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Topical Application Type of Fish Oil Promotes Re-Epithelialization in Burn Wound Healing in Rats

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ABSTRACT

Burns are a condition that is often found in the world in various cases such as accidents. The incidence of burns will probably increase as human activities become more complex. Wounds that are not treated immediately tend to become infected and cause death. Fish oil is one of the ingredients that has been studied for wound healing. Previous research shows that fish oil is rich in long-chain omega-3 fatty acids such as docosahexaenoic acid and eicosapentaenoic acid, which have anti-inflammatory effects. However, there has not been much research on the type of fish oil used and the wound healing process. The aim of this study was to determine the wound-healing activity of milkfish (*Chanos chanos* Forsskal.), patin (*Pangasius djambal*), and eel (*Anguilla bicolor*) fish oil. Tests were carried out on 25 mice as an experimental animal model for burn wounds. Data on percentage wound reduction and the re-epithelialization process were statistically calculated using one-way analysis of variance (ANOVA) followed by a post-hoc LSD test. The research results showed that milkfish oil, patin fish oil, and eel fish oil in a concentration of 10% on an ointment basis were able to reduce wounds significantly. Eel fish oil shows the greatest burn wound healing process with re-epithelialization when compared to other oils. The type of fish oil affects the wound healing process.

Keywords: Fish; Omega-3; Wound Healing; Re-Epithelialization

INTRODUCTION

Burns are the tissue damage produced by thermal stress (Razdan et al., 2023) . Burns may cause deep tissue damage under the surface (Sasongko et al., 2018). According to data from the World Health Organization (WHO), there were around 180.000 deaths caused by burns in the year 2018 (Hughes et al., 2021). Every year, over 195.000 people in Indonesia die as a consequence of burns (Angkoso & Kekalih, 2022). The high burn-related fatality rate is a source of worry for health professionals and researchers worldwide who are doing medication development studies. The human body may heal burn wounds by a variety of mechanisms such as coagulation, inflammation, matrix synthesis and deposition, angiogenesis, fibroplasia, epithelialization, contraction, and remodeling (Kazemzadeh et al., 2022). Increasing the pace of wound healing and lowering wound healing time has long been a major priority (Liang et al., 2022).

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Fish oil is a natural ingredient that is known to have an influence on the healing process of burn wounds (Sasongko et al., 2022). Burns cause an increase in saturated fatty acids and monounsaturated fatty acids compared to polyunsaturated fatty acids in plasma phospholipids (Salehi et al., 2023). These changes may be consistent with a pro-inflammatory response and suggest a possible increased utilization of lipids to synthesize membrane lipids to improve wound healing (Novak et al., 2017). Previous research shows that fish oil is rich in long-chain omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which have anti-inflammatory effects (Sasongko et al., 2020). The type of fish oil is thought to influence the therapeutic effect due to variations in nutritional content (Sasongko, Zulpadly, et al., 2023). Several types of fish oil that are known to be rich in omega-3 fatty acids, especially EPA and DHA, are milkfish oil (*Chanos chanos*), eel fish oil (*Anguilla bicolor*), and patin oil (*Pangasius djambal*) (Kusharto et al., 2014) ; (Sasongko,

Nugroho, et al., 2023).

Variations in the content of fatty acids and other components contained in fish oil allow for differences in the ability to heal burn wounds. In general, the wound repair process can be divided into three stages: inflammation, proliferation, and remodeling (Eming et al., 2014). The proliferation stage is the most important step in the wound repair process, which involves the proliferation and migration of various cells, including endothelial cells, fibroblasts, keratinocytes, and macrophages (Gong et al., 2023). More specifically, the proliferation stage can be divided into two parts, namely re-epithelialization and granulation tissue formation, which are complementary, closely related, and influence each other (Baltzis et al., 2014). Granulation tissue instantly fills the tissue defect, and the epidermis eventually covers the wound to full re-epithelialization, indicating wound healing (Gong et al., 2023). There have not been many studies on the effect of fish oil on burn wound healing. The aim of this study was to determine the wound-healing activity of milkfish, patin, and eel fish oil. In this study, the re-epithelialization process was evaluated as the main pathological parameter in the wound healing process.

MATERIALS AND METHODS

Materials

Milkfish purchased from the Mojosongo fish market, Central Java, aged 5–6 months with a body weight range of 300–400 g; eel fish purchased from the Colomadu eel fish farming place, Central Java, aged 4–5 months with a body weight range of 300–500 g; patin (*Pangasius djambal*) originating from the Mojosongo fish market, Central Java, aged 5–6 months with a body weight range of 300–500 g; vaseline album; cera alba; male white mice (*Mus musculus*) BALB-C strain aged 2–3 months weighing 20–30 g; and 10% povidone iodine ointment .

Fish oil extraction

Milkfish, patin, and eel fish oils are separately extracted using the boiling method. Each fish was cut into smaller pieces and ground using a blender. Then, the fish blender added the water (1:2 w/v) and put it into a pan. Then, it was heated with an electric stove at 100°C for 40 minutes (Sasongko et al., 2017). Each separate fish oil processing process is taken as milkfish oil (CFO), patin fish oil (PFO), and eel fish oil (AFO).

Fish oil sample preparation

The fish oil obtained was then prepared and formulated with a standard hydrocarbon ointment base (Table I). The formulation of hydrocarbon ointment is carried out by weighing vaseline album and cera alba according to what is needed. Then the two bases were melted in a porcelain cup using a water bath at a temperature of 61–65 ^{o}C (Sasongko et al., 2018). Then, pour the melted base mixture into a mortar, add half of the fish oil to reach the desired concentration formula, and stir until thoroughly mixed.

Table I. Fish oil formula in hydrocarbon ointment base

Material	Material weight (grams)			
Milkfish Oil	-	5	-	-
Eel Fish Oil	-	-	5	-
Patin Fish Oil	-	-	-	5
Cera Alba	7.5	6.75	6.75	6.75
Vaseline Album	42.5	38.25	38.25	38.25

Animals preparation

The experimental animals used were male mice (*Mus musculus*) aged 2–3 months, weighing 20–30 g, obtained from the Dunia Kaca Laboratory, Kemuning, Karanganyar, Central Java, Indonesia. Mice were placed in a 12-hour light cycle and a 12-hour dark cycle for a week and received unlimited food and drink. All testing protocols have received approval from the Health Research Ethics Committee of RSUD Dr. Moewardi Surakarta, Central Java (No: 1021/VII/HREC/2022).

Burn wound model

All animals were given 5 mg/kg Xylazine and 60 mg/kg Ketamine intraperitoneally (i.p.). After the mice became unconscious, we shaved their back hair with depilatory lotion and stroked them with 70% ethanol. Mice with hairless backs were exposed to a hot brass rod (diameters 10 mm) for 45 seconds to induce burn injuries (Gupta et al., 2015) .

Animal groups

After a week of acclimatization, 25 mice were separated into five groups and each group consisted of five animals (n = 5). All groups consisted of mice that experienced a burn injury model. Group 1 did not receive fish oil sample treatment and was only given hydrocarbon ointment base (control group). Group 2 was treated with ointment containing 10% povidone

iodine (Standard group). Group 3 was treated with samples of milkfish oil (CFO). Group 4 was treated with samples of patin oil (PFO). Group 5 was treated by giving samples of eel fish oil (AFO). The experiment was carried out for 21 days by giving a sample of ± 0.25 grams every morning, smeared on the burn area.

Assessment of wound size reduction

Measurement of the area of the burn wound was carried out on days 1, 7, 14, and 21 after treatment. On day 22, all mice were sacrificed by cervical dislocation and evaluated using various parameters. The number of days based on the nearly closed wound condition to clearly see the histopathology. The following equation calculated the percentage of recovery and total wound closure (%) at each time point compared to the original wound, based on the wound image :

$$\text{Wound size reduction}(\%) = \frac{(\text{initial wound area at first day} - \text{wound area at day n})}{\text{initial wound area at first day}} \times 100$$

Epithelialization analysis

On day 22, mice from each group were slaughtered by cervical dislocation to remove the scar tissue for histological analysis. Sample fixation was carried out in 10% formalin solution. After the samples were embedded in paraffin, 5 µm sections were cut using a microtome. Using established methods, tissue sections were stained with hematoxylin and eosin (H&E). Histological examination was carried out qualitatively and quantitatively to determine the general morphology and re-epithelialization process of the wound using a microscope with 400x magnification.

Statistical analysis

Data was presented for each group as mean ± standard deviation (SD). Statistical analysis was carried out using one-way analysis of variance (ANOVA) with a significance of 95% ($p<0.05$). To differentiate groups of experimental animals, a post-hoc LSD test was applied using statistics.

RESULTS

Figure 1 shows the burn wound healing activity based on macroscopic observations of wounds in each group on days 1, 7, 14, and 21. All treatment groups experienced wound healing activity from day 7 to day 21 observation. The wound is still widening from the first to the seventh day. On day 14, the standard group treated with povidone iodine ointment (10%) had signs of healing, with the wound beginning to reduce. In the other group, the injuries remained visible but had begun to diminish in size. Based on the post hoc LSD test in Table II, the treatment group had a significant difference ($p<0.05$) in wound area compared to the control group on days 7, 14, and 21. On day 21, the eel fish oil (AFO) treatment group had no differences. significant ($p<0.05$) with the standard group, while the milkfish oil (CFO) and patin oil (PTO) treatment groups had significant differences ($p<0.05$) with the standard group. This shows that eel fish oil has wound healing activity that is comparable to the standard group.

Figure 2 shows the percentage of wound healing activity from day 1 to day 21, with the highest percentage in the standard group, followed by the eel fish oil (AFO) treatment group and the milkfish oil (CFO) treatment group.

Figure 3 shows the mean amount of epithelial tissue after treatment on day 22. The standard group had the highest mean, followed by the eel fish oil (AFO) treatment group and the milkfish oil (CFO) treatment group. A comparison of the mean amount of epithelial tissue between the control group and other treatment groups showed an increase in the amount of epithelial tissue, which indicated that re-epithelialization had occurred, causing the wound area to decrease. Based on the results of the post hoc LSD test in Table II, it shows that the milkfish oil (CFO) and eel fish oil (AFO) treatment groups did not have significant differences compared to the standard group, so that the milkfish oil (CFO) and eel fish oil (AFO) treatment groups had activity. The re-epithelialization was comparable to that of the standard group.

DISCUSSION

The results of this study indicate that fish oil has wound healing activity which is in line with accelerating the re-epithelialization process. Tanideh et al. (2016) also revealed the re-epithelialization process of fish oil on wounds, where its anti-inflammatory properties reduce exudate and scar tissue. The study, while requiring a combination with other ingredients like honey, did not specify the type of fish oil used. Fish oil's omega-3 fatty acids can also serve as a nutritional supplement and a preventative measure to preserve skin health and homeostasis (Meng et al., 2021). The ability to heal wounds is due to the composition of fish oil in the form of omega-3 fatty acids, omega-6 fatty acids, omega-9 fatty acids, EPA and DHA. On day 1, all treatment groups had not experienced wound healing but there was the formation of scabs which still looked reddish and wet. This is an inflammatory phase where the body will experience hemostasis and produce blood

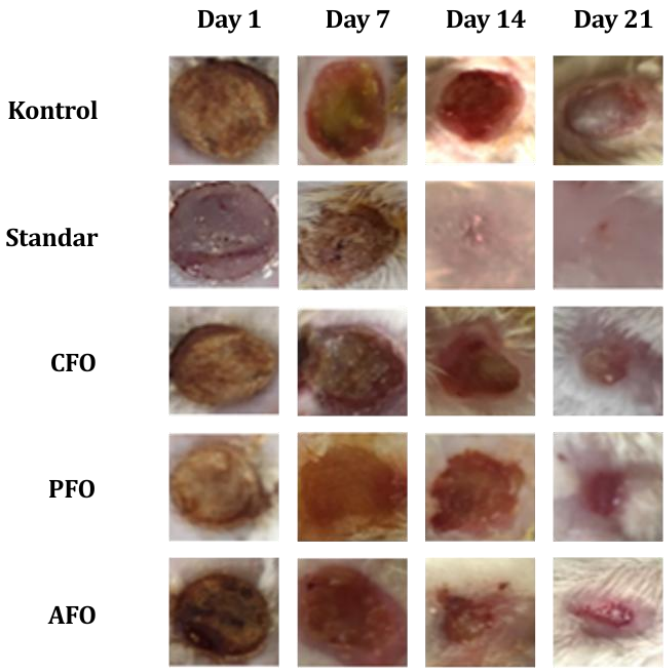

Figure 1. Macroscopic appearance of burn wounds in mice during the 21 days of the experiment

Table II. Wound extent of burn wounds in mice after topical administration of CFO, PFO, and AFO for 21 days

Group	Mean ± SD			
	Day 1	Day 7	Day 14	Day 21
Control	0.785 ± 0	0.774 ± 0.067	0.762 ± 0.054	0.662 ± 0.151
Standard	0.785 ± 0	0.605 ± 0.123 *	0.419 ± 0.212 *	0.129 ± 0.109 *
CFO	0.785 ± 0	0.711 ± 0.054	0.547± 0.176 *	0.305 ± 0.128 *
PFO	0.785 ± 0	0.736 ± 0.199	0.587± 0.034 *	0.319 ± 0.184 *
AFO	0.785 ± 0	0.713 ± 0.305	0.413 ± 0.089 *	0.267 ± 0.079 *

*, $p<0.05$ indicates significant difference compared to the control group

clots to cover the wound so that necrotic tissue forms (Xue et al., 2018) . Arachidonic acid, which is a derivative of omega-6 fatty acids in fish oil, plays an important role in this phase as a pro-inflammatory and anti-inflammatory. Arachidonic acid is converted by the enzyme cyclooxygenase (COX) into eucosanoids such as prostaglandin, prostacyclin and thromboxane. Prostasin plays a role in improving blood flow, while thromboxane causes blood platelets to stick together and clot. Apart from that, arachidonic acid is also converted by the lipoxygenase enzyme into leukotrienes and lipoxins. Leukotirene plays a role in phagocytosis of foreign compounds by attracting neutrophils and macrophages towards the wound and at the same time, neutrophils release chemical compounds to recruit more neutrophil cells. At a certain stage, the action of neutrophils must be prevented because it can damage cells and tissues caused by chemical compounds released by neutrophils. The formation of lipoxin can prevent the formation of leukorrhea so that the action of neutrophils can be stopped. Lipoxin is an anti-inflammatory mediator that prevents neutrophil cell infiltration leading to inflammation so that inflammation does not continue (Daisa et al., 2017).

On days 7 and 14, the wound shrinks, indicating a proliferation phase characterized by re-epithelialization and the formation of granulation tissue which occurs over 3 to 10 days (Mofazzal et al., 2018). Re-epithelialization consists of migration, proliferation and differentiation of epithelial cells by changing keratinocytes into a proliferative phenotype which is influenced by several *growth factors,* one of which is *Transforming growth factor- β* (TGF- β) (Krishnaswamy & Korrapati, 2014). Furthermore, keratinocytes migrate through the interaction of various extracellular matrix (ECM) proteins such

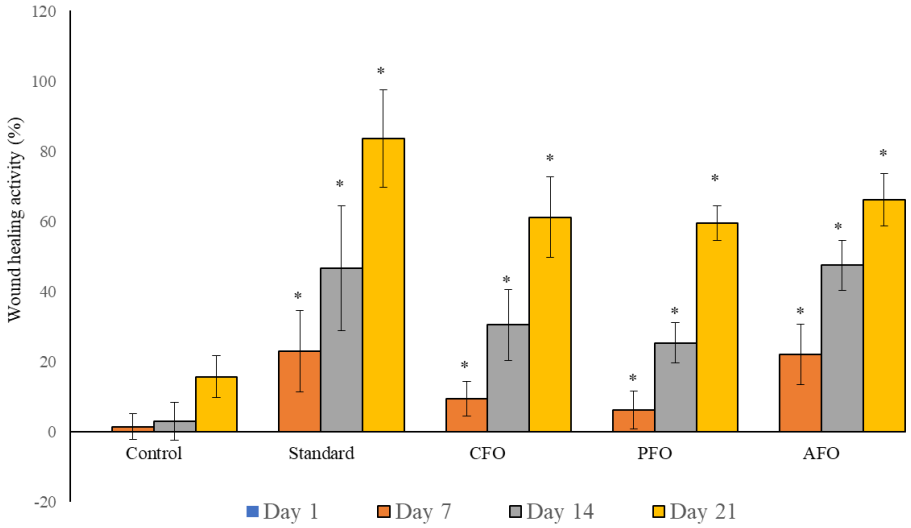

Figure 2. Percentage of burn wound healing activity in mice after topical administration of CFO, PFO, and AFO for 21 days. *, p<0.05 indicates significant difference compared to the control group.

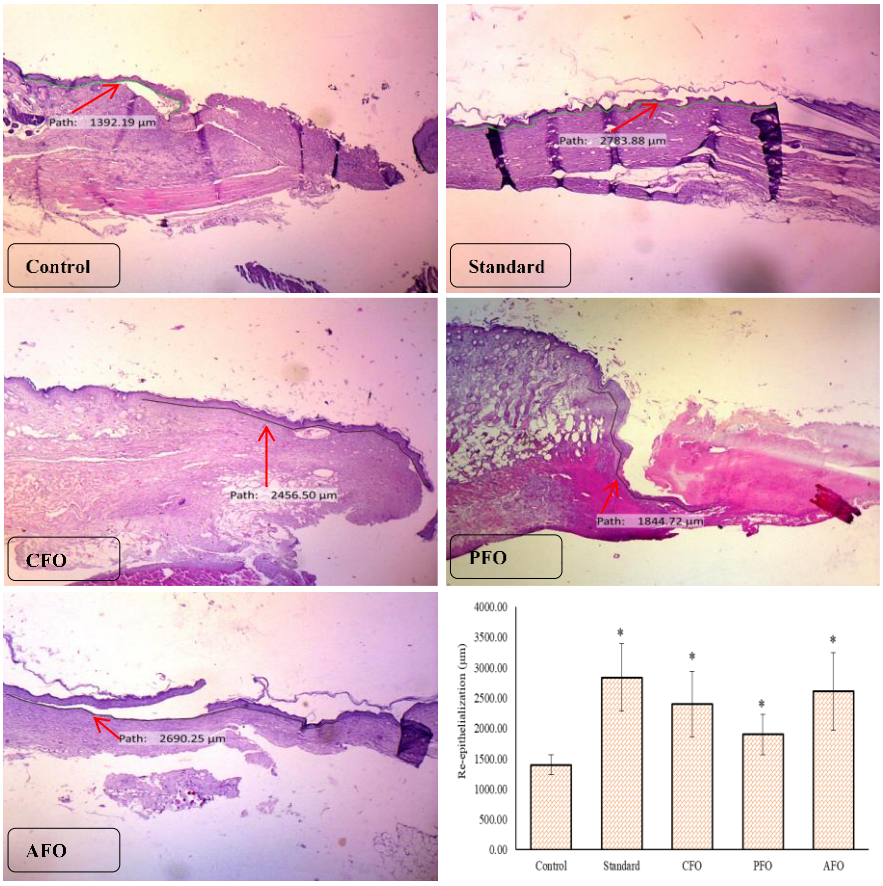

Figure 3. The process of re-epithelialization of burn wounds in mice after topical administration of CFO, PFO, and AFO for 21 days. *, p<0.05 indicates significant difference compared to the control group.

as fibronectin, vitronectin, and type I collagen via specific integrin mediators and form a temporary fibrin matrix. The fibrin matrix is temporarily replaced by granulation tissue, which consists of three types of cells: fibroblasts, macrophages, and endothelium. The formation of granulation tissue

is determined by the number of fibroblasts, endothelium and macrophages. Fibroblasts have an important role in the formation of granulation tissue. Macrophages will produce *growth factors* such as PDGF and TGF- β1 which cause fibroblasts to proliferate, migrate, deposit extracellular matrix, and stimulate the endothelium for angiogenesis. Angiogenesis begins when blood clots form due to the release of TGF-β, PDGF, and *fibroblast growth factor* (FGF). When hypoxia occurs, the production of VEGF is stimulated and, together with several cytokines, activates endothelial cells to form new blood vessels and repair damaged ones. The release of PDGF and TGF-β also stimulates fibroblasts to develop and contributes to the formation of type 3 collagen fibers and fibronectin in the extracellular matrix. This process continues with epithelialization, where epithelial cells grow from the edge of the wound to the entire wound area through the epithelial-mesenchymal transition (EMT) process (Marconi et al., 2021).

On day 21, it appeared that the wounds in the standard group had covered the entire surface and in the treatment group there were only a few open wounds. In this case, a remodeling phase occurs, where fibroblasts differentiate into myofibroblasts, which then produce extracellular matrix, especially collagen. Myofibroblasts play an important role in tensile forces, which result in actin and myosin interactions in the wound area (Soji-Omoniwa et al., 2022). Apart from mature epithelial cells, basement membrane deposition occurs which consists of localization of cell membrane components such as type 3 collagen, laminin-1 and heparan sulfate proteoglycans (Ningsih et al., 2019). *The matrix metalloproteinase (MMP)* enzyme carries out the process of splitting type 3 collagen into type 1 collagen. Interlocking collagen fibers, especially of the type I phenotype, are rearranged in small parallel bundles along tension lines when the synthesis process is balanced (Xue et al., 2018) . The EPA and DHA content in omega 3 can topically heal wounds by increasing the cytokines IL-6 and TGF- β (Karoud et al., 2020) . An increase in the IL-6 cytokine causes collagen production by fibroblasts to increase so that the increased amount of collagen makes the wound healing process occur quickly (Johnson et al., 2020). Increased TGF- β can stimulate increased wound healing processes by regulating various events in the proliferation phase such as re-epithelialization and granulation tissue formation (Alsenani et al., 2021) . The fatty acid content in fish oil is very high, but omega-3 fatty acids, especially EPA and DHA, have been widely reported to be responsible for wound healing activity (Meng et al., 2021).

Post hoc LSD test statistical analysis of the average amount of epithelial tissue (Figure 3) on day 22 showed that the standard group had the highest average amount of epithelial tissue, followed by the eel fish oil (AFO) and milkfish oil (CFO) treatment groups. This result is directly proportional to the percentage of wound healing activity where a high amount of epithelial tissue has a high percentage of wound healing activity as well. The results of the *post hoc LSD test statistical analysis* of the extent of wound healing (Table II) and the graph of the percentage of wound healing activity (Figure 2) from days 1 to 21 show that the standard group has the ability to heal quickly compared to other treatment groups. The standard group was given ointment treatment containing *povidone iodine*, which is a bond between *iodine* and *polyvinyl* as an antiseptic to prevent infection in wounds. Antiseptics are chemicals that prevent, slow down or stop the growth of microorganisms on the outer surface of the body and help prevent infection so that they can speed up the wound healing process by inhibiting the growth of bacteria in wounds (Babalska et al., 2021). On day 7, the control group experienced an expansion of the wound, this may be because the skin tissue around the wound was damaged, and the control group was only given a hydrocarbon ointment base which did not contain active substances that help in the wound healing process. Based on the LSD *post hoc test* of the extent of wound healing, the eel fish oil (AFO) treatment group did not have a significant difference with the standard group so that the eel fish oil (AFO) treatment group had wound healing that was comparable to the control group so that eel fish oil was better than fish oil. milkfish and patin. However, from the *post hoc LSD test*, the mean amount of epithelial tissue, the eel fish oil (AFO) and milkfish oil (CFO) treatment groups did not have a significant difference from the standard group so that both oils had comparable re-epithelialization activity to the standard group. The results of this study are consistent with previous studies that widely attribute the wound healing process to anti-inflammatory activity.

CONCLUSION

This study investigated the role of milkfish oil, patin oil, and eel fish oil in burn wound healing's re-epithelialization process. During the re-epithelialization process, different types of fish have different burn wound healing activities. This study did not carry out the quantification and

comparison of EPA and DHA fatty acid content. Therefore, future research can compare fatty acid content and wound healing activity.

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REFERENCES

Alsenani, F., Ashour, A. M., Alzubaidi, M. A., Azmy, A. F., Hetta, M. H., Abu-Baih, D. H., Elrehany, M. A., Zayed, A., Sayed, A. M., Abdelmohsen, U. R., & Elmaidomy, A. H. (2021). Wound Healing Metabolites from Peters' Elephant-Nose Fish Oil: An In Vivo Investigation Supported by In Vitro and In Silico Studies. *Marine Drugs*, *19*(11), 605. https://doi.org/10.3390/md19110605

Angkoso, H., & Kekalih, A. (2022). Prognostic Factors for Mortality of Pediatric Burn Injury in a National Tertiary Referral Center. *The New Ropanasuri Journal of Surgery*, *7*(2). https://doi.org/10.7454/nrjs.v7i2.1134

Babalska, Z. Ł., Korbecka-Paczkowska, M., & Karpiński, T. M. (2021). Wound Antiseptics and European Guidelines for Antiseptic Application in Wound Treatment. *Pharmaceuticals*, *14*(12), Article 12. https://doi.org/10.3390/ph14121253

Baltzis, D., Eleftheriadou, I., & Veves, A. (2014). Pathogenesis and Treatment of Impaired Wound Healing in Diabetes Mellitus: New Insights. *Advances in Therapy*, *31*(8), 817–836. https://doi.org/10.1007/s12325-014-0140-x

Daisa, F., Andrie, M., & Taurina, W. (2017). The Effectiveness Test of Oil Phase Ointment Containing Snakehead Fish (Channa striata) Extract on Open Stage II Acute Wounded Wistar Strain Male Rats. *Majalah Obat Tradisional*, *22*(2), 97. https://doi.org/10.22146/tradmedj.27920

Eming, S. A., Martin, P., & Tomic-Canic, M. (2014). Wound repair and regeneration: Mechanisms, signaling, and translation. *Science Translational Medicine*, *6*(265), 265sr6-265sr6. https://doi.org/10.1126/scitranslmed.3009337

Gong, Y., Jiang, Y., Huang, J., He, Z., & Tang, Q. (2023). Moist exposed burn ointment accelerates diabetes-related wound healing by promoting re-epithelialization. *Frontiers in Medicine*, *9*. https://www.frontiersin.org/articles/10.3389/fmed.2022.1042015

Gupta, P., Chhibber, S., & Harjai, K. (2015). Efficacy of purified lactonase and ciprofloxacin in preventing systemic spread of Pseudomonas aeruginosa in murine burn wound model. *Burns*, *41*(1), 153–162. https://doi.org/10.1016/j.burns.2014.06.009

Hughes, A., Almeland, S. K., Leclerc, T., Ogura, T., Hayashi, M., Mills, J.-A., Norton, I., & Potokar, T. (2021). Recommendations for burns care in mass casualty incidents: WHO Emergency Medical Teams Technical Working Group on Burns (WHO TWGB) 2017-2020. *Burns*, *47*(2), 349–370. https://doi.org/10.1016/j.burns.2020.07.001

Johnson, B. Z., Stevenson, A. W., Prêle, C. M., Fear, M. W., & Wood, F. M. (2020). The Role of IL-6 in Skin Fibrosis and Cutaneous Wound Healing. *Biomedicines*, *8*(5), Article 5. https://doi.org/10.3390/biomedicines8050101

Karoud, W., Ghlissi, Z., Krichen, F., Kallel, R., Bougatef, H., Zarai, Z., Boudawara, T., Sahnoun, Z., Sila, A., & Bougatef, A. (2020). Oil from hake (Merluccius merluccius): Characterization, antioxidant activity, wound healing and anti-inflammatory effects. *Journal of Tissue Viability*, *29*(2), 138–147. https://doi.org/10.1016/j.jtv.2020.01.002

Kazemzadeh, G., Jirofti, N., Mohebbi-Kalhori, D., Sarhaddi, F., & Taheri, R. (2022). Pathological examination of blended and co-electrospinning hybrid polycaprolactone/polyurethane nanofibers for soft tissue engineering applications. *Journal of Industrial Textiles*, *51*(4_suppl), 6816S-6837S. https://doi.org/10.1177/15280837221074070

Krishnaswamy, V. R., & Korrapati, P. S. (2014). Role of Dermatopontin in re-epithelialization: Implications on keratinocyte migration and proliferation. *Scientific Reports*, *4*(1), 7385. https://doi.org/10.1038/srep07385

Kusharto, C. M., Widyasari, R. A. H. E., Budywiryawan, Wiyono, E. S., & Sugengherisuseno. (2014). Nutritive Value and Fatty Acids Profile of Fresh Indonesian Eel (Anguilla bicolor) and Kabayaki. *Jurnal Sains Kesihatan Malaysia (Malaysian Journal of Health Sciences)*, *12*(1). http://ejournals.ukm.my/jskm/article/view/6993

Liang, Y., Li, M., Yang, Y., Qiao, L., Xu, H., & Guo, B. (2022). pH/Glucose Dual Responsive Metformin Release Hydrogel Dressings with Adhesion and Self-Healing via Dual-Dynamic Bonding for Athletic Diabetic Foot Wound Healing. *ACS Nano*, *16*(2), 3194–3207. https://doi.org/10.1021/acsnano.1c11040

Marconi, G. D., Fonticoli, L., Rajan, T. S., Pierdomenico, S. D., Trubiani, O., Pizzicannella, J., & Diomede, F. (2021). Epithelial-Mesenchymal Transition (EMT): The Type-2 EMT in Wound Healing, Tissue Regeneration and Organ Fibrosis. *Cells*, *10*(7), Article 7. https://doi.org/10.3390/cells10071587

Meng, F., Qiu, J., Chen, H., Shi, X., Yin, M., Zhu, M., & Yang, G. (2021). Dietary supplementation with N-3 polyunsaturated fatty acid-enriched fish oil promotes wound healing after ultraviolet B-induced sunburn in mice. *Food Science & Nutrition*, *9*(7), 3693–3700. https://doi.org/10.1002/fsn3.2330

Mofazzal Jahromi, M. A., Sahandi Zangabad, P., Moosavi Basri, S. M., Sahandi Zangabad, K., Ghamarypour, A., Aref, A. R., Karimi, M., & Hamblin, M. R. (2018). Nanomedicine and advanced technologies for burns: Preventing infection and facilitating wound healing. *Advanced Drug Delivery Reviews*, *123*, 33–64. https://doi.org/10.1016/j.addr.2017.08.001

Ningsih, J. R., Haniastuti, T., & Handajani, J. (2019). Re-epitelisasi luka soket pasca pencabutan gigi setelah pemberian gel getah pisang raja (*Musa sapientum* L) Kajian histologis pada marmut (Cavia cobaya). *JIKG (Jurnal Ilmu Kedokteran Gigi)*, *2*(1). https://doi.org/10.23917/jikg.v2i1.6644

Novak, F., Borovska, J., Vecka, M., Rychlikova, J., Vavrova, L., Petraskova, H., Zak, A., & Novakova, O. (2017). Plasma Phospholipid Fatty Acid Profile is Altered in Both Septic and Non-Septic Critically Ill: A Correlation with Inflammatory Markers and Albumin. *Lipids*, *52*(3), 245–254. https://doi.org/10.1007/s11745-016-4226-x

Prayugo, B., Ichwan, M., & Yamamoto, Z. (2021). Potensi ekstrak ikan gabus terhadap kesembuhan luka diabetes. *Jurnal Kedokteran Syiah Kuala*, *21*(2). https://doi.org/10.24815/jks.v21i2.20376

Razdan, K., Kanta, S., Chaudhary, E., Kumari, S., Rahi, D. K., Yadav, A. K., & Sinha, V. R. (2023). Levofloxacin loaded clove oil nanoscale emulgel promotes wound healing in Pseudomonas aeruginosa biofilm infected burn wound in mice. *Colloids and Surfaces B: Biointerfaces*, *222*, 113113. https://doi.org/10.1016/j.colsurfb.2022.113113

Salehi, S., Hosseinzadeh-Attar, M. J., Alipoor, E., Dahmardehei, M., Yaseri, M., Emami, M. R., & Siadat, S. D. (2023). Effects of hydrolyzed collagen alone or in combination with fish oil on gut microbiome in patients with major burns. *Burns*. https://doi.org/10.1016/j.burns.2023.08.017

Sasongko, H., Efendi, N. R., Budihardjo, A., Farida, Y., Amartiwi, T., Rahmawati, A. A., Wicaksono, A., & Sugiyarto. (2017). Solvent and extraction methods effects on the quality of eel (Anguilla bicolor) oil. *Journal of Physics: Conference Series*, *795*(1), 012021. https://doi.org/10.1088/1742-6596/795/1/012021

Sasongko, H., Nugroho, A. E., Nurrochmad, A., & Rohman, A. (2023). Nephroprotective effect of milkfish, patin, and snakehead fish oil by suppressing inflammation and oxidative stress in diabetic rats. *Indonesian Journal of Pharmacy*. https://doi.org/10.22146/ijp.7725

Sasongko, H., Nurrochmad, A., Nugroho, A. E., & Rohman, A. (2022). Indonesian freshwater fisheries' oil for health and nutrition applications: A narrative review. *Food Research*, *6*, 501–511. https://doi.org/10.26656/fr.2017.6(2).362

Sasongko, H., Qanit, W. R., W.s, R. S., S.P.Kristyawan, A. P., Sugihartini, N., Kundarto, W., & Ermawati, D. E. (2020). Cox-2 inhibition activities of creams containing anguilla bicolor and sea cucumbers extract on croton oil induced inflammation in mice. *Pharmaciana*, *10*(3), Article 3. https://doi.org/10.12928/pharmaciana.v10i3.14823

Sasongko, H., Saputro, B. A., Hidayati, R. W. N., S., R. S. W., & Sekarjati, T. A. (2018). The effect of hydrocarbon ointment containing eel fish (Anguilla bicolor bicolor) and snakehead fish (Channa striata) oil for wound healing in Wistar rats. *AIP Conference Proceedings*, *2019*(1), 050006. https://doi.org/10.1063/1.5061899

Sasongko, H., Zulpadly, M. F., & Farida, Y. (2023). Potential Fish Oil as Acute Hepatitis Candidate by Hepatoprotective Mechanism:

A-review. *JPSCR: Journal of Pharmaceutical Science and Clinical Research*, *8*(2), Article 2. https://doi.org/10.20961/jpscr.v8i2.68523

Soji-Omoniwa, O., Adebayo, S. O., Ayinde, R. O., Oyeniyi, A. F., Adeleye, D. A., Ezechukwu, T.-A., Chinedum, C., Emeje, E. F., Alebiosu, O., & Ajibola, O. E. (2022). Consumption of cod liver oil-enriched Vernonia amygdalina Leaf-based diet promoted wound healing in wound-inflicted type 2 diabetic Wistar rats. *AlQalam Journal of Medical and Applied Sciences*, 295–309.

Tanideh, N., Abdordide, E., Yousefabad, S. L. A., Daneshi, S., Hosseinabadi, O. K., & Samani, S. (2016). A comparison of the effects of honey, fish oil and their combination on wound healing in rat. *J. Coast. Life Med*, *4*, 683–688.

Xue, M., Zhao, R., Lin, H., & Jackson, C. (2018). Delivery systems of current biologicals for the treatment of chronic cutaneous wounds and severe burns. *Advanced Drug Delivery Reviews*, *129*, 219–241. https://doi.org/10.1016/j.addr.2018.03.002