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Research paper

The effect of *Syzygium aromaticum* flavonoid-rich fraction on wound healing

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ABSTRACT

Context: Recent studies have shown that the aqueous extract of *S. aromaticum* contains many flavonoids and can still be used for wound healing**.** ***Objective:*** to test *S. aromaticum* flavonoid fraction on wound healing. ***Methods:*** was extracted and analysed for flavonoid content. The fraction was then used in an in vivo wound healing study. In addition, 20 Sprague-Dawley rats weighing 250 to 300 g were used for the in vivo study. Dorsal excisional wounds of approximately 0.8 cm in length were created in each of the five planned groups of rats. The wound area and healing activity were observed every day for up to 10 days. ***Results***: flavonoid fraction heals wounds in rats. ***Conclusion:*** flavonoid fraction of *S. aromaticum* has the potential to be an ingredient for wound healing drugs

Keywords: *Syzygium aromaticum*; wound healing;

INTRODUCTION

Wound healing is a complex biological process in which several phases are interwoven: hemostasis, inflammation, proliferation and remodelling (Li *et al.*, 2007). The efficacy of the *S. aromaticum* FRF treatments in this study may result from their ability to substantially alter one such phase, particularly in exacerbating chronic inflammation and triggering collagen deposition, an essential element for scar-free healing (Singer and Clark, 1999; Broughton *et al.*, 2006). Wounds are physical disruptions to the continuity of the skin following a traumatic injury that result in tissue separation (Chhabra *et al.*, 2017). Wounds heal in phases caused by different biological responses and related to external factors such as the type, size and depth of the wound (Kolimi *et al.*, 2022). Biological research has found that wound healing is a series of processes, namely inflammation, proliferation and

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remodelling (Rodrigues *et al.*, 2019; Muñoz-Torres *et al.*, 2025). This healing process requires the integration of multiple cell populations, growth factors and extracellular signals (Rodrigues *et al.*, 2019).

Another aspect of wound healing is also about accelerating the healing process, both functionally and cosmetically (Tottoli *et al.*, 2020). Angiogenesis is very important for the formation of granulation tissue, as it supplies the wound with the necessary oxygen and nutrients (Johnson and Wilgus, 2014). Impairment of angiogenesis leads to slower wound healing and higher complication rates (Shi *et al.*, 2023). A commonly practised approach to wound care is the use of sterile saline, which is one of the most well-known and non-toxic cleansing agents as it is isotonic, biocompatible and does not destroy tissue during the healing process (Fernandez *et al.*, 2022). Another new product for wound healing is hydrogel, which has the potential to take over the moist healing environment in wounds (Wang et al., 2023; Arshad *et al.*, 2024). One of the reasons for using hydrogels is that they penetrate deep into the wound and form an impermeable barrier against bacterial invasion, which in turn promotes rapid wound closure (Kamoun *et al.*, 2017). The hydrogel becomes moist upon activation and begins to relieve pain, cool the injured area and provide relief (Gounden and Singh, 2024).

Nowadays, the use of herbal products for wound healing has become increasingly popular due to their minimal side effects (Pathak and Mazumder, 2024). In Malaysia, several herbs are recognised for their ability to aid wound healing. One of them is *Syzygium aromaticum* (L.) Merr. & Perry (*S. aromaticum*), commonly known as clove. It is believed to have medicinal value in the treatment of wounds (Cortés-Rojas *et al.*, 2014). Clove is extracted from the flower of the myrtle family and dried as a bud (Lone *et al.*, 2022). Eugenol is a bioactive compound found in cloves and has antimicrobial, anti-inflammatory, antioxidant and anaesthetic effects (Nisar *et al.*, 2021). Due to these effects, *S. aromaticum* could be effective in wound healing (Kowalewska and Majewska-Smolarek, 2023). It may also support tissue regeneration by simultaneously reducing oxidative stress, inflammation and microbial infections (Liñán-Atero *et al.*, 2024). An earlier study by Alanazi *et al.*, (2022) showed that *S. aromaticum* oil can improve wound healing. In addition, many studies have reported that the extract of *S. aromaticum* can inhibit bacterial growth and accelerate wound healing (Abdul Aziz *et al.*, 2023). However, this study focused only on its essential oil.

In this study, the focus was on the aqueous extract of *S. aromaticum*, which was a waste product after the extraction of the essential oil. This aqueous extract was then filtered for the isolation of the flavonoid-rich fraction (FRF). Preclinical reports suggest that this highly concentrated flavonoid fraction may cause accelerated wound contraction and promote scar formation (Zulkefli *et al.*, 2023). Therefore, the efficacy of *S. aromaticum* FRF in wound healing was investigated in this study. In addition, this study will also shed light on natural alternatives for wound treatment with *S. aromaticum* FRF.

METHODS

Preparation of S. aromaticum flavonoid-rich fraction (FRF)

The buds of *S. aromaticum* were purchased on the market and subjected to extraction to obtain the essential oil according to a method by Haro-González *et al*. (2021). In this study, the aqueous extract obtained as a residue from hydrodistillation was used as the sample to be tested. The buds of *S. aromaticum*

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were washed, dried at 50°C for 48 hours and then pulverised. The powder was weighed as 100 grams and mixed with distilled water at a ratio of [1:10] (w/v). The solution was then transferred to a hydrodistillation unit and heated at 100°C for 3 hours until the essential oil was distilled. The aqueous solution of the *S. aromaticum* extract was collected and filtered with a muslin cloth to remove insoluble particles. The filtered solution was concentrated at 55°C using a rotary evaporator. After evaporation, ethanol was added to the concentrated extract in the ratio [1:3] (v/v, extract: ethanol). The insoluble particles were then separated by centrifugation at 3000 rpm for 20 minutes. The supernatant liquid was collected and evaporated to obtain FRF. The FRF was dried under vacuum at 55°C and stored in an airtight container until use.

Estimation of total flavonoid content

The method of Harborne *et al.*, 1998 was used to estimate the total flavonoid content. First, 5g of *S. aromaticum* FRF sample was extracted using 60 ml of chloroform. The filtered extract was evaporated to dryness using a rotary evaporator. The sample was dissolved in 2 ml of ether and added with 2 ml of 10% ammonia solution. The color change was noted after the sample was dissolved by shaking.

Grouping of animal models

The study design and procedures were conducted according to the guidelines of the FRIM Institutional Animal Care and Use Committee (IACUC). Ethical approval to conduct this procedure was granted by the IACUC-FRIM (approval number: IACUC-FRIM/01/3b-2022). Initially, 20 healthy adult male Sprague-Dawley rats weighing 250-300 g were used for this study. The rats were divided into five groups of four rats each. This study was conducted to investigate the effects of the different treatments on wound healing. The treatment groups were: Group 1, *S. aromaticum* FRF, treated daily; Group 2, *S. aromaticum* FRF, treated every two days; and Group 3, *S. aromaticum* FRF, treated every three days. Meanwhile, the positive control group was treated with a hyaluronic acid-based hydrogel, while the negative control group received normal saline.

Excision wound model

The excisional wound model was performed according to the protocol of Mittal *et al*. (2016). Anesthesia was administered by intraperitoneal injection of Dolethal® (200 mg/ml) and was maintained until the rat became unconscious. The dorsal hair of each rat was shaved and cleaned. Excisional wounds of approximately 0.8 cm in diameter were created on the dorsal side using a sterile scalpel. The wounds were disinfected and the treatment was administered. The experiment was continued for 10 days. The wound area was measured once daily with a ruler, and each result was carefully recorded for each animal in all groups.

Measurement of wound contraction

Wound contraction was assessed by daily measurement of the wound diameter according to the method of Ahmad *et al.*, 2021. The wound area was traced with a 15 cm ruler and images of the wound were taken for analysis. The rate of wound closure was calculated based on the changes in wound area over time, indicating the rate of epithelialization and overall progress of wound healing. All measurements were recorded throughout the 10-day study period and statistically

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analyzed to evaluate the effectiveness of the treatments.Measurements were taken at specific time intervals, namely on Days 1, 3, 5, 7, and 10.

RESULTS

Estimation of total flavonoid content

Flavonoids were detected.

Measurement of wound contraction

In this study, the results of the reduction in wound size in the FRF treatments (Treatment 1, Treatment 2 and Treatment 3) showed the remarkable and significant potential of these treatments in promoting wound healing compared to a positive and negative control group. While the positive control group consistently reduced their wound size, the negative control group which was treated with normal saline only showed much slower progress, indicating the limited ability of untreated wounds to heal naturally (Frykberg and Banks, 2015; Morton and Phillips, 2016). Group 1 was more effective than the positive control, which was applied until day 10. A notable acceleration in healing was noted between days 3 and 5. There was no significant difference between treatment 1 and the positive control during the trial period. This result suggests that treatment 1 may increase the rate of progression, especially in the early stages of healing, which are critical and involve a lot of inflammation and proliferation processes (Guo and DiPietro, 2010). This healing process was consistent with previous work that focused on the importance of a moist environment and active wound treatment to facilitate optimal tissue regeneration (Atiyeh *et al*., 2002; Boateng *et al*., 2008). This rapid closure achieved by treatment with *S. aromaticum* FRF could be due to the ability of the sample to increase the angiogenesis process, control and modulate the activity of reactive oxygen species (ROS) such as H_2O_2 and promote keratinocyte migration, which is crucial for wound healing (Gonzalez *et al*., 2016; Martin and Nunan, 2015). In addition, treatment of samples with high flavonoid content could also target cellular signalling pathways involved in healing, as discussed by Das and Baker (2016).

In addition, Figure 3 shows that healing in the negative control group was slower throughout the study and the reduction in wound diameter was less consistent than in the other groups. In the positive control group, there was a more rapid reduction in wound size due to the hydrogel treatment, particularly between days 2 and 7. Interestingly, treatment 1 and treatment 3 mirrored the healing trend of the positive control and had some potential for faster wound closure. Treatment 2, however, achieved similar results to the positive control, but the wound size was slightly smaller in the first few days (days 1–3), which was made up for after day 4. On day 10, the wounds were almost healed in all groups except the negative control. These data indicate that treatment with *S. aromaticum* FRF, especially treatment 1 and treatment 3, can promote wound healing just as well as the positive control.

Table 2 shows that the different treatment groups had different wound closure rates in per cent. The negative control group showed the slowest healing with only 88.37% wound closure on day 10, which can be attributed to slow natural healing without any treatment support (Frykberg and Banks, 2015). In contrast, the positive control group accelerated wound healing with 93.47% wound closure at day 10, demonstrating the effectiveness of any standard wound treatment to

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support natural tissue repair through their ability to reduce inflammation and promote tissue remodelling (Singer and Clark, 1999).

Treatment 1 achieved the highest healing rate with 100% wound closure at day 10. After day 5, this group also showed remarkable improvement, achieving 69.77% wound closure and 79.07% at day 7, suggesting that the treatment acted on both the rapid inflammatory and proliferative phases. These results support studies emphasising the role of bioactive flavonoids in promoting fibroblast proliferation and re-epithelialization during wound healing (Guo and DiPietro, 2010; Gonzalez *et al.*, 2016).

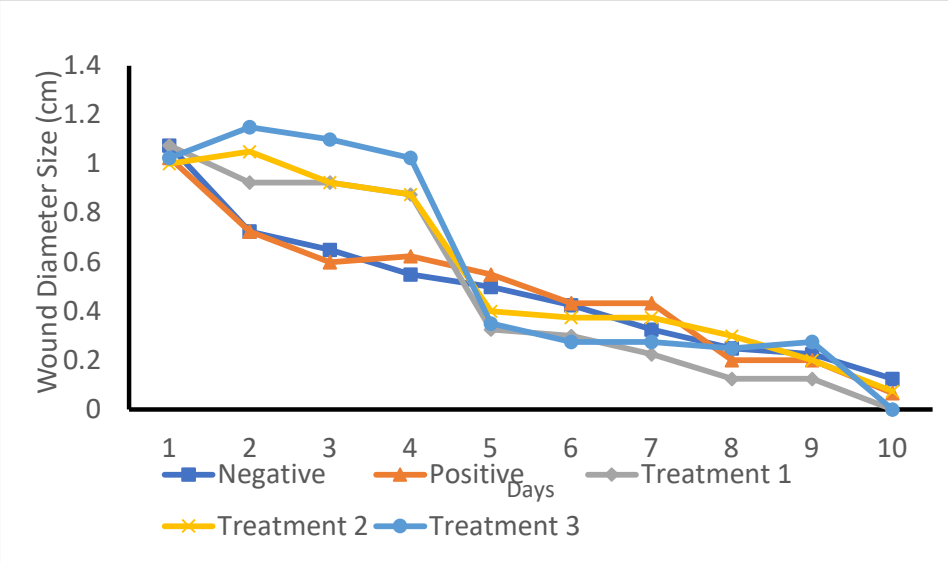

Figure 3: The wound healing progression for the five groups (Negative, Positive, Treatment 1, Treatment 2, and Treatment 3) was monitored over 10 days.

Groups	Day 1	Day 2	Day 3	Day 5	Day 10
Negative control	0	39.53	53.49	69.77	88.37
Positive control	0	41.46	46.34	57.76	93.47
Treatment 1	0	13.95	69.77	79.07	100
Treatment 2	0	7.5	60	62.5	92.5
Treatment 3	0	-7.32	65.85	73.17	100

Table 2: Wound closure progression percentages for each group over Days 1, 3, 5, 7, and 10.

In addition, group 2 showed progressive but effective healing. At day 10, treatment 2 achieved 92.5% wound closure, with a gradual increase from day 3 (7.5%) to day 7 (62.5%). The overall effect was similar to the positive control, making it a good candidate for clinical use, albeit slightly slower than treatment 1. This result may be due to the ability of the treatment to modulate key mediators of angiogenesis and collagen synthesis, two essential components of wound contraction (Eming *et al.*, 2014). Interestingly, treatment 3 showed some inconsistencies at the beginning of the study, as wound size initially increased on day 3 (-7.32%), but then closed completely by day 10 (100%). Initially, the observed

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increase could be due to transient inflammation or variability in measurement, as in other studies on wound healing dynamics (Velnar *et al.*, 2009). However, a wound closure of 65.85% was achieved on day 5, which increased steadily to 73.17% by day 7, indicating a delayed but significant efficacy of the treatment. This is consistent with other studies showing that delayed onset of healing due to sustained activation of growth factors can still lead to successful tissue repair (Li *et al.*, 2007; Das and Baker, 2016).

The increased efficacy of treatments 1 and 3 in promoting complete wound closure provides evidence for further improvement as therapeutic candidates for enhanced wound healing compared to the positive control. This is also consistent with previous findings that flavonoids can influence certain molecular signalling pathways involved in cell migration, angiogenesis and extracellular matrix remodelling (Bui *et al.*, 2014; Zulkefli *et al.*, 2023). The insignificant difference in performance between the FRF treatment and the positive control group also underlines its clinical relevance as a potential alternative to existing wound care therapies (Sen *et al.*, 2009).

Future research studies should be conducted to identify the molecular processes of FRF activity during wound healing. FRF should have the therapeutic potential to regulate inflammatory cytokines, enhance angiogenesis and increase collagen deposition. Such further studies need to be conducted with larger sample sizes and longer observation periods to obtain further confirmatory evidence of the long-term efficacy of the treatment and its impact on scar formation (Eming *et al.*, 2014; Guo and DiPietro, 2010). In addition, biochemical studies need to be conducted to help verify the molecular signalling pathways that are activated by FRF treatment. For example, the quantitative measurement of levels of pro-inflammatory cytokines and growth factors such as VEGF or TGF-β as a result of FRF therapy (Thomas, 2001; Shai and Maibach, 2005). Ultimately, long-term assessment of the quality of the scar and restoration of functional tissue will determine whether it will be useful in clinical practice. The application of modern wound healing techniques, which have been described in many studies, may help to solve the increasing problems in the healing of chronic and acute wounds.

CONCLUSION

The results indicate that treatment with *S. aromaticum* FRF could accelerate wound healing. FRF treatment has proven its value as an alternative or possible improvement to conventional wound therapies. This study has demonstrated that treatment with FRF has the potential for effective wound reduction, which may lead to further innovations in wound care.

DECLARATIONS OF INTEREST

None

DECLARATION OF HONOUR

We declare in our honor that our results are not fake and made up.

AI ASSISTANCE DISCLOSURE

The authors used [ChatGPT/GPT-5] to improve the clarity and readability of the manuscript. The authors carefully reviewed and edited the content to ensure accuracy and take full responsibility for the final text.

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