar., Seyed., Amir., Hossein., Sadeghi., douki., Majid., Salehi, "Development of carboxymethyl cellulose/gelatin hydrogel loaded with Omega-3 for skin regeneration," *Journal of Biomaterials Applications*, vol. 39, no. 4, pp. 377-395, 2024. DOI: 10.1177/08853282241265769.
- [40] Sunkyoung., Oh., Su-Hyung., Lee., Yushin., Jung., Hyo-Pyo., Lee., Ho., Jae., Han, "Arachidonic acid promotes skin wound healing through induction of human MSC migration by MT3-MMP-mediated fibronectin degradation," *Cell Death and Disease*, vol. 6, no. 5, pp. e1750-e1750, 2015. DOI: 10.1038/CDDIS.2015.114.
- [41] Chiang N., Serhan CN, "Specialized pro-resolving mediator network: an update on production and actions," *Essays in Biochemistry*, vol. 64, no. 3, pp. 443-462, 2020. DOI: 10.1042/EBC20200018.
- [42] Romano M., Patruno S., Pomilio A., Recchiuti A, "Proresolving Lipid Mediators and Receptors in Stem Cell Biology: Concise Review," *STEM CELLS Translational Medicine*, vol. 8, no. 10, pp. 992-998, 2019. DOI: 10.1002/sctm.19-0078.
- [43] Md Fadilah NI., Mohd Abdul Kader Jailani MS., Badrul Hisham MAI., Sunthar Raj N., Shamsuddin SA., Ng MH., Fauzi MB., Maarof M, "Cell secretomes for wound healing and tissue regeneration: Next generation acellular based tissue engineered products," *Journal of Tissue Engineering*, vol. 13, pp. 204173142211142, 2022. DOI: 10.1177/20417314221114273.
- [44] Parisa., Shabani., Parisa., Shabani., Zaniar., Ghazizadeh., Sattar., Gorgani-Firuzjace., Mohammad., Molazem., Sarah., Rajabi., Sadaf., Vahdat., Sadaf., Vahdat., Yaser., Azizi., Mahmood., Doosti., Nasser., Aghdami., Hossein., Baharvand., Hossein., Baharvand, "Cardioprotective effects of omega-3 fatty acids and ascorbic acid improve regenerative capacity of embryonic stem cell-derived cardiac lineage cells," *BioFactors*, vol. 45, no. 3, pp. 27-38, 2019. DOI: 10.1002/BIOF.1501.
- [45] Peter S., Jacob JJ, "Role of Omega-3 Fatty Acids in Cardiovascular Disorders," In: *Omega-3 Fatty Acids*. Cham: Springer International Publishing, pp. 513-530, 2016. DOI: 10.1007/978-3-319-40458-5_37.
- [46] Steward MM., Sridhar A., Meyer JS, "Neural regeneration," *Current Topics in Microbiology and Immunology*, vol. 367, pp. 163-191, 2013. DOI: 10.1007/82_2012_302.
- [47] Lin L., Zheng S., Lai J., Ye D., Huang Q., Wu Z., "Omega-3 Polyunsaturated Fatty Acids Protect Neurological Function After Traumatic Brain Injury by Suppressing Microglial Transformation to the Proinflammatory Phenotype and Activating Exosomal NGF/TrkA Signaling," *Molecular Neurobiology*, vol. 60, no. 10, pp. 5592-5606, 2023. DOI: 10.21203/rs.3.rs-2267425/v1.
- [48] Figueroa JD., De Leon M, "Neurorestorative Targets of Dietary Long-Chain Omega-3 Fatty Acids in Neurological Injury," *Molecular Neurobiology*, vol. 50, no. 1, pp. 197-213, 2014. DOI: 10.1007/S12035-014-8701-1.
- [49] Athanasios., Drigas., Maria., Karyotaki., Charalabos., Skianis, "An Integrated Approach to Neuro-development, Neuroplasticity and Cognitive Improvement," *International Journal of Recent Contributions from Engineering, Science & IT (IJES)*, vol. 6, no. 3, pp. 4, 2018. DOI: 10.3991/IJES.V6I3.9034.
- [50] Vilasagaram., Srinivas., Saikanth., Varma., Suryam., Reddy., Kona., Ahamed., Ibrahim., Asim., K., Duttaroy., Sanjay., Basak, "Dietary omega-3 fatty acid deficiency from pre-pregnancy to lactation affects expression of genes involved in neurogenesis of the offspring," *bioRxiv*, 2022. DOI: 10.1101/2022.10.14.512201.
- [51] Dyal SC, "The Role of Omega-3 Fatty Acids in Hippocampal Neurogenesis," In: *Omega-3 Fatty Acids in Brain and Neurological Health*, Elsevier, pp. 251-263, 2014. DOI: 10.1016/B978-0-12-410527-0.00021-1.
- [52] Li Z., Xiang S., Li EN., Fritch MR., Alexander PG., Lin H., Tuan RS, "Tissue Engineering for Musculoskeletal Regeneration and Disease Modeling," *Handbook of Experimental Pharmacology*, vol. 265, pp. 235-268, 2021. DOI: 10.1007/164_2020_377.
- [53] Bill T, "Protective effects of omega-3 fatty acids against skeletal muscle cell lipotoxicity," *MPhil Thesis, Australian Catholic University*, 2020. DOI: 10.26199/ACU.8VYW5.
- [54] Xin G., Eshaghi H, "Effect of omega-3 fatty acids supplementation on indirect blood markers of exercise-induced muscle damage: Systematic review and meta-analysis of randomized controlled trials," *Food Science & Nutrition*, vol. 9, no. 11, pp. 6429-6442, 2021. DOI: 10.1002/FSN3.2598.
- [55] Nesrin KAEFatah., SMMKheder., NAERESayed., AEMHHelal, "Effect of Omega 3 Polyunsaturated Fatty Acids Supplementation on Osteoarthritic Knees among Females," *International Journal of Health Sciences and Research*, vol. 6, no. 4, pp. 362-369, 2016. DOI: 10.1186%2Fs13018-023-03855-w.
- [56] Shah K., Majeed Z., Jonason J., O'Keefe RJ, "The Role of Muscle in Bone Repair: The Cells, Signals, and Tissue Responses to Injury," *Current Osteoporosis Reports*, vol. 11,

- no. 2, pp. 130–135, 2013. DOI: 10.1007/s11914-013-0146-3.
- [57] Su., Mi., Lee., Eu., Gene., Jeong., Yujin., Jeong., Seo-Hee., Rha., Seong., Eun., Kim., Won., Suk., An, “Omega-3 fatty acid and menaquinone-7 combination are helpful for aortic calcification prevention, reducing osteoclast area of bone and FoxO expression of muscle in uremic rats,” *Renal Failure*, vol. 44, no. 1, pp. 1883–1895, 2022. DOI: 10.1080/0886022X.2022.2142140.
- [58] Gonzalez AC., Costa TF., Andrade ZA., Medrado AR, “Wound healing - A literature review,” *Anais Brasileiros de Dermatologia*, vol. 91, no. 5, pp. 614–620, 2016. DOI: 10.1590/abd1806-4841.20164741.
- [59] Beat., Burger., Roberta., Nicolli., Sagiorato., Jéssica., R., Silva., Thamiris., Candreva., M., R., Pacheco., O., Martinez., Philip., C., Calder., Hosana, G., Rodrigues, “Eicosapentaenoic acid-rich oil supplementation activates PPAR- γ and delays skin wound healing in type 1 diabetic mice,” *Frontiers in Immunology*, vol. 14, 2023. DOI: 10.3389/fimmu.2023.1141731.
- [60] Alica., Hokynková., Marie., Nováková., Petr., Babula., Miroslava., Sedláčková., Hana., Paulová., Miroslava., Hlaváčková., Daniela., Charwátová., Tibor., Stračina, “Fatty Acid Supplementation Affects Skin Wound Healing in a Rat Model,” *Nutrients*, vol. 14, no. 11, pp. 2245-2245, 2022. DOI: 10.3390/nu14112245.