RESEARCH ARTICLE

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 [version 1; peer review: 1 approved, 1 not approved]

Ahmad Farouk Musa ¹, Jeswant Dillion², Mohamed Ezani Mohd Taib², Alwi Mohd Yunos², Saringat Baie³⁺, Rusli Bin Nordin ¹

¹Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Subang Jaya, 47500, Australia

²Department of Cardiothoracic Surgery, National Heart Institute, Kuala Lumpur, 50400, Malaysia

³School of Pharmaceutical Sciences, Science University of Malaysia, Penang, 11800, Malaysia

+ Deceased author

V1 First published: 17 Apr 2018, 7:469
<https://doi.org/10.12688/f1000research.13372.1>

Latest published: 17 Apr 2018, 7:469
<https://doi.org/10.12688/f1000research.13372.1>

Abstract

Background: Wound healing remains a primary problem in all surgical cases especially so when the length of incision is very significant as with cardiac bypass patients. The main objective of this study is therefore to assess the effect of *Haruan* fish extract (*Channa striatus*) on chest and leg wounds post-coronary artery bypass grafting (CABG) surgery with the optimum and standard patient care in two groups of randomized patients.

Methods: This is a randomized, double blind clinical trial being conducted at the National Heart Institute, Kuala Lumpur. Two randomized groups of similar demographic and co-morbid histories planned for CABG were enrolled into the study. Both groups were blinded to the capsules being given to them pre- and post-operatively. Assessments were also made on wound pain, mobilization and on the health-related quality of life (HRQOL) of patients using the Nottingham Health Profile (NHP).

Results: The group that received *Haruan* capsule showed better wound healing objectively. They had better pain scores, though there was no significant difference in terms of mobilization. Overall, the HRQOL in the study group showed improved quality of life.

Conclusion: Our study shows the superior effect of using *Channa striatus*, a local *Haruan* fish which is easily processed into capsules in promoting wound healing, reducing pain via its anti-nociceptive effect

Open Peer Review

Approval Status

	1	2
version 1
17 Apr 2018	view	view
1. Mahmood Moshiri , Next Pharma Inc., Toronto, Canada		
Kiarash Moshiri , Richmond Biotechnology Inc., Richmond Hill, Canada		
2. Brian Olshansky , Mercy Hospital- North Iowa, Mason City, USA		
University of Iowa hospitals and clinics, Iowa City, USA		
Covenant Hospital, Waterloo, USA		

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and improving quality of life of patients after coronary artery bypass grafting surgery. It is inferred that a faster recovery from surgery confers an advantage in terms of resources to overall economic benefits. Reduction in the percentage of wound infection also resulted in reduced hospital cost. All these factors could lead to the successful commercialization of *Haruan* as a nutraceutical product.

Trial registration: The trial was conducted from January 2012 until August 2014 and the trial number as registered with the National Medical Research Registry is [NMRR-17-360-34772](#) (Registered 13/03/2017).

Keywords

wound healing, quality of life (QOL), coronary artery bypass grafting (CABG), *Channa striatus*

This article is included in the [All trials matter](#) collection.

Corresponding author: Ahmad Farouk Musa (farouk@monash.edu)

Author roles: **Farouk Musa A:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Dillion J:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Mohd Taib ME:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Mohd Yunus A:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Baie S:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; **Bin Nordin R:** Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was funded by Monash University Malaysia under Major Grant, CRM279.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Farouk Musa A, Dillion J, Mohd Taib ME *et al.* **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 [version 1; peer review: 1 approved, 1 not approved]** F1000Research 2018, 7:469 <https://doi.org/10.12688/f1000research.13372.1>

First published: 17 Apr 2018, 7:469 <https://doi.org/10.12688/f1000research.13372.1>

Introduction

Wound healing involves complex interaction between cells and mediators, which starts once the wound is inflicted, and continues for weeks. Healing is still a major problem in any kinds of surgery, particularly in cardiothoracic surgery. This is a surgery that involves a long incision over the sternum where delayed sternal wound healing is not an uncommon sight. Sternal wound infections are a known cause of morbidity and might require intervention from plastic surgeons. In severe cases, it could even lead to mortality.

Sternal wound infection is fairly uncommon as compared to leg wounds, with a frequency between 0.7%¹ and 3.3%², but reports based on extended surveillance on post-discharge cases showed incidences up to 9.7%³. As expected, the end-result of sternal wound infection include wound dehiscence, mediastinitis, pericarditis, osteomyelitis and endocarditis⁴ with associated mortality between 14% and 47%⁵⁻⁹.

Leg wound infection, though not life-threatening as chest-wound, increases the overall morbidity of the patients. It is noted that there is a threefold increase in cost of managing patients with leg wound as compared to those with an uncomplicated postoperative course⁷. Complications such as wound breakdown, cellulitis, lymphangitis, fat necrosis, and delayed healing are known sequelae of leg wound infection. It is not surprising that the incidence has been reported to be as high as 24%¹⁰⁻¹³.

We have noticed that despite the different types of dressings being used, the rate of infection did not vary that much¹⁴⁻¹⁷. The reason for this seemingly indifferent incidence of wound infection is due to the fact that the healing was by primary intention¹⁷. The cause for such an infection is primarily deep-seated problem of the pre-operative and intra-operative rather than merely the superficial issue of wound dressing¹⁸.

With that understanding, perhaps a better way in promoting wound healing would be a systemic approach rather than topical; with all other factors remaining constant. Extracts of *Channa striatus*, locally known as *Haruan* (snakehead), a fresh water, air-breathing, carnivorous fish, has been proven to influence the different phases of the wound healing process^{19,20}. Laboratory studies conducted on Sprague Dawley rats have shown that *Channa striatus* has antinociceptive effects that could reduce postoperative pain²¹⁻²³. *Channa striatus* has been shown to contain all essential amino acids for wound healing, particularly glycine. Glycine is a major component of human skin collagen that acts synergistically with other essential amino acids that facilitate in tissue healing process. It also has a high content of arachidonic acid and polyunsaturated fatty acids that can promote prostaglandin synthesis, which is a very important compound that creates and removes inflammation, which is part of the healing process¹⁹. It has also been shown that *Channa striatus* promotes remodelling of collagen by the synthesis of inter, and intra molecular protein cross-linking, producing a marked increase in the tensile strength that accentuates wound

healing²⁴. Furthermore, the fish also has certain fatty acids that have been reported to possess anti-inflammatory activity such as stearic acid and oleic acid²⁵.

Up to this point, all the above studies that looked into the healing and nociceptive properties of *Channa striatus* have been on animal models. This is the first study that is conducted on human subjects. We therefore conducted a prospective randomized control trial (RCT) and assess not only wound healing and wound infection after CABG, but also the health related QOL of such patients, considering the anti-inflammatory and antinociceptive effect of *Channa striatus*. The potential value of patenting such natural product and its usage on other types of surgical wounds, including laparotomy and Caesarean section; compounded with the commercial value associated, makes it even more attractive.

Methodology

Study design

Laboratory. The *Haruan* used in this study was locally reared in a special pond for *Haruan*; the sex of the fish was not determined. The depth of the pond should not be more than 4 feet for the fish to surface and breath, since *Haruan* is air breathing and carnivorous. Temperature is maintained around 25°C and pH must be maintained between 5.0 – 5.5 and salinity between 0 – 10 ppm. The *Haruan* capsules produced were derived from the flesh of the fish and were manufactured using strict good manufacturing practice (GMP) Guidelines by Major Interest Sdn. Bhd.

Haruan (whole fish) are procured fresh to the laboratory. These fishes are kept at -18°C until preparation. The fishes are thawed prior to gutting and cleaning. The cleaned fishes are weighed and placed into the autoclave bin. The water mixture for autoclaving is prepared in relative to fish weight with respect to the volume of the water used. Therefore, a 1:0.5 mixture would contain 1kg of fish with 0.5 kg (500ml) of water. . No preservatives were used in the preparation of *Haruan* capsules.

Sterilization is carried out using Hiclave HVE-50 autoclave (Hirayama, Tokyo, Japan) with temperature setting of 110°C for 15 minutes. Upon completion of the sterilization, the fish are mixed and meshed thoroughly using a clean ladle, which has been wiped with 70% alcohol. This mixture is then transferred into a large lined aluminium pan with a dimension of 24 × 18 × 1 inches and dried using a 12 tray industrial oven at 60°C for 48 hours continuously.

Upon completion, the sheets of crispy flakes are grinded using a comminuting mill and a hand grinder, Kimah Grinder Machine (CSJ-300, Penang, Malaysia) to ensure thin bone fragments are properly powdered. The resulting powder is mixed homogenously in a clear large plastic bag. Upon homogenous mixing, the powder is sieved using Retsch AS200 analytical sieve shaker (Haan, Germany), with woven wire mesh sieves of 850 micron aperture.

Production of *Haruan* capsules

The refined powder was filled into empty hard gelatin capsules of pharmaceutical grade which is 1005 TSE/BSE produced by Nasmir Hard Gelatin Capsules Sdn. Bhd. (Catalogue number 1NH001, Pulau Pinang, Malaysia) based on bench scale filling method using Kimah electronic capsule arranging machine, Model 400-F1 (Penai, Malaysia). The empty hard gelatin capsule shells used are of size 0 and made of halal gelatin each weighing 0.08mg. The capsules were visually inspected for defect and are weighed for standard distribution of 250 mg using Sartorius analytical digital balance (Göttingen, Germany). The standardized capsules are packed into sterile bottles using a Kimah electronic counting machine, Model JB-2B (Penai, Malaysia). The bottles are inserted with pre-packed silica beads for moisture absorbance and cotton balls to prevent spillage.

Clinical study

A randomized controlled trial (RCT) was completed with patients with coronary artery disease requiring coronary artery bypass grafting surgery were prospectively and randomly divided into two parallel groups. One group received *Channa striatus* capsule formulation derived from the fillet of *Channa striatus* and the control group received placebo (maltodextrine). The trial was conducted from January 2012 until August 2014 and the trial number as registered with the National Medical Research Registry is [NMRR-17-360-34772](#) (Registered 13/03/2017).

Sample size calculation

We used the **PS Software** version 3.1.2 for power and sample size calculation. We have planned a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject. Based on a previous study²⁶ we planned a study of independent cases and controls with 1 control per case. Prior data indicated that the failure rate among controls was 0.027. If the true relative risk of failure for experimental subjects relative to controls is 6.9, then we needed to study 58 experimental subjects and 58 control subjects to be able to reject the null hypothesis that this relative risk equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We used an uncorrected chi-squared statistic to evaluate this null hypothesis. Assuming a drop-out rate of 20%, the minimum sample size required was about 70 (58 + 12) subjects per group. In this study, we managed to recruit 253 patients, and 183 completed the three months follow-up. We therefore surpassed the minimum requirement of sample size of 140 subjects, allowing us reach a power of study of 0.8.

Sampling

Inclusion criteria:

1. Male or female
2. More than 18 years of age
3. Elective, urgent, or emergency coronary artery revascularization

Exclusion criteria:

1. Less than 18 years old
2. Refusal to have surgery
3. Inability to give informed consent
4. Documented allergy to fish or fish product

Pre-operative

The two randomized groups based in the National Heart Institute (IJN) were matched according to sex, age, New York Heart Association (NYHA) criteria (indicates patients' hearts condition and the severity of their symptoms. Class I to Class IV), ejection fraction, and diabetic status. Randomization was done via simple computer-generated randomization with odd or even RN numbers in each group. Operative and peri-operative conditions were also similar for both groups. All subjects received an identical prophylactic antibiotic regime consisting of Cefazolin 2gm at induction and 1 gm 12 hourly for 48 hours. Gentamicin 2mg/kg was also given at induction.

Intra-operative

A uniform method of wound closure and disinfection protocol was followed. Skin was disinfected with Betadine followed by povidone iodine 10%. The method for wound closure was similar for both groups, namely double layer sutures up to the intra-cutaneous skin. Going from deep up to the surface, the pre-sternal fascia was closed with 1-0 Vicryl suture in a continuous type followed by closure of the subcutaneous tissue. Skin was closed with Monocryl 3/0 in subcuticular manner. For the leg wound, the subcutaneous tissue was closed with Vicryl 0, followed by continuous skin suture with Maxon 3/0.

Titanium clips were used to secure branches of the internal mammary artery on the chest wall and branches of the saphenous vein in the leg. Some saphenous veins branches were ligated with Silk 3/0 instead. When closing the sternum, steel wire sutures were used.

Post-operative

Both groups took either, 2 capsules (500mg) of *Channa striatus*, or 2 capsules of placebo (maltodextrine) daily for a minimum of six weeks, starting from day one post-operatively. If the patient was still ventilated, the capsules were broken, and the content administered via a Ryle's tube. Investigators and healthcare workers, as well as participants, were blinded to the capsules received. Only the manufacturers who supplied the drug were aware of the meaning of the label on the capsule, letter E or O.

Consent and ethics

Prior to randomization of participants, the study was explained, including risk and benefits to suitable candidates, and written consent was obtained. Consenting participants were then randomized into the trial. The study was conducted with ethical approval from the National Heart Institute Malaysia (IJNEC/04/2011) and National Medical Research Register ([NMRR-17-360-34772](#)).

Measurement

Wound Infection. Both sternal and leg wounds were inspected and assessed daily until subjects were discharged. Information at 6 weeks and 3 months postoperatively was collected from patients in the clinic or over the telephone. Each wound was scored using the ASEPSIS system (Refer to [Supplementary Material 1](#)). We realized that this is a more objective method in assessing wound infection rather than being subjective and open to biases. The end result from this scoring system will determine whether the wound is considered significant or not by obtaining a score of 21–30. If the wound is more serious with a deep seated wound infection, it will have a score of 21–30, and should there be evidence of bone infection, then the score would be >41.

Wound pain. A Visual Analogue Scale (VAS) of 0 to 10 cm was used to assess the degree of wound pain. A score of 0 cm represents “no pain” and a score of 10 represents “severe pain”. Pain assessment will be recorded from day 1 and will continue daily until the subject is discharged. It will be further assessed during the clinic visit at 6 weeks and 3 months postoperatively.

Mobilization. Similarly, a VAS of 0 to 10 cm was used to assess the degree of mobilization. A score of 0 cm represents “inability to walk” and 10 cm represents “excellent mobilization.” Assessment of mobilization was made on post-operative days 3 and 4 since there was restrictions in mobility on days 1 and 2 after surgery. Similarly, it was assessed again during the clinic visit at 6 weeks and 3 months postoperatively.

Health related quality of life. In this study, we decided to assess the health-related quality of life (HRQOL) using the Nottingham Health Profile (NHP) – Part 1. The NHP is known to be very efficient in clinical studies. It looks into parameters such as discomfort and pain apart from the general well-being of a patient. And it is found to be more objective in assessing the health status of the patients. There were 38 subjective statements which were divided into six sections on NHP Part 1 namely physical mobility, social isolation, emotional reaction, energy, pain, and sleep. Each section will have a score range from between 0–100 by adding the item weight to each answer that is deemed positive.

The questionnaire was distributed to both groups of patients before CABG and at six weeks and three months during clinic visit postoperatively. The questionnaires were administered using the questionnaire-interview approach.

Statistical analysis

Data was analysed with **IBM SPSS** Statistics version 24.0 and examined for normality using the Kolmogorov-Smirnov test and stem-and-leaf plot. When normal, we proceeded with parametric tests; however, if not normal, we proceeded with the non-parametric tests.

The results were presented as means $\pm$ standard deviations for scaled measurements; with numbers and percentages for categorical measurements. The unpaired t-test was used to

examine mean differences for wound infection, wound healing, pain, and mobilization across the two groups. Differences in proportions was examined using the Chi-square test.

In examining the mean QOL score, differences between the two groups (pre-operative, six weeks, and three months), the mixed mode two-way repeated measure ANOVA with post-hoc multiple comparison test (between and within subjects) of the two groups was performed.

To determine the factors influencing the change of QOL after CABG, with the dependent variable being binary (improved or worsened), we performed an initial simple logistic regression (SLogReg), and examined the statistical significance of each independent variable such as the amount of revascularization and duration of surgery on the outcome. We then performed a multiple logistic regression (MLogReg) including variables with a level of significance ≤ 0.20 in the multivariate logistic regression and controlling for the effects of possible confounding variables (sex, age, NYHA Criteria, ejection fraction, and diabetic status). A *p* value of 0.05 was taken as the level of significance.

Refer to [Figure 1](#) for the study flow chart.

Results

253 patients were recruited from January 2012 till August 2014. Only 183 patients (72.3%) completed the study up to three months follow-up. A total of 40 patients (15.8%) were lost during follow-up and 5.5% discontinued their enrolment in the study. The main reason why these patients were lost during follow-up was for a simple reason that they did not turn-up for the scheduled follow-up. This is due to the fact that IJN is the largest heart centre in the Malaysia and the patients were from all over the country. And since many were former government servants and stay in the rural areas all over the country, travelling to the city centre was not only time-consuming but expensive. Seven patients (2.8%) had their operations cancelled.

The patients were predominantly male (86.2%), the majority being Malay (86.7%), followed by Indians (15.4%) and Chinese (7.9%).

The mean weight was 71.92 ± 13.10 kg ranging from 45–132 kg and the mean BMI was 27 ± 4.3 kg/m².

125 (49.4%) of them received Capsule O (placebo) and 128 (50.6%) received Capsule E that contains *Haruan* extract.

Out of the 246 patients who underwent CABG, 224 patients (91.06%) had an elective operation, while only 8.94% were emergency cases.

Off-pump CABG was performed on only 16.7% of patients as compared to the conventional on-pump (83.3%). Mean operation time was 186.94 ± 48.9 minutes ranging from 75 to 350 minutes. The mean bypass time was 82.08 ± 27.55 minutes.

Figure 1. Study flow chart.

65 patients (26.42%) developed atrial fibrillation (AF) post-operatively while 10 patients (4.07%) developed supraventricular tachycardia (SVT).

Only 10 patients (4.07%) had their chest re-opened. Known complications such as renal failure occurred in only 2 patients (0.81%) and stroke in another 2 patients (0.81%) as well. Overall, the mortality rate was 3.6% with nine patients dead.

Mean hospital stay was 10 ± 11.86 days and mean ICU stay was 2.97 ± 7.67 days. Both the duration of ICU stay (2.31 ± 2.65), and hospital stay (9.24 ± 8.58) was shorter for patients on Capsule E in comparison to Capsule O (3.69 ± 10.7 and 11.1 ± 14.6 , respectively), although this was not statistically significant ($p=0.170$, 0.230 , respectively).

The ASEPIS score showed no statistically significant difference between Capsule E and O on Day 3, 6, 6 weeks and 3 months ($p=0.243$, 0.805 , 0.117 , 0.980 , respectively).

There was no statistically significant difference in the mean pain score using the visual analogue scale (VAS) between the two groups post-operatively (Capsule E: 0.39 ± 0.25 , Capsule O: 0.43 ± 0.24 , $p=0.290$) and no difference on mobilization ($p=0.668$).

Assessment of HRQOL comparing both groups showed no significant difference at discharge (p -values: emotion= 0.48 , physical= 0.54 , energy= 0.16 , social= 0.071 , sleep= 0.87 , and pain= 0.29) and assessment at 6 weeks and 3 months follow-up showed no statistically significant difference for all six components of HRQOL except for social level at 3 months ($p=0.04$).

Refer to [Figure 2](#) for study results flow chart.

Limitations

There were a few limitations to this study. The first is in getting the patients' consent in enrolling into the study. A few patients had this misconception that *Haruan* would cause hypertrophic wound or sometimes even keloid. This was the misperception that they had and no amount of talking or persuasion would convince them. And of course, considering that their enrolment is voluntary, their withdrawal from the study is unavoidable. Hence there were almost 30% of patients who did not manage to complete the study. The second limitation is regarding the compliance of the patients to take the capsules provided to them. While they were on the ward, this issue of compliance did not arise, since the *Haruan* capsules or the placebo were served by the attending staff nurses. However, compliance was not ensured when the patients were discharged from the wards. The third is regarding how the Nottingham Health Profile was administered. We decided for the questionnaire to be conducted by the researcher and not independently answered by the patients without the presence of the researcher. This could have resulted in some bias when answering the question on

NHP by the patients. While we understand that this interview mode is not free from bias, it is still the least burdensome method, which only requires the respondent to speak the same language as the interviewer, and to have a basic verbal and listening skills. Considering that almost all Malaysians speak Malay and a majority of them speak English as well, this is probably a more effective way. We believe that the interview method would allow us to clarify ambiguous questions, and maintain the motivation.

Dataset 1. Health Related Quality of Life for all participants

<http://dx.doi.org/10.5256/f1000research.13372.d196593>

Dataset 2. Surgical wound healing data for all participants

<http://dx.doi.org/10.5256/f1000research.13372.d196594>

Discussion

Wound healing has always been an obsession among surgeons. And despite the advance in surgical dressings over the years, surgeons have always been trying to find novel ways in promoting wound healing. *Haruan* or *Channa striatus* has been known amongst the locals since ancient times to promote healing, and has been used as a form of nutritional supplement. Normally the fish is consumed after it is fried, grilled or boiled; as a traditional remedy for wound healing especially after delivery of caesarean section. There, however, are no clinically randomized trials so far that have been conducted to prove or disprove this belief.

Our study – the first as far as the authors are concerned – has shown the clinical benefit of *Channa striatus* in promoting wound healing among CABG patients. The study was conducted in a double-blind manner, and only after the results were analyzed, were the researchers informed of the content of Capsule E and Capsule O. There was no way for the researchers to know before hand of the content of the capsules.

The results scientifically confirm the long-held belief of the benefit of *Haruan* fish. The properties of *Haruan* to promote wound healing have been postulated. Perhaps it was the way in which *Haruan* had positive influence on the immune system in regulating the prostaglandin synthesis via the possession of ω -3 polyunsaturated fatty acids has made it effective in stimulating the healing process²⁰.

The healing process requires both amino acids and fatty acids. And these have been found in abundance in *Haruan* fish. Compounds such as glycine, alanine, proline, arginine, serine, leucine, isoleucine, and phenylalanine are known to combine with aspartic and glutamic acid to form polypeptides. These form the basic foundation for healing to take place. Studies have demonstrated that these amino acids and fatty acids are present in *Haruan*²⁰.

*NHP – Nottingham Health Profile

*VAS – Visual Analog Scale

Figure 2. Study results flow chart.

Similarly, *Haruan* also contains a high content of arachidonic acid, 20:4 ω 6. This arachidonic acid is thought to be related to the wound healing property of *Haruan*²⁰. The platelet aggregation and adhesion to the endothelial tissue that initiates blood clotting is thought to be induced by arachidonic acid.

Researchers at the Analytical Biochemistry Research Centre at the Universiti Sains Malaysia have done proteomic profiling on *Haruan* extract and found out that 25% and 26% of the total protein detected in freeze- and spray-dried *C. striatus* extract respectively are actin, myosin, and tropomyosin²⁷. A recent study has also shown that actins are essential for a range of cellular functions including; the maintenance of cell shape, polarity, cell division, cytokinesis, vesicle and organelle movement, cell signaling, establishing and maintaining cell junctions, and the regulation of transcription²⁸. And this process is postulated to take effect during the process of re-epithelialisation, which is part of proliferative phase during a healing process²⁸.

It is also known that actin acts in synchrony with myosin in promoting wound healing. This biomechanical process in driving cell motility has previously been shown²⁹.

Tropomyosin, which controls the isoform-specific regulation of diverse actin filaments, is also suggested to play a role during wound healing³⁰. This finding is also confirmed by Lees *et al*³¹, in their report on the role of tropomyosin as a regulator of actin functioning during the process of wound healing.

So it is possible that actin, myosin and tropomyosin, which can be found in *Haruan*, contributed to the expedition of the wound healing process.

Two types of collagen, namely type I and type II, have also been detected in *Haruan* through proteomic profiling^{27,32}. Collagen is a well-known substance that gives tensile strength during wound healing. In fact, it has been shown that collagen and other components of the extra-cellular matrix mainly formed the granulation tissue³³. It is said that the granulation tissue then contracted, slowly closing the wound, and at the same time aligning the collagen fibres in the extracellular matrix³³. This leads us to believe that the collagen found in *Haruan* promotes the maturation of granulation tissue, and hence, expedite wound healing.

Apart from the healing properties, *Haruan* has also been proven to promote the quality of life of patients' post-CABG. The HRQOL study shows that there was significant change in the energy, pain, emotion and physical level.

These findings demonstrate the much-acclaimed "rejuvenating effect" of *Haruan*. It is not an exaggeration to propose that the high content of fatty acids and certain amino acids coupled with

the anti-nociceptive effects^{34,35} might have indicated that they somehow contributed to the natural well-being of patients' post-CABG.

Conclusion

Our clinical study, though laborious, has demonstrated the effects of using *Channa striatus*, a local fish known as *Haruan*, which is easily processed into capsules in promoting wound healing, reducing pain *via* its anti-nociceptive effect and improving quality of life of patients after coronary artery bypass grafting surgery. This is the first randomized, double blind clinical trial being conducted on this matter although there have been anecdotal evidence on the efficacy of *Haruan*. It is inferred that a faster recovery from surgery confers an advantage in terms of resources to an overall economic benefit. Reduction in the percentage of wound infection also resulted in reduced hospitalization cost. We believe this will lead to the successful commercialization of *Haruan*, which could be reared commercially as a nutraceutical product.

Data availability

Dataset 1 - Health Related Quality of Life for all participants
[10.5256/f1000research.13372.d196593](https://doi.org/10.5256/f1000research.13372.d196593)³⁶

Dataset 2 - Surgical wound healing data for all participants
[10.5256/f1000research.13372.d196594](https://doi.org/10.5256/f1000research.13372.d196594)³⁷

Competing interests

No competing interests were disclosed.

Grant information

This study was funded by Monash University Malaysia under Major Grant, CRM279.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgment

We would like to acknowledge the full cooperation of the Surgeons at the Cardiothoracic Department of the National Heart Institute, Kuala Lumpur, the nursing staff especially those of the Cardiac Intensive Care Unit, High Dependency Unit, Surgical Wards and Surgical Clinics and to the staff of the Research Department for making this study a success. We would also like to acknowledge the massive contribution of the late Prof Saringat Baie in developing the *Haruan* capsules. His work is now being continued by his protégé Dr Mohd Nazri Ismail at the Analytical Biochemistry Research Centre, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia. He is contactable at mdnazri@usm.my.

Supplementary material

Supplementary Material 1 – definition of ASEPSIS

ASEPSIS is an acronym for Additional treatment, the presence of Serous discharge, Erythema, Purulent discharge and Separation of the deep tissue, the Isolation of bacteria and the duration of inpatient Stay. Points were allotted to the ASEPSIS system for the extent of wound disturbance showing serous (0–5) or purulent (0–10) exudate, erythema (0–5), and separation of the deep tissues (0–10). Points were also added up for criteria up to three months following surgery: antibiotic treatment, 10 points; drainage under local anaesthetic, 5 points; debridement under general anaesthetic, 10 points; positive microbiology isolate, 10 points; extended hospital stay beyond ten days due to wound infection, 5 points. The total score will then be used to reflect the severity of infection as shown:

0–10: satisfactory healing

11–20: disturbance of healing

21–30: minor wound infection

31–40: moderate wound infection

> 41: severe wound infection

Supplementary Material 2 – Protocol for the current study

[Click here to access the data.](#)

Supplementary Material 3 – Completed CONSORT checklist

[Click here to access the data.](#)

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Reviewer Report 23 March 2020

<https://doi.org/10.5256/f1000research.14518.r61255>

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Brian Olshansky

¹ Mercy Hospital- North Iowa, Mason City, IA, USA

² University of Iowa hospitals and clinics, Iowa City, IA, USA

³ Covenant Hospital, Waterloo, IA, USA

The reviewer congratulates the investigators for undertaking a challenging study that considers wound healing in patients undergoing coronary artery bypass graft surgery. The authors delineate the methodology for performing this double-blind randomized placebo-controlled trial that compares use of the Haruan fish extract to a placebo to evaluate wound healing and quality-of-life in patients undergoing coronary artery bypass graft surgery. The authors state that wound healing is a primary problem in surgical cases and, based on preliminary information, they study the Haruan fish extract. It would be good to have a standardized extract to test and to determine which may be the active components of this extract. In this study, the design seems reasonable and the outcome measures of wound pain mobilization and health-related quality-of-life using the Nottingham Health Profile is appropriate. In the abstract, the authors state that those who received the Haruan capsule showed better wound healing and had better pain scores as well as improvement in quality-of-life. The analyses seem appropriate as does the determination of the size of the study. Unfortunately only 72.3% completed the study in up to three months of follow-up. Additionally, the study applies mainly to males of the Malay background. Unfortunately, in the results section, there is very little evidence that the Haruan capsule actually had any benefit. It would be good to have some tables and charts demonstrating the efficacy, or not, with Haruan capsule. With regard to mean hospital stay, the results were not significant. Perhaps the study was underpowered to determine significance but, nevertheless, the results were not significant. In terms of the ASEPSIS score, there were no significant differences throughout the follow-up. Additionally, there were no significant differences in mean pain score using the visual analog scale and no difference in mobilization. With regard to the health related quality-of-life, there were no significant differences at discharge and in follow-up. Therefore, this reviewer is puzzled that the abstract states benefit when the results do not show this. Much of the issue may be related to limitations but this manuscript does not confer evidence that the Haruan capsule actually has benefit. Further, any hypothesis that wound healing would be improved by the Haruan extract is not supported here. In the discussion there is enthusiasm about using this Haruan extract with

statements that this extract actually improves wound healing but it did not. This reviewer does not understand how the authors can implicate benefit or even discuss mechanisms when there is no evidence based on the results that this actually works. One other thing relates to the costs of hospitalization mentioned in the conclusion but not discussed in any detail in the manuscript.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, electrophysiology, alternative medical therapies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 30 April 2019

<https://doi.org/10.5256/f1000research.14518.r44565>

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Mahmood Moshiri

Next Pharma Inc., Toronto, Ontario, Canada

Kiarash Moshiri

Richmond Biotechnology Inc., Richmond Hill, ON, Canada

I think this is an excellent paper and is adding more knowledge to the literature. I really like the conceptualization of assessing the effect of *Haruan* fish extract (*Channa striatus*) on chest and leg

wounds post-coronary artery bypass grafting (CABG) surgery. Dr Musa and his co-authors have discussed appropriately in the context of the current literature. Interestingly, the authors have used suitable methods and in my opinion, they have provided sufficient information and source data to allow other researchers to repeat different steps of wound healings in other organs of the body. I believe, no additional changes are required. The design, including sample size, wound infection, mobilization, health related quality of life, production of *Haruan* capsules, specifically the flow chart, and the methods, are perfectly prepared. Results are presented accurately and the conclusions are justified and supported by the data.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pathologist, Cardiovascular Pathology Experience (10 years), Clinical Nutritionist (FICN).

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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