Chapter

Haruan Extract (Channa striatus) as an Effective Mediator in Promoting Wound Healing

Ahmad Farouk Musa and Cheang Jia Min

Abstract

Wound healing remains a major issue in surgery. None of the existing treatment modalities in caring for wounds can yet claim to be the holy grail of wound management. *Channa striatus*, locally known in Malaysia as *Haruan*, is a freshwater air-breathing carnivorous fish that is proven to influence the different phases of wound healing. As a medicinal fish, not only does *Haruan* have a high content of amino and fatty acids, which are essential in collagen fibre synthesis during wound recovery, it also abounds in arachidonic acid and polyunsaturated fatty acids that promote prostaglandin synthesis, a vital component of the healing process. Moreover, its antinociceptive effects could potentially reduce wound pain, an important factor in wound healing. Proteomic studies show that a quarter of the total protein detected in freeze- and spray-dried *C. striatus* extract are actin, myosin and tropomyosin – all molecules that play a role in the wound healing process. Proteomic profiling also reveals that *Haruan* possesses two types of collagen namely collagen type-I and type-II that confer tensile strength during the healing process. It is proven that collagen along with other components of the extracellular matrix form the granulation tissue which, when contracted, closes the wound and concomitantly aligns the collagen fibres in the extracellular matrix. Hence, it is inferred that *Haruan* promotes the maturation of granulation tissue, thereby expediting the wound healing process itself. Consequently, it could mediate a faster recovery from surgical wound coupled with a lower incidence of wound infection due to an improved and accelerated wound healing process. Additionally, *Haruan* has demonstrated its ability in promoting angiogenesis and cell proliferation in wound bed preparation for skin grafting. Furthermore, a *Haruan* aerosol concentrate can act as a wound dressing at the donor site thereby enhancing the healing process while simultaneously exhibiting some antinociceptive properties. *Haruan*’s exceptional ability in promoting wound healing together with its potential use in skin grafting would be instrumental in the field of surgery. In essence, the cumulated benefits from all the processes involved would translate into a significant reduction of hospitalisation cost; that would immensely benefit not only the patient, but also the government.

Keywords: Haruan, Channa striatus, wound healing, proteomic studies, skin grafting, economic burden
1. Introduction

A wound is a mechanical injury to the body leading to disruption of the normal anatomical structure and function. It can be classified into acute and chronic wounds. Acute wounds normally proceed through the reparative process in an orderly and timely manner to restore anatomical and functional integrity. Conversely, wounds that demonstrate signs of delayed and interrupted healing and fail to go through the normal healing process are termed chronic wounds [1–3].

Wound healing reflects a cascade of complex, highly regulated biological events to restore the body’s anatomical function back to its pre-injured state. Unlike acute wounds that heal by primary intention where the edges of the wound are apposed and held together with minimal scarring, chronic wounds heal by secondary intention [4, 5]; they form granulation tissue which fills the wound defects.

2. History of wound care and wound dressing

Wound management involves providing an optimum environment to promote healing, control bleeding and prevent infection. The history of wound care traces its origin to the Sumerians, a civilisation believed to be older than 2,000 BC [6]. In their manuscript, three healing gestures – cleansing the wounds, making the plasters and bandaging the wounds – were identified [7].

The ancient Egyptians and Greeks also contributed to the evolution of wound management. The Egyptian medical papyri documented the principle of wound closure to aid healing and the utilisation of honey, grease and lint as the main constituents of the most common plaster. It was believed that lint, a derivative of vegetable fibre, serves an absorbent role; grease or animal fat forms a barrier against bacteria; and honey, the most frequently cited ingredient in multiple topical wound preparations, possesses various healing and antibacterial properties favourable for wound healing [8, 9].

Interestingly, the Greeks were the first to recognise the difference between infected and uninfected wounds, using terms such as “fresh” or “non-healing” to describe wounds [10, 11]. Galen of Pergamum (120–201 AD) is a Greek surgeon who made remarkable contributions to wound and haemorrhage management. He emphasised the maintenance of wound moisture and the application of styptics consisting of basic elements with antibiotic properties for optimum wound healing [12, 13]. Despite advances in modern technology, Galen’s basic principles are still incorporated into the development of current wound dressings.

Additionally, the Hippocratic collection discussed the addition of wine to obstinate ulcer for maximal wound healing [13]. Indeed, in ancient times, a number of magical and mythological agents were utilised as wound dressings; they include honey, plaster, wine and milk. While some of them demonstrate significant pharmacological roles, others merely have ritualistic meanings [13].

In the modern era, a wide array of dressings and wound care products with their properties tailored to special wound care needs were invented. In fact, Winter’s study [10–13], which concluded that moisturised wounds heal quicker than dry wounds, sparked an explosive burst in the evolution of wound
dressings. Thanks to modern technology, novel techniques such as the adoption of growth factors, bioengineered tissue, negative pressure therapy and hyperbaric oxygen therapy are nowadays implemented in wound management. Nonetheless, none of the existing modalities can claim to be the holy grail of wound management.

Alongside the cosmetic advancement in the past decades, skin grafting – a source of epithelium for both acute and chronic wounds – has become increasingly prevalent [14, 15]. However, quite surprisingly, skin grafting is not a new concept; for the past 3500 years, it has been extensively practised by a string of renowned physicians. These include Aulus Cornelius Celsus (25 BC - 50 AD), the Roman author of the first systematic treatise on Medicine; Claudius Gelenus (129 AD - 210 AD) popularly known as Galen, a prominent Greek physician; Jaques-Louis Reverdin (1842–1929), the Swiss surgeon who performed the first “fresh skin” allograft; and George David Pollock (1817–1897), a British surgeon known as a pioneer of skin grafts [16–24]. Throughout the years, the roles and functions of skin grafting have expanded. Nowadays, skin graft is an indispensible therapy in burn reconstruction, major traumatic injuries and surgical defects [25, 26]. Nonetheless, it still suffers from major drawbacks such as compromised skin grafts, skin graft rejection and skin graft contractions particularly in elderly patients, immunocompromised individuals and those on immunosuppressant medications [27–35].

Meanwhile, TIME – a concept that stands for Tissue, Infection or Inflammation, Moisture, and Epithelial edge advancement – is a new framework of wound bed preparation initiated by Schultz and his team in 2003 to achieve optimal wound healing [36, 37]. As the freshwater fish Haruan is naturally gifted with numerous antinociceptive and antimicrobial capabilities, high water content and ample amounts of amino acids and polyunsaturated fatty acids essential for granulation tissues formation and epithelialisation, it fits the components of Tissue, Infection and Moisture in the TIME framework. Therefore, we can postulate that Haruan fish also has the potential to function as an effective wound dressing.

3. Stages of wound healing

The phases of wound healing is a continuum that encompasses homeostasis, inflammatory, proliferative and maturation phases under stringent regulation of growth factors, cytokines, and chemokines [38]. Admittedly, the various phases of the wound healing process can overlap and go awry anytime. The inflammatory phase is the shortest of all phases and, if arrested, wound healing will be delayed and fibrosed tissue may be formed. Meanwhile, in the proliferative phase, the wound is shrunken in size until the maturation phase. Despite the surface of the wounds being closed completely, full tensile strength might take up to twelve months to develop [3, 4, 38–40]. Table 1 below describes the different stages, mechanisms and molecules at interplay during the wound healing process.

Unfortunately, despite the enormous efforts made in skin repair, a wound can never achieve the maximum tensile strength of a normal skin. Additionally, owing to its tight regulation by a multitude of factors, proper wound healing can be easily impeded. Indeed, chronic non-healing wounds are a common phenomenon. Figure 1 describes both the intrinsic and extrinsic factors that affect wound healing.
4. What is Haruan

*Channa striatus* or snakehead murrel, commonly known as *Haruan* or *Gabus* in the Southeast Asian region, originates from the family *Channidae* or *Ophiocephalidae* [41]. It is a tropical, aerobic, carnivorous freshwater species measuring around 100 cm. It is sexually active at 30 cm, with a dark dorsal surface and...
sides, and mottled with a combination of black and ochre; it also has a white belly, a
large head resembling a snake and a fully-toothed mouth with large scales. It preys
on smaller fishes and frogs for survival. Since *C. striatus* is an obligate air-breather,
it survives by burrowing in muds of lakes, rivers or canals, keeping its skin and
air-breathing apparatus moist while surviving on stored fats [42, 43]. Wild Haruan
lives a solitary life except in the spawning season. Figure 2 shows a solitary Haruan
in an aquarium with a glass reflection showing its white belly.

![Figure 2. Wild Haruan - Channa striatus - in an aquarium.](image)

Pairs breed during most months of the year, laying hundreds of amber-coloured eggs. The eggs, guarded by both parents, are non-adhesive and they hatch within one to three days. The adults have compact muscles and a less bony structure which give them the desirable characteristics of a predatory fish [43]. Besides, they are highly aggressive predators with the ability to travel overland to exploit new bodies of water [42]. Figure 3 describes the characteristics of *Channa striatus* or Haruan.

![Figure 3. Summary of the characteristics of Haruan species [41–43].](image)
Skin Grafts - Role in Successful Wound Closure

- Obligate air-breathing species
- Cavernous freshwater fish
- Common habitats: small ditches, ponds, rivers, lakes, rice fields
- Ideal water temperature for survival: around 20–30°C
- Depth of water: below two meters
- pH of habitat: 4.30 to 7.90

Haruan fish can be farmed though it is considered a pest or predatory species in Europe, North America and Australia, being a voracious predator and a competitor of native fish species [44, 45]. When it is reared in a controlled habitat, the parameters of the aquatic environment such as the pH, temperature and water depth should be kept as close to its natural habitat as possible. For its diet, Haruan fish can be fed with a wide range of food products including formulated food [46–48].

However, compared to other species such as Keli or Tilapia fish, Haruan fish farming is not popular for two reasons: firstly, being a predator, it can easily eat up the surrounding aquatic animals and small terrestrial rodents; secondly, its commercial benefits have not been extensively publicised to receive enough attention [49, 50].

In Malaysia, Haruan fish is cherished as a wholesome delicacy; it is served in a multitude of preparations ranging from steamed, grilled, spiced, fried, roasted, in the form of soup to even raw [51]. According to a study [52] conducted by Haemamalar and his team in Krau Wildlife Reserve, Haruan fish was reported to be one of the sources of freshwater fish among the Orang Asli (aboriginal people) tribunates.

Additionally, Haruan serves as a natural remedy for the local population. The National Health and Morbidity Survey carried out in 2014 [53], which looked at the prevalence of food supplements and the reasons for their intake, demonstrated that of the 0.68% of Malaysians consuming Haruan as a dietary supplement, 90.82% did so based on its alleged health benefits.

Thanks to the Chinese and Malay communities, Haruan has acquired a reputation for wound healing for the past several decades [54]. Poh et al did a research [55] involving a total of 134 Chinese mothers during the months of childbirth; they found out that Haruan fish was reported by a quarter of the participating women as either a necessary or a recommended food owing to its wound healing property [56]. Nonetheless, the wound healing effect of Haruan was merely anecdotal until two recently published clinical trials [57, 58] scientifically confirmed this common belief.

5. Preparation of Haruan

5.1 Cooking

Different cooking methods of Haruan fish can generate different outcomes. For instance, Haruan fish fillets preserve their nutritional value when grilled but absorb too much oil when fried, which can be detrimental to health [59]. Meanwhile, when prepared in soup, the time and heat utilised have to be properly adjusted for the snakehead fish to retain its nutritional value [60].
5.2 Topical agent

*Haruan* fish can also be converted into a topical agent in the form of spray or cream. This preparation involves the addition of a propellant (spray) or aqua cream (cream) to the *Haruan* extract [61, 62]. When *Haruan* is formulated into aerosol concentrate and sprayed on a wound, it will form a thin layer of dressing that acts as a protective barrier against the outside environment [63]. This minimises the physical pain as well as the mental suffering associated with dressing application and removal [64].

5.3 Haruan capsules

The principal author of this chapter worked collaboratively with the School of Pharmacy, Universiti Sains Malaysia, to process *Haruan* capsules for his research work together with fellow surgeons at the National Heart Institute, Kuala Lumpur, several years ago. Admittedly, oral *Haruan* supplement has a higher amount of concentrate which is believed to yield more merits compared to eating the flesh itself. Besides, for surgical or major traumatic wounds that involve multiple tissue layers, oral administration of *Haruan* extract is deemed superior to topical application [65, 66]. The detailed steps in the preparation of *Haruan* capsules are described in Figure 4.

6. Laboratory works

6.1 Chemical properties

*Haruan* is considered a crucial source of protein (78.32 ± 0.23%), lipid (2.08 ± 0.08%) and vitamin A (0.265 ± 0.013 mg) [49, 67, 68]. A proximate analysis of *Haruan* revealed that the ratio of crude protein, crude fat to crude ash in *Haruan* is 23.5:7.18 [67, 68]. In fact, *Haruan* is rich in amino acids and fatty acids, particularly glycine and arginine, which help minimise protein losses and enhance collagen synthesis essential for wound healing [56, 69, 70].

Interestingly, *Haruan* also synthesises polyunsaturated fatty acids, which accelerate wound healing via the mediation of prostaglandin and thromboxane synthesis [49, 68, 71–73]. Furthermore, apart from the major fatty acids such as stearic acid and linoleic acid [56, 74], *Haruan* possesses an unusually high profile of arachidonic acid (AA) and docosahexaenoic acid (DHA) which lower the risk of coronary artery disease [56, 67, 68, 75–77]. In terms of dietary nutritional elements, micronutrients such as magnesium, copper, zinc, iron, calcium and manganese and trace amounts of nickel and lead are also present in *Haruan* [78–80].

6.2 Antimicrobial effects

Exposed to an aquatic environment full of microbiota, fish usually develop their own immunity to safeguard against pathogens [81–83]. As a front-liner and
paramount component of the innate immune system, fish mucus possesses a broad array of proteins and enzymes such as lysozyme, immunoglobulin, complement proteins, lectins and proteolytic enzymes that can phagocytose and digest microorganisms [84–90]. Furthermore, it constantly secretes and sloughs off the skin to avoid adherence and prolonged colonisation by parasites [84–89]. Hence, fish skin mucus is regarded as a potential antibacterial therapeutic agent [91, 92]. The multiple roles of *Haruan* mucus are described in Figure 5.

Figure 5. Roles of the fish mucus [91, 92].

In recent years, extensive work has been conducted to analyse the antibacterial effects of the mucus of fish species [93–97], including the *Channa* species. Several research studies [48, 98–104] were performed over the years to evaluate the antibacterial and antifungal activities of *Haruan*. Most of the studies [99–104] revealed that *Haruan* displays some antimicrobial activities, except two studies [98, 99] which detected negligible inhibitory effects against *Staphylococcus aureus* and *Escherichia coli* strains respectively. As wound infection and dehiscence – two disastrous yet frequent complications of surgical wounds – are the common factors of delayed wound healing, the antimicrobial activity of *Haruan* is an added merit for wound dressing [105–107].

6.3 Antinociceptive properties

Pain can have a deleterious impact on wound healing [108, 109]. Coupled with chronic inflammation, prolonged pain can trigger a vicious cycle that hinders wound healing [110]. Fortunately, appropriate wound dressings with sufficient pain control can enormously improve wound healing outcomes, with accelerated wound healing and, consequently, a shorter hospital stay [111].

The antinociceptive effects of *Haruan* in postoperative and traumatic patients have long been discussed and reported. For instance, an earlier *Haruan* study [112] conducted abdominal constriction and tail flick test on mice and found that *Haruan* not only possesses peripherally-acting antinociceptive activity, but
Haruan Extract (Channa striatus) as an Effective Mediator in Promoting Wound Healing
DOI: http://dx.doi.org/10.5772/intechopen.99207

its extracts could also act synergistically with other painkillers such as morphine to relieve postoperative pain and discomfort. These findings are supported by another study conducted by Solihah et al [113] who presented a similar positive result. The underlying mechanism is thought to be attributed to the presence of fatty acids and amino acids, particularly arginine, glycine and arachidonic acid, in addition to the involvement of the L-arginine-nitric oxide-cGMP pathway [42, 114]. In fact, the antinociceptive effects Haruan remain relatively stable in a wide range of temperature and pH; this allows the essence to be extracted and processed safely for future use [115].

6.4 Wound healing capabilities

Freshwater fish constitute 60–70% of the animal protein intake in Malaysia [116]. Previous studies demonstrated that Haruan contains a high content of albumin which promotes the formation of collagen [117–119]. Moreover, it has a considerable amount of copper and zinc that can help accelerate wound healing by maintaining cell stability, besides promoting wound remodelling and the formation of blood vessels and fibrosis or scar [119–124]. Additionally, the presence of elements such as hydroxyproline, glycine, arachidonic acid and arginine in Haruan is another essential source of collagen [124–126].

It is therefore no surprise that the collagen content in Haruan is relatively high. Indeed, collagen plays a determining role in expediting wound healing via various mechanisms. According to Kwan et al who performed proteometric profiling of Haruan, two types of collagen, namely type I and type II collagen, were detected [127, 128]. Both of them increase the tensile strength [129]. In fact, when the increased tensile strength and glycosaminoglycan of Haruan was examined and compared to cetrimide, it was reported that Haruan is superior to cetrimide in improving wound contraction and the fibroblastic phase of wound healing [61, 130, 131]. Furthermore, it was found that the collagen in Haruan can help promote the maturation of granulation tissue which accelerates wound healing. Haruan can act in synchrony with the other components of the extracellular matrix to form a granulation tissue which subsequently contracts and seals the wound. Concurrently, it aligns the collagen fibres in the extracellular matrix. If the area of involvement is wide enough, the granulation tissue could be reserved for split skin grafting. The various steps of collagen involvement in wound healing are described in Figure 6.

Figure 6. Wound healing effects of collagen [132–135].
According to the researchers [128] who performed proteomic profiling of Haruan extract at the Analytical Biochemistry Research Centre, Universiti Sains Malaysia, the proportion of actin, myosin and tropomyosin to the total protein in freeze-dried and spray-dried Haruan water extract are 25% and 26% respectively. While it is known that these three structures play a significant role in muscle contraction in the sliding filament theory, many were unaware that they also work hand-in-hand in the wound healing process. Tropomyosin can help control cell functioning of actin while actin can regulate vital cellular functions during re-epithelisation involving cell division, cytokinesis and cell signalling, seal the embryonic wound as well as interact with myosin in the regulation of cell motility [132–134]. The functions of actin, myosin, and tropomyosin during the wound healing process are diagrammatically summarised in Figure 7.

![Figure 7. Functions of actin, myosin, and tropomyosin in wound healing [57, 128].](image)

### 7. Clinical trials on Haruan

To the best of our knowledge, only two clinical trials have reported the effects of Haruan in wound healing to date.

One study [57] was conducted by the principal author of this chapter. The researchers performed a double-blinded, randomised, controlled trial in 2018 at the National Heart Institute to look at the effects of Haruan fish extracts on the chest and leg surgical wounds of 253 patients after they have undergone coronary artery bypass surgery (CABG). Noting the detrimental impact of wound pain on wound healing and the interplay between wound pain, morbidity, quality of life and hospital stay [135–137], parameters such as wound pain and healing, mobilisation and quality of life were specifically evaluated. It was found that the wound scoring system favoured those patients who received Haruan capsules instead of placebo at day-6, six-weeks and three months postoperatively. They also discovered that Haruan extracts could alleviate wound pain, and improve quality of life with respect to energy, pain, emotion, sleep and physical level except social level based on the Nottingham Health Profile questionnaire that assesses the quality of life [57]. Therefore, Haruan extract is considered a cost-effective solution in wound healing because it decreases the percentage of wound infection thereby reducing the cost of hospitalisation. Moreover, with the patient’s surgical recovery hastened, it can tremendously reduce the economic burden not only to the hospital but to the country as well.
Meanwhile, a similar study [58] conducted by Wahab et al targeted 76 post-lower segment Caesarean Section women, a study population which are the dominant consumers of Haruan in Malaysia due to old beliefs and food taboos [55, 56]. The study concluded that Haruan could improve the wound’s cosmetic appearance and, accordingly, patient’s satisfaction. These findings are in line with a randomised controlled trial [138] which reported that Haruan extract consumers harboured a remarkably higher rate of uterine involution than the placebo group. Conversely, in the same study, the outcomes of wound healing and pain were noted to be comparable; this can be attributed to the interval used for the pain score assessment and the concomitant use of analgesics.

8. Potential role of Haruan in skin grafting

Skin grafting is the transfer of cutaneous tissue to cover large wounds. It can take two forms: split skin grafting, which involves the epidermis and a portion of the dermis, and full-thickness skin grafting which involves the epidermis and the entire dermis [139]. While deliberating on the pros and cons of split skin grafting as compared to full thickness skin grafting is beyond the scope of this paper, it is noteworthy that a split skin graft does not have its own blood supply; it relies on the wound bed. This is where Haruan might play an important role. In their seminal work on the bioactive proteins in C. striatus, Kwan et al [140] have shown that the fish proteins promote angiogenesis and cell proliferation. The stable, healthy and well-vascularised wound bed potentiated by Haruan action allows for skin grafts to be well taken.

The main challenge to ensure that Haruan play its magical role in promoting angiogenesis and cell proliferation lies in the wound bed preparation before skin grafting. To ensure that the wound bed is healthy, wound debridement is of utmost importance. This could be done in several ways: via a scalpel, a dermatome, or even by using a hydro-surgery device until the wound bed is really clean and healthy with some bleeding at the wound bed [141]. It has to be stressed here that without a clean and healthy wound bed, and wound edges cleared from any necrotic or purulent tissue, the added value of Haruan would be lost and the skin graft will not have a proper healing.

When the wound bed is well prepared, skin grafts will normally go through three different stages as follows:

a. Imbibition: Oxygen and nutrients from the wound bed are passively absorbed by the skin graft [142].

b. Inosculation: A vascular connection is established between the cut vessels on the underside of the skin graft and the wound bed [143].

c. Revascularisation: Neangiogenesis or new blood vessels grow into the graft from the wound bed [144].

After undergoing these stages, the skin grafts will usually need another five to seven days to adhere to the wound bed followed by the process of maturation that could last from several months to years; this includes pigmentation changes, softening and flattening [139]. As described earlier, Haruan abounds in amino acids in such as glycine, lysine and arginine, and fatty acids such as arachidonic acid, palmitic acid and docosahexaenoic acid – they all help to enhance wound healing through the initiation of several pathways including the remodelling of collagen that gives the strength to the wound, besides stimulating wound contraction [145].
Having discussed at length regarding the recipient site, we should also look at whether *Haruan* plays any role in wound healing at the donor site. Theoretically, the donor site requires wound care only in terms of wound dressing. Since the wound edges are not approximated at the donor site and are left to heal via secondary intention, they will be filled by granulation tissue matrix [146] and can be covered by a simple dressing only. Presumably this is another area in skin grafting where *Haruan* dressing might play a role. An aerosol concentrate containing *Haruan* water extract was formulated in an aerosol system to produce a thin film over the wound bed and serve as a dressing at the donor site [147]. The aerosol concentrate that would form a thin layer of dressing over the wound could enhance the healing process at the donor site as proven in an animal model [148], besides showing pronounced antinociceptive properties [149].

### 9. Other usages of *Haruan*

Apart from its aforementioned desirable features, *Haruan* has also been reported to confer feasible outcomes in a myriad of diseases.

Osteoarthritis is a degenerative joint disease characterised by synovial inflammation and articular cartilage degradation that leads to chronic pain and inflammation [150, 151]. In osteoarthritis, a wide variety of inflammatory mediators are secreted and activated [140]. After several previous studies which demonstrated the anti-inflammatory capabilities of *Haruan*, the role of *Haruan* in osteoarthritis has been extensively explored [152–154]. Few scientific reports on the efficacy of *Haruan* in osteoarthritic patients revealed promising outcomes where *Haruan* was shown to be superior in reducing inflammatory changes in the synovial membrane, improving the pain, symptoms and quality of life of osteoarthritic sufferers while maintaining the structure of the cartilage of the control group [155–159]. As osteoarthritis is a common complication of major traumatic wound injury, which necessitates skin grafting owing to the disfigurement and disabling condition, oral administration of *Haruan* can exert a double action, improving both wound healing and osteoarthritis.

Other functions of *Haruan* mentioned in the medical literature include its usage in allergic rhinitis [160, 161], dermatitis [162, 163], gastric ulcer [164, 165], cancer [166, 167], hypertension [168, 169] and depression [170, 171]. Unfortunately, due to the paucity of studies to date, further high-powered studies are warranted to clarify and define the role of *Haruan* in these diseases.

### 10. Discussion

Hong *et al* [65] did a scoping review on the effectiveness of *Haruan* extracts on wound healing; they concluded that current evidence favours the use of *Haruan* extracts to expedite wound healing. Indeed, optimal wound bed preparation and proper wound closure are the two fundamental goals of skin grafting regardless of the graft type [172–174]. With its extraordinary antimicrobial, antinociceptive and anti-inflammatory properties, *Haruan* is undeniably a handy tool for skin grafting. From a psychological perspective, *Haruan* can minimise post-operative pain and discomfort, achieve satisfactory aesthetic wound effect and improve patient postoperative quality of life. For skin grafting that covers a wound area only partially, *Haruan* can promote wound closure since it encourages the epithelialisation of wound. When a wound recovery is speed up with less wound infection, the duration of hospital stay will also be shortened. Consequently, expenses related to skin grafting will be cut down.
It is still inconclusive which particular biomolecules play a role in the wound healing property. However, with the advancement of technology especially in the field of proteomics, we have managed to conduct a more comprehensive protein profiling [175, 176]. Although proteomics helps us to understand the interactions between the proteins in the fish and the wound, the previous protein profiling [177] were not as accurate as the new one due to the lower sensitivity of the old equipment. Conversely, the current work using Gel Elution Liquid Fractionation Entrapment Electrophoresis (GELFREE) system can maximise protein profiling [127]. The researchers at the Analytical Biochemistry Research Centre of the Universiti Sains Malaysia [127, 128] also looked at the post-translational modifications (PTMs) of proteins which might be involved in the wound healing process to complement the protein profiling results. PTMs, as the name suggests, occurs following the translation of amino acids in the later part of the protein biosynthesis. They play an important role in protein regulation and are also involved in the regulation of a number of physiological functions. This helps us to appreciate how the consumption of *Haruan* contributes to the wound healing mechanism.

It is a known fact that structural proteins such as actin, myosin and tropomyosin are vital in the formation of muscle tissue within an organism. From the protein profiling, it was shown that 37% of all the proteins detected in the fish meat are structural proteins which play a specific role in enhancing wound healing. For example, actin gives rise to the formation of myofibroblasts which differentiated from fibroblasts containing bundles of actin microfilaments with contractile proteins such as non-muscle myosin [178–180]. On the one hand, both fibroblasts and myofibroblasts regulate traction force and coordinate contraction during wound closure [181]. On the other hand, tropomyosin, has been reported to regulate cell migration, particularly fibroblast and myofibroblasts [182]. This results in the promotion of rapid wound healing whenever tropomyosin is manipulated in the wound area [183, 184]. Hence, the abundant presence of structural proteins in the fish meat could be a key reason why it helps in the wound healing process.

Apart from structural proteins, *Haruan* meat also possesses numerous enzymes including trypsin. Trypsin has been shown to enhance the healing process by potentiating fibrocyte differentiation [185]. Trypsin has also been used as a biomedicine for treating wound [186]. A clinical study conducted by Gudmunssdsdóttir et al [175] showed that native-proteins were digested by cold-adapted cod trypsin and produced an encouraging effect on the wound. These findings supported the idea that the abundant level of trypsin in *Haruan* meat helps in facilitating the wound healing process.

Collagen, which is essential for wound healing, is also present in the *Channa striatus* meat with Collagen Type-I being the most abundant [127]. Collagen is required in the different stages of wound healing including the binding process to fibronectin that helps in platelet aggregation [187], triggering angiogenesis by transforming myocytes into macrophages [188], in addition to giving support to budding capillaries [189]. A recent study by Helary et al [190] has also shown that apoptosis was prevented during chronic wound treatment by the use of concentrated collagen hydrogel that promotes cell proliferation and protects fibroblasts. Recently, mammalian collagen has been replaced by fish collagen [191] which is considered a regenerative medicine [192], a sign that the abundant collagen found in fish meat does help to advance the wound healing process.

Results from the proteomic study [127] also show that *C. striatus* meat is rich in calcium related proteins such as calmodulin and parvalbumin. We are aware that calcium (Ca\textsuperscript{2+}) plays a major role in maintaining homeostasis of the skin and is considered a key signalling molecule during wound healing [193, 194]. Ca\textsuperscript{2+} binding proteins are also known to assist in Ca\textsuperscript{2+} signalling and skin intracellular trafficking, which includes calmodulin and calmodulin-like proteins [195]. It is also known that
Calmodulin assists in keratinocytes maturation [196], proving its significant role in the wound healing process. The important role played by both calmodulin and parvalbumin in the wound healing cascade deserves to be highlighted. Expression of parvalbumin in ependymal cells has been shown to assist in tissue remodelling and wound closure [197]. Hence, it is clear that both parvalbumin and calmodulin help to transfer Ca2+ to the affected area, thereby promoting wound healing.

Proteomic profiling also revealed that more than 50% of the total proteins detected in *C. striatus* are uncharacterised proteins [128]. The functions of these proteins are still unknown due to the paucity of research. These proteins have been labelled as such due to the absence of any detectable homology to those proteins of known functions at both the sequence and structural level [198]. However, it is possible that one or more of the uncharacterised proteins found in Haruan play a role in the wound healing process. Indeed, the high quantity of uncharacterised proteins detected via proteomics, that is, the proteome database for *C. striatus*, is far from complete. At this point in time, we can safely say that while existing data have given us an insight into the proteins of Haruan, more rigorous effort must be made into the research of the uncharacterised proteins that might be involved in accelerating the wound healing process – the indisputable characteristic of *C. striatus* or Haruan.

11. Conclusion

As a wound cosmetic enhancer as well as an antimicrobial, anti-inflammatory and antinociceptive agent, *Haruan* fish is a promising medicinal food product for wound healing. Current evidence has illustrated the effectiveness of *Haruan* in wound healing, particularly in postoperative patients. This book chapter has highlighted the wonders of *Haruan* in wound healing associated with skin grafting. Unfortunately, in spite of the emerging role and increasing popularity of *Haruan* in wound healing, the use of *Haruan* extracts in skin grafting remains insufficient. When its merits have been fully explored, *Haruan* extracts could become a viable alternative to the current wound dressing regimen in skin grafting in the near future.

Acknowledgements

The authors would like to express their gratitude to Nageeb Gounjaria for proof-reading and editing the manuscript.

Author details

Ahmad Farouk Musa* and Cheang Jia Min
Jeffrey Cheah School of Medicine & Health Sciences, Monash University Malaysia, Malaysia

*Address all correspondence to: farouk@monash.edu

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Haruan Extract (Channa striatus) as an Effective Mediator in Promoting Wound Healing
DOI: http://dx.doi.org/10.5772/intechopen.99207

References

[1] Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound repair and regeneration. 1994; 2(3):165-70.

[2] Swanson T, Keast D, Cooper R, Black J, Angel D, Schultz G, Carville K, Fletcher J. Ten top tips: identification of wound infection in a chronic wound. Wounds International. 2015; 6(2):22-7.

[3] Spear M. Acute or chronic? What's the difference? Plastic Surgical Nursing. 2013; 33(2):98-100.

[4] Vuolo J. Wound care made incredibly easy. Lippincott, Williams and Wilkins; 2009.

[5] Jones ML. A short history of the development of wound care dressings. British Journal of Healthcare Assistants. 2015; 9(10):482-5.

[6] Uzun M. A review of wound management materials. Journal of Textile Engineering & Fashion Technology. 2018; 4(1):00121.

[7] Majno G. The healing hand: Man and wound in the ancient world. Harvard University Press; 1991.

[8] Ovington LG. The evolution of wound management: ancient origins and advances of the past 20 years. Home Healthcare Now. 2002; 20(10):652-6.

[9] George Broughton II, Janis JE, Attinger CE. A brief history of wound care. Plastic and reconstructive surgery. 2006; 117(7S):6S-11S.

[10] Rovee DT. Evolution of wound dressings and their effects on the healing process. Clinical materials. 1991; 8(3-4):183-8.

[11] Shah JB. The history of wound care. The Journal of the American College of Certified Wound Specialists. 2011; 3(3):65-6.

[12] Ahmad W, Aquil Z, Alam SS. Historical background of wound care. Hamdan Medical Journal. 2020; 13(4):189.

[13] Daunton C, Kothari S, Smith L, Steele D. A history of materials and practices for wound management. Wound Practice & Research: Journal of the Australian Wound Management Association. 2012; 20(4).

[14] Forrest RD. Early history of wound treatment. Journal of the Royal Society of Medicine. 1982; 75(3):198.

[15] Fuchs C, Pham L, Henderson J, Stalnaker KJ, Anderson RR, Tam J. Multi-faceted enhancement of full-thickness skin wound healing by treatment with autologous micro skin tissue columns. Scientific reports. 2021; 11(1):1-3.

[16] Ehrenfried A. Reverdin and Other Methods of Skin-Grafting: Historical. The Boston Medical and Surgical Journal 1909; 161(26):911-7.

[17] Ang GC. History of skin transplantation. Clinics in Dermatology. 2005; 23(4):320-4.

[18] Hauben DJ, Baruchin A, Mahler A. On the history of the free skin graft. Annals of Plastic Surgery 1982; 9(3):242-5.

[19] Hattery E, Nguyen T, Baker A, Palmieri T. Burn Care in the 1800s. Journal of Burn Care & Research 2015; 36(1):236-9.

[20] McDowell F. Successful attempt of reconstruction of a nose from a completely separated piece of skin from...
the leg, by Bünger, Marburg, Germany (Journal der Chirurgie und Augenheilkunde, 4: 569, 1822). Translated from German by Hans May, Plastic and reconstructive surgery 1969; 44(5):486-90.

[21] Fariña-Perez LA. Jaques-Louis Reverdin (1842-1929): The surgeon and the needle. Archivos españoles de urologia. 2010; 63(4):269-74.

[22] Freshwater MF, Krizek TJ. Skin grafting of burns: A centennial. J Trauma 1971; 11(862):4.

[23] Freshwater MF, Krizek TJ. George David Pollock and the development of skin grafting. Annals of Plastic Surgery. 1978; 1(1):96-102.

[24] Kohlhauser M, Luze H, Nischwitz SP, Kamolz LP. Historical evolution of skin grafting: A Journey through time. Medicina 2021; 57(4):348.

[25] Shimizu R, Kishi K. Skin graft. Plastic Surgery International. 2012; 2012.

[26] Vyas KS, Vasconez HC. Wound healing: Biologics, skin substitutes, bio-membranes and scaffolds. In Healthcare 2014 (Vol. 2, No. 3, pp. 356-400). Multidisciplinary Digital Publishing Institute.

[27] Orgill DP. Excision and skin grafting of thermal burns. New England Journal of Medicine. 2009; 360(9):893-901.

[28] Browne Jr EZ. Complications of skin grafts and pedicle flaps. Hand clinics 1986; 2(2):353-9.

[29] Reddy S. The incidence and risk factors for lower limb skin graft failure. Dermatology Research and Practice 2014.

[30] Kimata Y, Uchiyama K, Ebihara S, Sakuraba M, Iida H, Nakatsuka T, Harii K. Anterolateral thigh flap donor-site complications and morbidity. Plastic and reconstructive surgery. 2000; 106(3):584-9.

[31] Enshaei A, Masoudi N. Survey of Early Complications of Primary Skin Graft and Secondary Skin Graft (Delayed) Surgery after Resection of Burnwaste in Hospitalized Burn Patients. Global journal of health science. 2014; 6(7):98.

[32] Reddy S, El-Haddawi F, Fancourt M, Farrant G, Gilkison W, Henderson N, Kyle S, Mosquera D. The incidence and risk factors for lower limb skin graft failure. Dermatology research and practice. 2014; 2014.

[33] Turissini JD, Elmasrafi T, Evans KK, Kim P. Major risk factors contributing to split thickness skin graft failure. Georgetown Medical Review. 2019; 3(1):7755.

[34] Isitt CE, McCloskey KA, Caballo A, Sharma P, Williams A, Leon-Villapalos J, Vizcaychipi MP. An analysis of surgical and anaesthetic factors affecting skin graft viability in patients admitted to a Burns Intensive Care Unit. Scars, Burns & Healing 2016; 2:2059513116642089.

[35] Talbot TR, Schaffner W. Relationship between age and the risk of surgical site infection: A contemporary re-examination of a classic risk factor. J Infec Dis 2005; 191(7): 1032-5.

[36] Schultz G, Mozingo D, Romanelli M, Claxton K. Wound healing and TIME; new concepts and scientific applications. Wound Repair and Regeneration 2005; 13(4): S1-1.

[37] Harries RL, Bosanquet DC, Harding KG. Wound bed preparation: TIME for an update. International Wound Journal. 2016; 13(S3):8-14.

[38] Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound
healing. Wound Repair and Regeneration 2008; 16(5):585-601.

[39] Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. Wound Repair and Regeneration. 1996; 4(4):411-20.

[40] Wallace HA, Basehore BM, Zito PM. Wound healing phases. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

[41] Brian W. Contribution to the knowledge of the Snakeheads of Iran (Family Channidae). Iran. J. Ichthyol 2016; 3(1):65-72.

[42] Kok LW. Snakeheads – their biology and culture. Recent Advances in Aquaculture. 1982; 180-213.

[43] Das M, Chakraborty SC, Ahmed F, Basak RK. Predatory behaviour of a snakehead fish (Channa striatus Bloch). Bangladesh Journal of Fisheries Research 1998; 2(2):127-37.

[44] Courtenay WR, Williams JD. Snakeheads (Pisces: Channidae): A biological synopsis and risk assessment. United States Geological Survey 2004; United US Department of Interior.

[45] Christy MT, Kirkpatrick W. Indicative 10 Project Extension Material: Striped snakehead (Channa striata) 2017; Department of Primary Industries and Regional Development.

[46] Qin J, Fast AW, DeAnda D, Weidenbach RP. Growth and survival of larval snakehead (Channa striatus) fed different diets. Aquaculture. 1997; 148(2-3):105-13.

[47] Qin JG, Fast AW. Food selection and growth of young snakehead Channa striatus. Journal of Applied Ichthyology 1997; 13(1):21-5.

[48] Radzak HA, Akim AM, Sazali SS, Baharum Z, Nata DH, Jalil AA, Sharimala T, Sumasundram AM, Mokhtaruddin N. Total phenolic content, antioxidant, cytotoxicity and hepatoprotective activities of aqueous extract of Channa striatus (Haruan). IOSR Journal of Nursing and Health Science (IOSR-JNHS) 2014; 3(6):52-9.

[49] Jais AM. Pharmacognosy and pharmacology of Haruan (Channa striatus), a medicinal fish with wound healing properties. Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas. 2007; 6(3):52-60.

[50] Shafri M, Abdul Manan MJ. Therapeutic potential of the Haruan (Channa striatus): from food to medicinal uses. Malaysian Journal of Nutrition. 2012; 18(1):125-36.

[51] Ahmad NI, Wan Mahiyuddin WR, Tengku Mohamad TR, Ling CY, Daud SF, Hussein NC, Abdullah NA, Shahrudin R, Sulaiman LH. Fish consumption pattern among adults of different ethnicities in Peninsular Malaysia. Food & Nutrition Research. 2016; 60(1):32697.

[52] Haemamalar K, Zalilah MS, Neng Azhanie A. Nutritional status of orang asli (che wong tribe) adults in Krau Wildlife Reserve, Pahang. Malaysian Journal of Nutrition. 2010; 16(1):555-68.

[53] Aris T, Ahmad NA, Tee GH, editors. National health and morbidity survey 2014: Malaysian Adults Nutrition Survey (MANS). Institute For Public Health; 2014.

[54] Jamaludin SS. Postpartum food restriction of rural Malay women. Asian Journal of Humanities and Social Sciences (AJHSS). 2014; 2(4):32-41.

[55] Poh BK, Wong YP, Karim NA. Postpartum dietary intakes and food taboos among Chinese women attending maternal and child health clinics and maternity hospital, Kuala Lumpur.
Malaysian Journal of Nutrition. 2005; 11(1):1-21.

[56] Jais AM, McCulloch R, Croft K. Fatty acid and amino acid composition in Haruan as a potential role in wound healing. General Pharmacology: The Vascular System. 1994; 25(5):947-50.

[57] Musa AF, Dillion J, Taib ME, Yunos AM, Baie S, Nordin RB. A study on the effect of Haruan fish extract (Channa striatus) on wound healing and quality of life of coronary artery bypass grafting (CABG) patients: A prospective, double-blind, randomized, controlled trial. F1000Research 2018; 7(469):469.

[58] Ab Wahab SZ, Abdul Kadir A, Nik Hussain NH, Omar J, Yunus R, Baie S, Mohd Noor N, Hassan II, Wan Mahmood WH, Abd Razak A, Wan Yusoff WZ. The effect of Channa striatus (Haruan) extract on pain and wound healing of post-lower segment caesarean section women. Evidence-Based Complementary and Alternative Medicine. 2015; 2015:849647.

[59] Marimuthu K, Thilaga M, Kathiresan S, Xavier RH, Mas RH. Effect of different cooking methods on proximate and mineral composition of striped snakehead fish (Channa striatus, Bloch). Journal of food science and technology. 2012; 49(3):373-7.

[60] Engku Hanisah EU, Etty Syarmila IK, Farahniza Z, Norhasidah S, Abdul Salam B, Maaruf AG. Comparative Studies of Antioxidant Activities between Edible Bird Nest, Chicken and Snakehead Fish Soups. Department of Food Science, School of Chemical Sciences and Food Technology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia; 2014.

[61] Laila L, Febriyenti F, Salhimi SM, Baie S. Wound healing effect of Haruan (Channa striatus) spray. International wound journal. 2011; 8(5):484-91.

[62] Abedi S, Far FE, Hussain MK. Effects of Haruan (Channa striatus) Based Cream on Acute. Research Journal of Biological Sciences. 2012; 7(4):181-7.

[63] Febriyenti NA, Baie S. Formulation of aerosol concentrates containing Haruan (Channa striatus) for wound dressing. Malaysian Journal of Pharmaceutical Sciences. 2008; 6(1):43-58.

[64] Febriyenti F, Noor AM, Baie SB. Physical evaluations of Haruan spray for wound dressing and wound healing. International Journal of Drug Delivery 2011; 3(1):115-24.

[65] Hong LW, Theyveeka Selvy A, Rajoo P, Yuan OY, Liong AK, Nair D, Mohamed AF, Zainal Z, Rosli N. Channa Striatus effectiveness in wound-healing: A Scoping Review. IJRAR-International Journal of Research and Analytical Reviews (IJRAR) 2020; 7(1):300-8.

[66] Jerônimo MS, Barros AD, Morital VE, Alves EO, Souza NL, Almeida RM, Nóbrega YK, Cavalcanti Neto FF, Amorin R, Borin MD, Bocca AL. Oral or topical administration of L-arginine changes the expression of TGF and iNOS and results in early wounds healing. Acta cirurgica brasileira 2016; 31(9):586-96.

[67] Rahman MA, Molla MH, Sarker MK, Chowdhury SH, Shaikh MM. Snakehead fish (Channa striata) and its biochemical properties for therapeutics and health benefits. SF J Biotechnol Biomed Eng 2018; 1(1):1005.

[68] Haniffa MA, Sheela PA, Kavitha K, Jais AM. Salutary value of Haruan, the striped snakehead Channa striatus – a review. Asian Pacific Journal of Tropical Biomedicine. 2014; 4:88-15.

[69] Chyun JH, Griminger P. Improvement of nitrogen retention by arginine and glycine supplementation.
and its relation to collagen synthesis in traumatized mature and aged rats. The Journal of Nutrition. 1984; 114(9):1697-704.

[70] Gam LH, Leow CY, Baie S. Amino acid composition of snakehead fish (Channa striatus) of various sizes obtained at different times of the year. Malaysian Journal of Pharmaceutical Sciences 2005; 3(2):19-30.

[71] Bowman WC, Rand MJ. Textbook of Pharmacology. Blackwell Scientific Publications; 1980.

[72] Gibson RA. Australian fish—An excellent source of both arachidonic and ω-3 polyunsaturated fatty acids. Lipids 1983; 18(11):743-52.

[73] Jais AM, Matori MF, Kittakoop P, Sowanborirux K. Fatty acid compositions in mucus and roe of Haruan, Channa striatus, for wound healing. General Pharmacology: The Vascular System. 1998; 30(4):561-3.

[74] Zuraini A, Somchit MN, Solihah MH, Goh YM, Arifah AK, Zakaria MS, Somchit N, Rajion MA, Zakaria ZA, Jais AM. Fatty acid and amino acid composition of three local Malaysian Channa spp. fish. Food Chemistry 2006; 97(4):674-8.

[75] Leaf A, Weber PC. Cardiovascular effects of n-3 fatty acids. New England Journal of Medicine 1988; 318(9):549-57.

[76] Rahnan SA, Huah TS, Nassan O, Daud NM. Fatty acid composition of some Malaysian freshwater fish. Food chemistry 1995; 54(1):45-9.

[77] Ngui WS, Hassan NH, Ramlan N, Zubairi SI. Malaysia snakehead Channa striatus and micropeltes: Physico-chemical properties of fillet fish oil and water-soluble extract. Chemical Engineering Transactions. 2017; 56:61-6.

[78] Heimann W. Fundamentals of Food Chemistry. Prentice Hall Europe 1980.

[79] Lands WE. Fish and Human Health. Academic Press Inc., 1986.

[80] Liu E, Shailaja S, Hoo BS, Mat Jais AM, Lee TL. Thromboelastographic Assessment of the Effect of Snakehead Fish Extracts on Whole Blood Coagulation. InProc. Anaesthesia General Scientific Symposium 2001.

[81] Wang S, Wang Y, Ma J, Ding Y, Zhang S. Phosvitin plays a critical role in the immunity of zebrafish embryos via acting as a pattern recognition receptor and an antimicrobial effector. Journal of Biological Chemistry 2011; 286(25):22653-64.

[82] Subramanian S, Ross NW, MacKinnon SL. Comparison of antimicrobial activity in the epidermal mucus extracts of fish. Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology 2008; 150(1):85-92.

[83] Bhatt P, Kumaresan V, Palanisamy R, Ravichandran G, Mala K, Amin SN, Arshad A, Yusoff FM, Arockiaraj J. A mini review on immune role of chemokines and its receptors in snakehead murrel Channa striatus. Fish & shellfish immunology 2018; 72:670-8.

[84] Das S, Ward LR, Burke C. Prospects of using marine actinobacteria as probiotics in aquaculture. Applied microbiology and biotechnology 2008; 81(3):419-29.

[85] Tiralongo F, Messina G, Lombardo BM, Longhitano L, Li Volti G, Tibullo D. Skin Mucus of Marine Fish as a Source for the Development of Antimicrobial Agents. Frontiers in Marine Science 2020; 7:760.

[86] Dash S, Das SK, Samal J, Thatoi HN. Epidermal mucus, a major determinant in fish health: A review. Iranian Journal of Veterinary Research. 2018; 19(2):72.

[87] Arockiaraj J, Gnanam AJ, Muthukrishnan D, Gudimella R,
Milton J, Singh A, Muthupandian S, Kasi M, Bhassu S. Crustin, a WAP domain containing antimicrobial peptide from freshwater prawn *Macrobrachium rosenbergii*: Immune characterization. Fish & Shellfish Immunology 2013; 34(1):109-18.

[88] Arasu A, Kumaresan V, Sathyamoorthy A, Palanisamy R, Prabha N, Bhatt P, Roy A, Thirumalai MK, Gnanam AJ, Pasupuleti M, Marimuthu K. Fish lily type lectin-1 contains β-prism architecture: Immunological characterization. Molecular Immunology 2013; 56(4):497-506.

[89] Ingram GA. Substances involved in the natural resistance of fish to infection—a review. Journal of Fish Biology 1980; 16(1):23-60.

[90] Ellis AE. Immunity to bacteria in fish. Fish & Shellfish Immunology 1999; 9(4):291-308.

[91] Kumari U, Nigam AK, Mitial S, Mitial AK. Antibacterial properties of the skin mucus of the freshwater fishes, *Rita rita* and *Channa punctatus*. European Review for Medical and Pharmacological Sciences 2011; 15(7):781-6.

[92] Reverter M, Tapissier-Bontemps N, Lecchini D, Banaigs B, Sasal P. Biological and ecological roles of external fish mucus: a review. Fishes 2018; 3(4):41.

[93] Austin B, McIntosh D. Natural antibacterial compounds on the surface of rainbow trout, *Salmo gairdneri* Richardson. Journal of Fish Diseases 1988; 11(3):275-7.

[94] Bragadeeswaran S, Priyadharshini S, Prabhu K, Rani SR. Antimicrobial and haemolytic activity of fish epidermal mucus *Cynoglossus arel* and *Arius caelatus*. Asian Pacific Journal of Tropical Medicine 2011; 4(4):305-9.

[95] Kuppulakshmi C, Prakash M, Gunasekaran G, Manimegalai G, Sarojini S. Antibacterial properties of fish mucus from. European Review for Medical and Pharmacological Sciences. 2008; 12:149-53.

[96] Hellio C, Pons AM, Beapoil C, Bourgougnon N, Le Gal Y. Antibacterial, antifungal and cytotoxic activities of extracts from fish epidermis and epidermal mucus. International Journal of Antimicrobial Agents 2002; 20(3):214-9.

[97] Bragadeeswaran S, Thangaraj S. Hemolytic and antibacterial studies on skin mucus of eel fish, *Anguilla anguilla* Linnaeus, 1758. Asian J Biol Sci 2011; 4(3):272-6.

[98] Rao V, Marimuthu K, Kupusamy T, Rathinam X, Arasu MV, Al-Dhabi NA, Arockiaraj J. Defense properties in the epidermal mucus of different freshwater fish species. Aquaculture, Aquarium, Conservation & Legislation 2015; 8(2):184-94.

[99] Mat Jais AM, Zakaria ZA, Luo A, Song YX. Antifungal activity of Channa striatus (Haruan) crude extracts. International Journal of Tropical Medicine 2008; 3(3):43-8.

[100] Dhanaraj M, Haniffa MA, SV AS, Manikandaraja D. Antibacterial activity of skin and intestinal mucus of five different freshwater fish species viz., *Channa striatus*, *C. micropeltes*, *C. marulius*, *C. punctatus* and *C. gachua*. Malaysian Journal of Science 2009; 28(3):257-62.

[101] Wei OY, Xavier R, Marimuthu K. Screening of antibacterial activity of mucus extract of snakehead fish, *Channa striatus* (Bloch). European Review for Medical and Pharmacological Sciences 2010; 14(8):675-81.

[102] Allameh SK, Daud H, Yusoff FM, Saad CR, Ideris A. Isolation,
identification and characterization of Leuconostoc mesenteroides as a new probiotic from intestine of snakehead fish (Channa striatus). African Journal of Biotechnology. 2012; 11(16):3810-6.

[103] Kumar NP, Marimuthu K, Rao RV, Xavier R, Kathiresan S, Suresh CV, Sreeramanan S. Antimicrobial activity of different tissues of snakehead fish Channa striatus (Bloch). Asian Pacific Journal of Tropical Disease. 2012; 2:S302-5.

[104] Zawawi NZ, Shaari R, Nordin ML, Hamdan RH, Peng TL, Zalati CS. Antibacterial and cytotoxic activity assessment of Channa striatus (Haruan) extract. Veterinary World 2020; 13(3):508.

[105] Guo SA, DiPietro LA. Factors affecting wound healing. Journal of Dental Research 2010; 89(3):219-29.

[106] Healy B, Freedman A. Infections. BMJ 2006; 332(7545):838-41.

[107] Yao K, Bae L, Yew WP. Post-operative wound management. Australian Family Physician 2013; 42(12):867-70.

[108] Woo KY. Exploring the effects of pain and stress on wound healing. Advances in Skin & Wound Care 2012; 25(1):38-44.

[109] Pediani R. What has pain relief to do with acute surgical wound healing. World Wide Wounds 2001; 50(2):76.

[110] Muldoon J. Pain, inflammation and wound healing. Nurse Prescribing. 2017; 15(SupI0):14-8.

[111] Brown A. Strategies to reduce or eliminate wound pain. Nursing Times 2014; 110(15):12-5.

[112] Jais AM, Dambisya YM, Lee TL. Antinociceptive activity of Channa striatus (Haruan) extracts in mice.
[120] Borkow G, Melamed E. Copper, An Abandoned Player Returning to the Wound Healing Battle. InTech Open 2021.

[121] Coger V, Million N, Rehbock C, Sures B, Nachev M, Barcikowski S, Wistuba N, Strauß S, Vogt PM. Tissue concentrations of zinc, iron, copper, and magnesium during the phases of full thickness wound healing in a rodent model. Biological Trace Element Research 2019; 191(1):167-76.

[122] Arendsen LP, Thakar R. Basset P, Sultan AH. The impact of copper impregnated wound dressings on surgical site infection following caesarean section: A double-blind randomised controlled study. Eur J Obstet Gynaecol Reprod Biol 2020; 251:83-8.

[123] Lin PH, Sermersheim M, Li H, Lee PH, Steinberg SM, Ma J. Zinc in wound healing modulation. Nutrients 2018; 10(1):16.

[124] Marriage-Arcari R. The role of Zinc in wound healing. Journal of Wound Care Canada 2016; 14(3):18-22.

[125] Rosmawati EA, Tawali AB, MI MS. Chemical Composition, Amino Acid, and Collagen Content of Snakehead (Channa striatus) Fish Skin and Bone. Scientific Research Journal 2018; 6(1):1-4.

[126] Abustam E, Tawali AB, Said MI, Sari DK. Effect of body weight on the chemical composition and collagen content of snakehead fish Channa striata skin. Fisheries Science 2018; 84(6):1081-9.

[127] Kwan SH, Baie S, Ismail MN. Profiling of proteins and post translational modifications of Channa striatus dried meat. Current Proteomics 2016; 13(1):9-19.

[128] Kwan SH, Baie S, Mohammed N, Ismail MN. Proteomic profiling of freeze- and spray-dried water extracts of snakehead fish (Channa striatus): In search of biomolecules for wound healing properties. S Asian J Life Sci 2015; 3(1): 22-41.

[129] Hassan SA, Rosnelifaizur R, Maya YM, Samarendra SM, Saringat B, Naing NN, Wan-Arfah N. Effect of oral Channa striatus in laparotomy wound healing of malnourished rats. International Medical Journal 2020; 27(1):67-70.

[130] Baie SH, Sheikh KA. The wound healing properties of Channa striatus-cetrimide cream—tensile strength measurement. Journal of Ethnopharmacology 2000;71(1-2):93-100.

[131] Baie SH, Sheikh KA. The wound healing properties of Channa striatus-cetrimide cream-wound contraction and glycosaminoglycan measurement. Journal of Ethnopharmacology 2000; 73(1-2):15-30.

[132] Rangaraj A, Harding K, Leaper D. Role of collagen in wound management. Wounds 2011; 7(2):54-63.

[133] Chattopadhyay S, Raines RT. Collagen-based biomaterials for wound healing. Biopolymers 2014; 101(8):821-33.

[134] Harsha L, Brundha MP. Role of collagen in wound healing. Drug Invention Today 2020; 13(1).

[135] Woo KY. Exploring the effects of pain and stress on wound healing. Advances In Skin & Wound Care 2012; 25(1):38-44.

[136] Newbern S. Identifying pain and effects on quality of life from chronic wounds secondary to lower-extremity vascular disease: an integrative review. Advances In Skin & Wound Care 2018; 31(3):102-8.

[137] Price P, Krasner DL. Health-related quality of life and chronic wounds:
Evidence and implications for practice. Chronic Wound Care. HMP Communications. 2012: 77-84.

[138] Bakar MR, Kadir AA, Wahab SZ, Karim AH, Hussain NH, Noor NM, Omar J, Baie SB, Mahmood WH, Razak AA, Yunus R. Randomized controlled trial on the effect of Channa striatus extract on measurement of the uterus, pulsatility index, resistive index of uterine artery and superficial skin wound artery in post lower segment caesarean section women. PloS One 2015; 10(7):e0133514.

[139] Braza ME, Fahrenkopf MP. Split-thickness skin grafts. In StatPearls [Internet]; 2020.

[140] Kwan SH, Abdul Aziz NHK, Ismail MN. Bioactive proteins in Channa striata promote wound healing through angiogenesis and cell proliferation. Protein & Peptide Letters 2020; 27(1):48-59.

[141] Oosthuizen B, Mole T, Martin R, Myburgh JG. Comparison of standard surgical debridement versus the VERSAJET PlusTM Hydrosurgery system in the treatment of open tibia fractures: prospective open label randomized controlled trial. Int J Burns Trauma 2014; 4(2):53-8.

[142] Rudolph R, Klein L. Healing process in skin grafts. Surg Gynaecol Obstet 1973; 136(4):641-54.

[143] Converse JM, Smahel J, Ballantyne DL, Harper AD. Inosculation of vessels os skin graft and host bed: A fortuitous encounter. Br J Plast Surg 1975; 28(4):274-82.

[144] Lindenblatt N, Calcagni M, Contaldo C, Menger MD, Giovannoli P, Vollmar B. A new model for studying the revascularization of skin grafts in vivo: The role of angiogenesis. Plas Reconstr Surg 2008; 122(6):1669-80.

[145] Aghoghovwia OA, Uahunmwangho EJ, Izah SC. Wound healing potentials of some fin fishes. Int J Res Stud Biosci 2018; 6(5):33-39.

[146] Alhajj M, Bansal P, Goyal A. Physiology, granulation tissues. In StatPearls [Internet]; 2020.

[147] Febriyenti F, Noor AM, Baie S. Formulation of aerosol concentrate containing Haruan (Channa striatus) for wound dressing. Mal J Pharm Sci 2008; 6(1): 43-58.

[148] Baie S, Sheikh KA. The wound healing properties of Channa striatus – cetrimide cream – tensile strength measurement. J Ethnopharm 2000; 71(1):93-100.

[149] Laila L, Febriyenti F, Salhimi M, Baie S. Wound healing effect of Haruan (Channa striatus) spray. Itl World J 2011; 8(5):484-91.

[150] Punzi L, Galozzi P, Luisetto R, Favero M, Ramonda R, Oliviero F, Scanu A. Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. RMD Open 2016; 2(2):e000279.

[151] Muhtadi SA, Sutrisna EM. The potential antidiabetic and anti-inflammatory activity of Zingiber zerumbet ethanolic extracts and Channa striata powder on albino Wistar mice. Drug Invention Today 2019; 12(1):148-53.

[152] Somchit MN, Solihah MH, Israf DA, Zuraini A, Arifah AK, Jais AM. Effects of three local Malaysian Channa spp. fish on chronic inflammation. Oriental Pharmacy and Experimental Medicine 2004; 4(2):91-4.

[153] Azidah AK, Arifah AK, Roslida AH, Jais AM, Omar J, Sadagatullah AN, Ishak A, Noor NM, Musa AT. A randomized, double-blind study comparing multiple doses of Channa...
striatus supplementation for knee osteoarthritis. Oriental Pharmacy and Experimental Medicine 2017; 17(4):345-54.

[154] Shafii N, Omar J, Sirajudeen K, Kadir AA, Baie SH, Wahab SZ, Yunus R, Noor NM, Hussein NH, Razak AA, Mahmood WH. Changes in the inflammatory markers with supplementation of Channa striatus extract in post lower segment caesarean section. International Medical Journal 2017; 24(3):268-71.

[155] Al-Saffar FJ, Ganabadi S, Fakuraz S. Response of Channa striatus extract against monosodium iodoacetate induced osteoarthritis in rats. Journal of Animal and Veterinary Advances 2011; 10(4):460-9.

[156] Ganabadi S. 525 Channa striatus extract supplementation significantly increased protein gene product 9.5-immunoreactive nerve fibres compared to Zingiber officinale extract in collagenase induced osteoarthritis. Osteoarthritis and Cartilage 2009; 17:S281-2.

[157] Kadir AA, Ab Wahab SZ, Zulkifli MM, Noor NM, Baie SB, Haron J. The therapeutic effect of oral Channa striatus extract on primary knee osteoarthritis patients. Agro FOOD Industry Hi Tech 2014; 25(3):44-8.

[158] Kadir AA, Kadir AA, Hamid RA, Mat Jais AM, Omar J, Sadagatullah AN, Badrin S, Win TT, KNS Sirajudeen, Salleh A. Evaluation of Chondroprotective Activity of Channa striatus in Rabbit Osteoarthritis Model. Biomed Research International 2019.

[159] Kadir AA. Snakehead fish (Channa Striatus) in the management of osteoarthritis: Clinical research and possible mechanism of action. Chinese Journal of Traditional Medicine. 2018; 1(1):1-7.

[160] Bakar MN, Abdullah B, Mohamad I, Lazim NM, Yahya NK, Kadir AA. Efficacy of snakehead fish (Channa striatus) extract supplementation in allergic rhinitis patients: A randomized double-blind placebo-controlled trial. International Medical Journal 2019; 26(4):297-300.

[161] Susibalan BD, Abdullah B, Lazim NM, Kadir AA. Efficacy of snakehead fish (Channa striatus) in subjects with allergic rhinitis: a randomized controlled trial. Oriental Pharmacy and Experimental Medicine 2018; 18(3):209-15.

[162] Isa II, Bakar SA, Tohid SF, Mat Jais AM. Channa striatus cream down-regulates tumour necrosis factor (TNF)-alpha gene expression and alleviates chronic-like dermatitis in mouse model. Journal of Ethnopharmacology 2016; 194:469-74.

[163] Meera K, Tarita T, Johar A, Bin Mat Jais AM. Topical Channa striatus 5% cream for inflammatory skin conditions: A phase I randomized double-blind, controlled trial. Iranian Journal of Dermatology 2016; 19(3):67-72.

[164] Ali Khan MS, Mat Jais AM, Hussain J, Siddiqua F, Gopala Reddy A, Shivakumar P, Madhuri D. Gastroprotective effect of freeze-dried stripped snakehead fish (Channa striata Bloch.) aqueous extract against aspirin induced ulcerogenesis in pylorus ligated rats. International Scholarly Research Notices 2014.

[165] Azemi AK, Abd Rahim MH, Mamat SS, Mat Jais AM, Zakaria ZA. Antiulcer activity of methanol-chloroform extract of Channa striatus fillet. Pakistan Journal of Pharmaceutical Sciences 2018; 31(1):143-151.

[166] Arockiaraj J, Palanisamy R, Arasu A, Sathyamoorthi A, Kumaresan V, Bhatt P, Chaurasia MK,
Haruan Extract (Channa striatus) as an Effective Mediator in Promoting Wound Healing
DOI: http://dx.doi.org/10.5772/intechopen.99207

Pasupuleti M, Gnanam AJ. An anti-apoptotic B-cell lymphoma-2 (BCL-2) from Channa striatus: Sequence analysis and delayed and advanced gene expression in response to fungal, bacterial and poly I: C induction. Molecular immunology 2015; 63(2):586-94.

[167] Buhari I, Roslida A, Hidayat M, Mat Jais AM. Haruan Fish Extract as Potential Agent for Cancer Therapy. J. Cancer Sci. Ther 2015; 7:186-9.

[168] Ghassem M, Arihara K, Babji AS, Said M, Ibrahim S. Purification and identification of ACE inhibitory peptides from Haruan (Channa striatus) myofibrillar protein hydrolysate using HPLC–ESI-TOF MS/MS. Food Chemistry 2011; 129(4):1770-7.

[169] Pujiajstuti DY, Ghoyatul Amin MN, Alamsjah MA, Hsu JL. Marine organisms as potential sources of bioactive peptides that inhibit the activity of angiotensin I-converting enzyme: a review. Molecules 2019; 24(14):2541.

[170] Abdul Shukkoor MS, Baharuldin MT, Mat Jais AM, Mohamad Moklas MA, Fukurazi S. Antidepressant-like effect of lipid extract of Channa striatus in chronic unpredictable mild stress model of depression in rats. Evidence-Based Complementary and Alternative Medicine 2016.

[171] Abdul Shukkoor MS, Baharuldin MT, Mat Jais AM, Mohamad Moklas MA, Fukurazi S. Antidepressant-like effect of lipid extract of Channa striatus in chronic unpredictable mild stress model of depression in rats. Evidence-Based Complementary and Alternative Medicine 2016.

[172] Holden J. Top tips for skin graft and donor site management. Wound Essentials 2015; 10(2):7-13.

[173] Hierner R, Degreffe H, Vranckx JJ, Garmyn M, Massagé P, van Brussel M. Skin grafting and wound healing—the “dermato-plastic team approach”. Clinics in Dermatology 2005; 23(4):343-52.

[174] Beldon P. What you need to know about skin grafts and donor site wounds. Wound Essentials 2007; 2:149-55.

[175] Martyniuk CJ, Denslow ND. Exploring androgen-regulated pathways in teleost fish using transcriptomics and proteomics. Integr Comp Biol 2012; 52: 605-704.

[176] Doherty MK, Brownridge P, Owen MA, Davies SJ, Young IS, Whitfield PD. A proteomics strategy for determining the synthesis and degradation rates of individual proteins in fish. J Proteomics 2012; 75(14): 4471-77.

[177] Gam LH, Leow CY, Baie S. Proteomic analysis of snakehead fish (Channa striata) muscle tissue. Malaysian J Biochem Mol Biol 2006; 14(1):25-32.

[178] Serini G & Gabbiani G. Mechanisms of myofibroblast activity and phenotypic modulation. Exp Cell Res 1999; 250(2):273-83.

[179] Burridge K & Chrznowska-Wodnicka M. Focal adhesions, contractility, and signalling. Annu Rev Cell Div Biol 1996; 12(1):463-519.

[180] Kreis TE & Birchmeier W. Stress fibre sarcomeres of fibroblasts are contractile. Cell 1980; 22(2):555-61.

[181] Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 2002; 3(5):349-63.

[182] Lees JG, Bach CT, O’Neill GM. Interior decoration: Tropomyosin in actin dynamics and cell migration. Cell Adhes Migr 2011; 5(2):181-86.
[183] Reynolds L, Conti F, Lucas M, Grose R, Robinson S, Stone M, Saundees G, Dickson C, Hynes R, Lacy-Hulbert A. Accelerated re-epithelialization in 3-integrin-deficient mice is associated with enhanced TGF-1 signalling. Nat Med 2005; 11(2):167-174.

[184] Lees JG, Ching VW, Adams D, Bach CT, Samuel MS, Kee AJ, Hardeman EC, Gunning P, Cowin AJ, O’Neill GM. Tropomyosin regulates cell migration during skin wound healing. J Invest Dermatol 2013; 133(5):1330-39.

[185] White MJ, Glenn M, Gomer RH. Trypsin potentiates human fibrocyte differentiation. PloS One 2013; 8(8):e70795.

[186] Gudmundsdóttir A & Pálsdóttir HM. Atlantic cod trypsin: From basic research to practical application. Mar Biotechnol 2005; 7(2):77-88.

[187] Termine JD, Belcourt AB, Conn KM, Kleinman H. Mineral and collagen-binding proteins of foetal calf bone. J Biol Chem 1981; 256(20):10403-08.

[188] Postlethwaite AE, Seyer JM, Kand AH. Chemotactic attraction of human fibroblasts to type I, II, and IV collagens and collagen-derived peptides. Proc Natl Acad Sci USA; 1978;75(2):871-5.

[189] Gogia PP. The biology of wound healing. Ostomy Wound Manag 1991; 38(9):12,14-6,18-22.

[190] Helary C, Zaria M, Giraud-Guille MM. Fibroblasts within concentrated collagen hydrogels favour chronic skin wound healing. J Tissue Eng Regener Med 2012; 6(3):225-37.

[191] Benjakul S, Nalinanon S, Shahidi F. Fish collagen: Food Biochemistry and Food processing, 2nd Edition; Wiley and Sons: New York 2012, pp. 365-87.

[192] Hayashi Y, Yamada S, Guchi KY, Koyama Z, Ikeda T. 6 Chitosan and fish collagen as biomaterials for regenerative medicine. Adv Food Nutr Res 2021; 65:107.

[193] Hahn K, DeBiasio R, Taylor DL. Patterns of elevated free calcium and calmodulin activation in living cells. Nature 1992; 359(6397):736-38.

[194] Lansdown AB. Calcium: A potential central regulator in wound healing in the skin. Wound Repair Regen 2002; 10(5):271-85.

[195] Bennet RD, Mauer AS, Pittelkow MR, Strehler EE. Calmodulin-like protein upregulates myosin-10 in human keratinocytes and is regulated during epidermal wound healing in vivo. J Invest Dermatol 2009; 129(3):765-69.

[196] Lasdown A, Sampson B, Rowe A. Sequential changes in trace metal, metallothionein, and calmodulin concentrations in healing skin wounds. J Anat 1999; 195(3):375-86.

[197] Szabolcsi V & Celio MR. De novo expression of parvalbumin in ependymal cells in response to brain injury promotes ependymal remodelling and wound repair. GLIA 2014; 63(4):567-94.

[198] Lubec G, Afjehi-Sadat L, Yang JW, John JPP. Searching for hypothetical proteins: Theory and practice based upon original data and literature. Prog Neurobiol 2005; 77(1):90-127.