Macrophage-regulating cream - ON101 (*Plectranthus amboinicus/Centella asiatica*) as an adjunct for hard-to-heal lower limb wounds: A single-centre real-world experience

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Background: The management of lower limb wounds remains a significant clinical challenge, sometimes characterised by impaired healing and macrophage dysfunction. This study evaluates the preliminary efficacy and safety of ON101 topical cream, a novel macrophage-regulating cream containing *Plectranthus amboinicus/Centella asiatica* extract, as an adjunctive treatment for hard-to-heal lower limb wounds.

Methods: A retrospective analysis was conducted on 13 patients with hard-to-heal lower limb wounds at a single institution in Singapore. Following surgical debridement as required, wounds were treated with ON101 cream, which modulates macrophage activity to promote a pro-healing environment, alongside standard wound care. Wound areas were measured at baseline and at two, four, and eight weeks post-treatment initiation.

Results: Use of the macrophage-regulating cream resulted in a statistically significant wound area reduction at two weeks (mean 39.9%, p=0.0189), four weeks (54.2%, p=0.0286), and eight weeks (73.8%, p=0.0388). Complete wound healing was achieved in 9 out of 13 patients (69.2%). The cream was easily applied and well tolerated, with no documented adverse effects or allergic reactions.

Conclusion: This early clinical experience suggests that ON101 cream, by targeting macrophage regulation, is an effective and safe adjunct therapy that significantly enhances healing in lower limb wounds. These promising results support its therapeutic potential and justify further investigation in larger, prospective trials.

Key words
- Centella
- Debridement
- Diabetes complications
- Diabetic foot
- Macrophages
- Peripheral vascular diseases
- Skin ulcer
- Wound healing

Acute wounds typically heal within four to six weeks through four overlapping phases: coagulation, inflammation, proliferation and remodelling (Wallace et al, 2025; Eming et al, 2014; Falanga, 2005). Inadequate progression through these critical phases culminates in suboptimal wound healing, leading to chronic wounds. Chronic wounds are notoriously challenging to treat and are characterised by persistent infections, prolonged inflammatory responses, microbial biofilms and dermal or epidermal cells that lack responsiveness to reparative stimuli (Ongarora, 2022). The complexity of these wounds is often compounded by underlying comorbidities, such as diabetes and peripheral vascular disease, that cause impaired arterial, venous or neuropathic processes (Serjeant et al, 2005; Papi and Papi, 2016), which can impede the natural healing process and lead to complications, including chronic wounds and limb loss (Boulton et al, 2005). Most of such chronic wounds manifest on the lower extremities (Eming et al, 2014). As a result, the management of lower limb wounds requires a multifaceted approach that addresses both the wound itself and the underlying conditions contributing to delayed healing. Given the extended duration of wound healing, there is a continuous search for innovative adjunctive therapies that can enhance and hasten the wound healing process and promote limb salvage. These adjuncts may include advanced dressings, biological agents and topical treatments that aim to accelerate tissue regeneration and improve overall wound outcomes (Murphy and Evans, 2012). As the landscape of wound management evolves,

it is imperative to explore and validate new treatment modalities that can effectively address the complexities associated with lower limb wounds, ultimately improving patient outcomes and reducing the burden of chronicity (Jeffcoate et al, 2018).

Aim

The aim of our study was to review our experience using a novel macrophage-regulating topical cream (ON101) in treating hard-to-heal lower limb wounds.

About ON101 cream

The ON101 cream has emerged as a promising novel adjunct for optimising wound healing in lower limb injuries. The cream contains the active substances 1% *Centella asiatica* and 0.25% *Plectranthus amboinicus* extract-F4 (PA-F4). Other ingredients include cetyl stearyl alcohol, liquid petrolatum, methyl paraben, propyl paraben, Span 60, Tween 60, propylene glycol, white petrolatum and purified water (Health Sciences Authority, 2023). It significantly enhances the reparative mechanisms associated with wound healing by expediting the transition from the inflammatory phase to the proliferative phase, concurrently facilitating the chemokine-mediated alteration of the microenvironment from a milieu predominantly characterised by M1 macrophages to one substantially governed by M2 macrophages (Kotwal and Chien, 2017). This transition is of paramount importance, given that M2 macrophages are integral to tissue repair and regeneration, thereby facilitating the overall healing continuum in lower limb wounds (Boniakowski et al, 2017).

Materials and methods

Study design and population

The study was a retrospective review of patients with lower limb wounds that were prescribed ON101 cream as an adjunct in wound therapy by a multidisciplinary team. The team included doctors from Vascular Surgery and Orthopaedic Surgery, specialty wound nurses and podiatrists.

Inclusion criteria included wounds located over the lower limbs. Wounds needed to be deemed hard-to-heal (one that fails to heal with standard therapy in an orderly and timely manner) for ON101 cream to be initiated. Wounds of different aetiological types were considered, including arterial ulcers, venous ulcers, mixed arteriovenous, neuropathic and neuroischaemic ulcers. Wounds resulting from minor amputation, surgical debridement, trauma or pressure injury were also included.

Exclusion criteria involved patients with documented non-compliance with medications, off-loading precautions or defaulted on dressing changes at the time of enrolment. Subsequent non-compliance during treatment was recorded and considered when evaluating clinical outcomes. Radiation or malignancy-related wounds were excluded. Wounds with abscesses, cellulitis or clinical signs of active clinical infection were excluded, although they could be included following surgical debridement or minor amputation and a positive tissue culture did not preclude the use of ON101 cream as a treatment adjunct.

As this was a retrospective case series involving analysis of routinely collected data, ethics approval was waived according to institutional policy (NHG Domain Specific Review Board).

Intervention and measurement

Culture-directed antibiotics and surgical debridements or minor amputations were performed as deemed necessary by the multidisciplinary team. Revascularisation was performed for patients with significant peripheral arterial disease, as required by the vascular surgery team.

ON101 cream (Fespixon®; Oneness Biotech Co, Ltd, Taiwan) was prescribed for use over a wound during regular wound dressing, with frequency ranging from every other day to once a week, depending on the clinical status of the individual patients' wounds and the frequency of dressing changes. The length, breadth and areas of the wounds were manually measured with a ruler and measurements were taken prior to the initiation of ON101 cream, at two weeks post-initiation, four weeks post-initiation and at the eighth week mark. Absolute reduction in wound area (cm^2) after the second, fourth and eighth weeks was recorded and the percentage reduction of the wound area at these time points since the initial wound was also recorded. The duration required for complete healing or definitive closure, wherein the wound could undergo secondary or delayed closure, was also documented, if present. The need for any major amputations and morbidities/mortalities since the initiation of ON101 cream for the patients was also noted down. Patients were monitored fortnightly in the outpatient clinic to assess for complete epithelialisation of wounds or until the wound area was considered sufficiently reduced to attempt secondary closure.

Statistical analysis

Statistical analysis was conducted using

Scan the QR code to access Table 3.

GraphPad Prism version 10.5.0 (673) for macOS (GraphPad Software, San Diego, California, USA). The one-tailed paired Student's t-test was performed on continuous variables to assess whether a statistically significant difference existed in absolute wound areas between baseline and subsequent follow-up time points (initial wound area and wound area at week two; initial wound area and wound area at week four; initial wound area and wound area at week eight). A p-value of less than 0.05 was considered statistically significant. For the study population, the mean and standard deviation were reported when the data set followed a normal distribution. However, if the data deviated from the normal distribution, the median and interquartile range (IQR) are used instead.

Results

Patient demographics and baseline characteristics

The cohort consisted of 13 patients, 11 males and 2 females, with a median age of 60 and an IQR of 13 years and a total of 13 lower limb wounds. The majority of the patients (92.3%) had diabetes, with a median HbA1c of 8.3% and an IQR of 2%. Four (30.8%) of the patients had end-stage renal failure requiring dialysis, ten (76.9%) had hypertension and nine (69.2%) had peripheral vascular disease. Six (46.2%) patients underwent revascularisation. Ten of the wounds were on the foot, while three were on the ankle/calf regions. Patient demographics are shown in Table 1 and comorbidities/baseline characteristics are shown in Table 2.

Table 1. Patient demographics

Characteristic	N (percentage) or median with IQR
Study population	13 (100%)
Male, Female	11 (84.6%), 2 (15.4%)
Median age and interquartile range (IQR)	60 with IQR of 13.00 years
Ethnicity	
Chinese Malay Indian Other races	7 (53.8%) 5 (38.5%) 1 (7.7%) 0
Diabetes	12 (92.3%)
Median Hba1c and IQR	8.3% IQR of 2.0%
ESRF	4 (30.8%)
Hypertension	10 (76.9%)
Smoking history	
Current smoker Ex-smoker Non-smoker	5 (38.5%) 1 (7.7%) 7 (53.8%)
Peripheral arterial disease Revascularisation	9 (69.2%) 6 (46.2%)

Abbreviations: ESRF, end-stage renal failure; N, number

Wound area and wound area mean percentage reduction

Significant reductions in wound areas were documented across the wounds in this study. At the two-week mark, there was a mean wound area decrease from 6.76 cm² to 3.82 cm² (p=0.0189), corresponding to a mean reduction of 39.9% from the initial wound. At the four-week mark, there was a mean decrease in wound area to 3.33 cm² from baseline (p=0.0286), corresponding to a mean reduction of 54.2% since the start. At the eight-week mark, there was a mean wound area decrease to 2.52 cm² (p=0.0388), indicating a 73.8% reduction from the initial wound [Figure 2]. Individual patients' wound areas are also available in Figure 1.

Nine patients attained wound closure, including one who underwent secondary surgical closure, with a median recorded time to closure of 57 days. Two patients achieved complete wound healing at week four, and five patients had achieved complete wound healing by week eight. One patient underwent secondary closure of the wound but subsequently had wound dehiscence at the site of closure. Of the four patients who did not attain complete wound healing, three were initially compliant with the prescribed treatment regimen and therefore fulfilled the study inclusion criteria. However, these patients subsequently became non-compliant with either ON101 cream application or off-loading measures during the course of treatment. Of these, one patient underwent a calcanectomy due to complications of calcaneal osteomyelitis. There were no major limb amputations. One patient had a persistent chronic wound that is currently still undergoing wound review. One individual succumbed to mortality three months following the attainment of complete wound healing, due to an unrelated aetiology. No allergic or adverse reactions were observed with ON101 cream. A summary of the wound characteristics and clinical outcomes is shown in Table 3.

Case studies

Here we present six cases from the study

Table 2. Patient comorbidities and baseline characteristics

Patient	Age	Gender	Ethnicity	Smoker	Comorbidities	HbA1c	Revascularisation
1	60	Male	Chinese	Current smoker	PAD/DM/HTN/IHD/ESRF on HD/APS/Calciphylaxis	8.3	Yes
2	58	Male	Malay	Current smoker	PAD/DM/HTN/IHD/ESRF on HD/Gout	8.4	Yes
3	60	Male	Malay	Current smoker	PAD/DM/HLD	13.8	Yes
4	57	Female	Chinese	Never smoked	PAD/DM/HTN/HLD/ICMP	9.6	Yes
5	62	Male	Malay	Never smoked	HIV/DM/Obesity/recurrent DVT	7.1	No
6	52	Male	Chinese	Ex-smoker	PAD/T1DM/HTN/IHD/ESRF on HD	7.4	No
7	58	Male	Chinese	Never smoked	PAD/DM/HTN/HLD/IHD/ESRF on HD	8.7	Yes
8	70	Female	Chinese	Never smoked	PAD/DM/HTN/HLD/Endometrial Ca	7.7	No
9	71	Male	Chinese	Current smoker	PAD/DM/HTN/HLD/CVA	8.3	No
10	71	Male	Indian	Never smoked	DM/HTN/HLD/CKD/obesity	10.9	No
11	81	Male	Chinese	Never smoked	PAD/DM/HTN/HLD/IHD/CVA	7.4	Yes
12	64	Male	Malay	Never smoked	DM/HTN/HLD/CKD	7.1	No
13	26	Male	Malay	Current smoker	Intramedullary tumor T3-T5 complicated by hemorrhage, underwent urgent decompression laminectomy with evacuation of clot, with poor return of motor function, multiple pressure sores	4.9	No

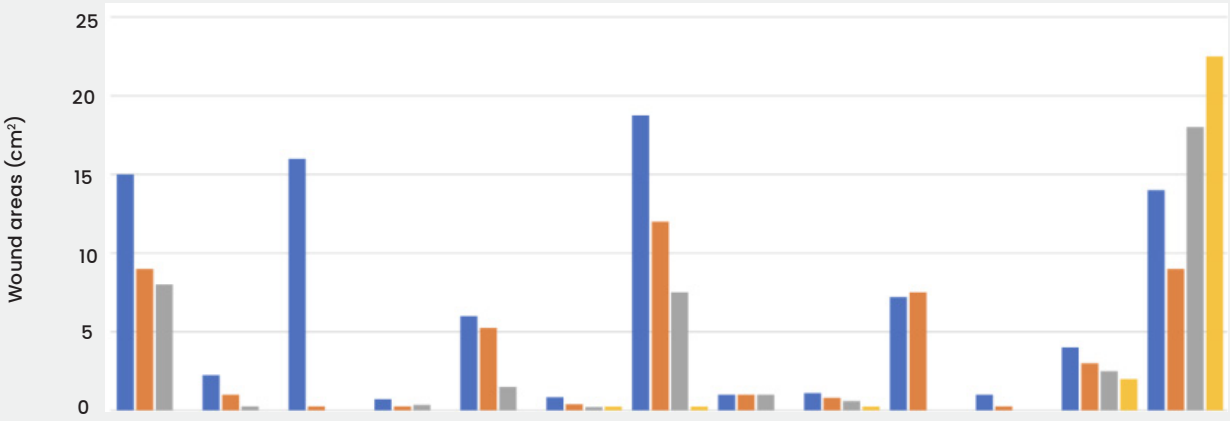
Abbreviations: PAD, Peripheral Arterial Disease; DM, Diabetes Mellitus; T1DM Type 1 Diabetes Mellitus; HTN, Hypertension; IHD, Ischaemic Heart Disease; ESRF, End Stage Renal Failure; HD, Haemodialysis; APS, Anti-phospholipid syndrome; ICMP, Ischaemic Cardiomyopathy; CVA, Cerebrovascular Accident; CKD, Chronic Kidney Disease, Endometrial Ca, Endometrial Cancer; DVT, Deep Vein Thrombosis; HLD, Hyperlipidemia

population, illustrating the background history of their wounds, accompanied by photographic documentation of the wounds, to illustrate their evolution following application of ON101 cream.

Case 1

A 60-year-old Chinese male, currently a smoker with a past medical history of diabetes mellitus, HbA1c 8.3%, peripheral arterial disease (PAD) and end-stage renal failure (ESRF), presented in May 2024 with right third to fifth toe wet gangrene. There was no evidence of osteomyelitis on X-ray. The right Ankle Brachial Pressure Index (ABPI) was 1.14 and the right Toe Brachial Pressure Index (TBPI) was 0.65. The right lower limb arterial duplex showed superficial femoral artery, tibio-peroneal trunk and anterior tibial artery stenosis. He underwent revascularisation of the right lower limb and subsequent right third to fifth toes ray amputation. In view of worsening wound progression, he underwent debridement with right second toe ray amputation and fillet flap. He was subsequently placed on Negative

Wound areas at week 0, week 2, week 4 and week 8 for each individual patient



	1	2	3	4	5	6	7	8	9	10	11	12	13
Week 0	15	2.25	16	0.72	6	0.84	18.75	1	1.1	7.2	1	4	14
Week 2	9	1	0.25	0.25	5.25	0.4	12	1	0.8	7.5	0.25	3	9
Week 4	8	0.25	0	0.36	1.5	0.21	7.5	1	0.6	N/A	0	2.5	18
Week 8	0	0	0	N/A	0	0.24	0.24	N/A	0.24	N/A	0	2	22.5

Abbreviations: N/A, Not applicable - as patient stopped ON101 cream regime prematurely due to non-compliance, or secondary wound healing was achieved.

Figure 1

Figure 1. Patients' wound areas at week 0, 2, 4 and 8.

Figure 2. Mean percentage wound area reduction from baseline following ON101 cream application at weeks 2, 4 and 8. Error bars represent standard deviations (SD).

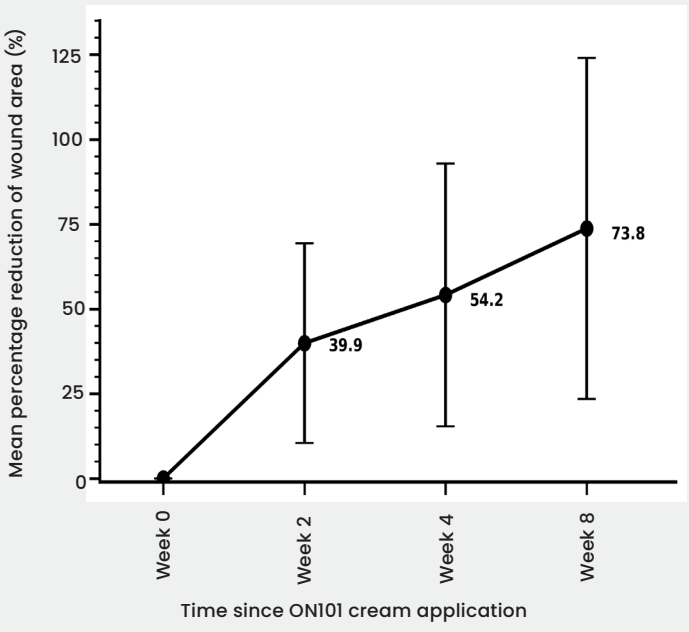


Figure 2 Mean ± SD; n=13 (Week 2), 12 (Week 4) and 10 (Week 8).

Pressure Wound Therapy (NPWT). Wound culture results showed mixed growth and he was started on appropriate antibiotics. The patient presented back two months later, with a non-healing right second to fifth toe ray amputated wound. ON101 cream was started. The wound was reviewed two weeks later, with a significant reduction in size from 2cm × 7.5cm to 1.8cm × 5cm. An approximately 50% reduction in wound area was achieved in four weeks and complete epithelialisation was achieved in 57 days [Figure 3].

Case 2

A 58-year-old Chinese male, non-smoker, with a past medical history of diabetes mellitus, HbA1c 8.7%, PAD and ESRF, presented with left big toe gangrene. There was no evidence of osteomyelitis. Left ABPI was not applicable due to incompressible calcified vessels; TBPI was less than 0.14. The left lower limb arterial duplex showed below-knee vessel disease. He underwent revascularisation of the left lower limb and subsequent left big toe ray amputation. Due to worsening wound progression, he underwent multiple surgical debridements and eventual completion of trans-metatarsal amputation. He was then placed on NPWT until the wound was stable, before going for split skin grafting. Wound cultures grew *Pseudomonas aeruginosa* and he was started on culture-directed antibiotics. ON101 cream was initiated as the skin graft did not fully integrate into the wound bed. Wound review two weeks post-application showed a 36% reduction in wound area from 7.5cm × 2.5cm to 6cm × 2cm. Within four weeks, there was a 60% wound area reduction to 5cm × 1.5cm [Figure 4]. As the wound was located on the weight-bearing surface, off-loading proved challenging for the patient. Complete epithelialisation was finally achieved after 145 days.

Case 3

A 60-year-old Malay male, current smoker with a past medical history of diabetes mellitus, HbA1c 13.8% and PAD, presented with left fifth toe wet gangrene extending to the third and fourth metatarsal. There was also underlying osteomyelitis seen on X-ray. TBPI was 0.31, while ABPI was falsely high due to calcified vessels. He underwent left lower limb angioplasty due to arterial duplex showing multifocal stenosis along the common femoral artery to the below-knee vessels. He then underwent left fourth and fifth toe ray amputation and subsequent split skin grafting. He was treated with only a short course of antibiotics as post-debridement cultures showed no growth.

Poor compliance with wound management after discharge led to wound breakdown. ON101 cream was initiated with a wound size of 8cm × 2cm. Within two weeks, the wound was largely epithelialised and full wound closure was achieved in four weeks [Figure 5].

Case 4

A 52-year-old Chinese male, ex-smoker, with a past medical history of diabetes mellitus, HbA1c 7.4%, PAD and ESRF, presented with a neuroischemic ulcer over the right plantar 1st metatarsophalangeal joint. TBPI was 0.22, while ABPI was falsely elevated due to heavily calcified vessels. Revascularisation was not done as it was clinically deemed to have low benefit. ON101 cream was initiated with interim callus debridement and offloading. Wound size was 1.4cm × 0.6cm on initiation [Figure 6]. There was an approximately 50% reduction in wound surface area to 0.8cm × 0.5cm. However, due to poor offloading compliance, the wound deteriorated slightly while the granulation remained fair. Complete wound healing was achieved in 23 weeks.

Case 5

An 81-year-old Chinese male, non-smoker, with a past medical history of diabetes mellitus, HbA1c 7.4% and PAD presented with a chronic non-healing wound for seven months. The first metatarsal bone on the right foot was exposed, with suspicion of osteomyelitis on X-ray. He underwent revascularisation of the right lower limb and subsequent wound debridement. Post-debridement bone cultures were clear of any bacterial growth. The wound, however, was still healing poorly despite NPWT. ON101 cream was initiated a month after initial presentation for a 1cm by 1cm wound, achieving a wound reduction of more than 50% within a week [Figure 7]. Full wound closure was achieved within three weeks of ON101 cream application.

Case 6

A 26-year-old Malay male, current social smoker, who was dependent on others for activities of daily living and mobilised in the community using a motorised wheelchair following spinal surgery in 2009, presented with a chronic non-healing right foot lateral malleolus ulcer. There was evidence of underlying osteomyelitis seen on X-ray. He underwent three rounds of extensive wound debridement followed by secondary wound closure with NPWT. The surgical site eventually broke down and was left to heal with secondary intention. ON101 cream was initiated 3 months

Figure 3. Case study 1

A. Initial presentation with right third to fifth toe wet gangrene.

B. Initiation of ON101 cream. Wound measurement 7.5cm x 2cm.

C. Two weeks: wound measurement 5cm x 1.8cm.
D. Four weeks: wound measurement 2cm x 4cm.
E. Eight weeks: wound fully epithelialised.

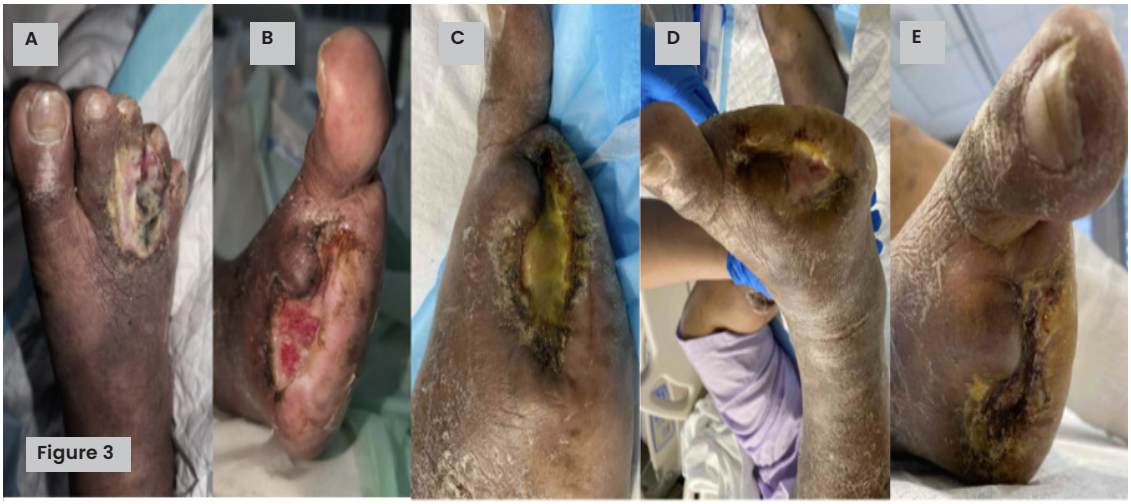


Figure 4. Case study 2

A. Initiation of ON101 cream. Wound measurement 7.5cm x 2.5cm.

B. Two weeks: Wound measurement 6cm x 2cm.
C. Four weeks: Wound measurement 5cm x 1.5cm.
D. Eight weeks: Wound measurement 0.6cm x 0.4cm.
E. Wound fully epithelialised.

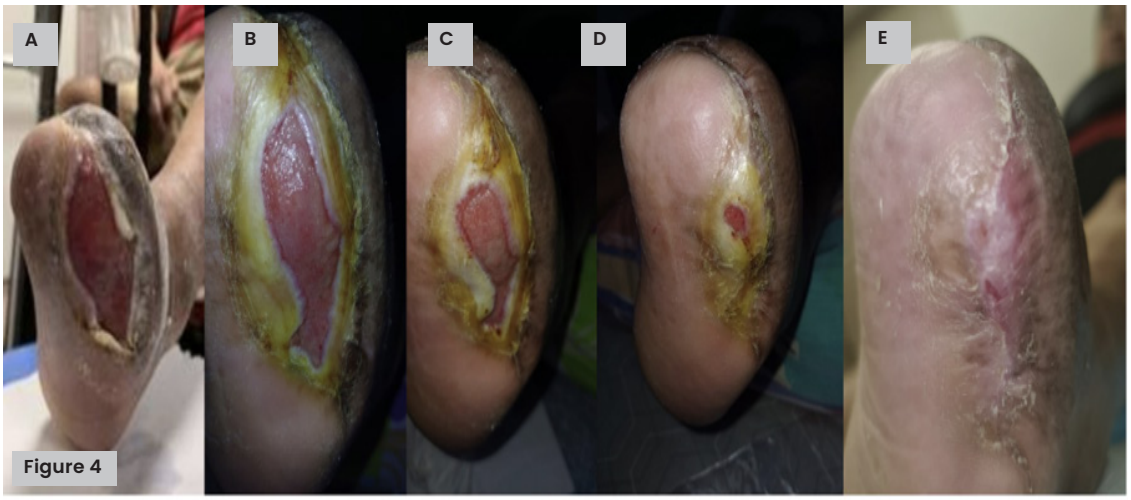


Figure 5. Case study 3

A. Initial presentation.
B. Post SSG review. Wound measurement 8cm x 4cm.
C. Initiation of ON101 cream. Wound measurement 8cm x 2cm.
D. Two weeks: Wound largely epithelialised.
E. Four weeks: Wound fully epithelialised.



Figure 6. Case study 4

A. Initiation of ON101 cream, Wound measurement 1.4cm x0.6cm.
B. Two weeks: Wound measurement 0.8cm x 0.5cm.
C. Five weeks: Wound measurement 1cm x 0.2cm.
D. 12 weeks: Wound measurement 1cm x 0.5cm x 0.3cm.
E. 23 weeks: Wound fully epithelialised.





Figure 7. Case study 5

A. Post-surgical debridement of a chronic non-healing right medial foot wound.

B. Four weeks post NPWT.
C. Initiation of ON101 cream. Wound measurement 1cm x 1cm.
D. Two weeks: Wound measurement 0.5cm x 0.5cm.
E. Three weeks: Full epithelialisation.



Figure 8. Case study 6

A. Application of ON101 cream, Wound measurement 4cm x 3.5cm.
B. Two weeks: Wound measurement 3cm x 3cm.
C. Four weeks: Wound measurement 4cm x 4.5cm.
D. Eight weeks: Wound measurement 5cm x 4.5cm.
E. Wound fully epithelialised.

later with a wound size of 4cm × 3.5cm. The wound responded well, with a 36% reduction in wound surface area within two weeks. The ON101 cream had expired, so treatment was switched to conventional dressings instead. Subsequently, wound healing stalled and the wound size increased to 5cm × 4.5cm [Figure 8]. Given the initial improvement with ON101 cream, he was placed back on it ten months after initial presentation. Full wound closure was achieved four months after he was placed back on ON101 cream.

Discussion

The results of our study show the efficacy of ON101 *Plectranthus amboinicus/Centella asiatica* extract cream as an adjunctive treatment for hard-to-heal lower limb wounds. Prior to initiation of the macrophage-regulating cream, all the cases had multiple interventions with limited success. The significant reductions in wound area observed at two, four and eight weeks post-initiation of ON101 cream and the mean percentage wound area reductions of 39.9%, 54.2% and 73.8%, respectively, show the potential of this topical agent in enhancing wound healing processes. The transition from the inflammatory to the proliferative phase of wound healing, facilitated by the active components of ON101 cream, highlights its role in optimising the wound microenvironment and promoting tissue regeneration (Health Sciences Authority, 2023; Kotwal and Chien, 2017; Boniakowski et al, 2017). Despite the benefits of using the ON101 cream, we also acknowledge that it is essential to consider the broader implications of integrating such adjunct therapies into standard wound care protocols. The multifactorial nature of chronic wounds necessitates a comprehensive approach that not only addresses the wound itself but also the systemic factors contributing to delayed healing, such as diabetes and peripheral vascular disease (Jiang et al, 2020). Furthermore, the role of advanced wound dressings and adjunctive therapies, such as NPWT, should not be overlooked, as they have been shown to significantly enhance healing rates and reduce complications, particularly in patients with complex wound presentations (Zaver and Kankanalu, 2023). By fostering a collaborative, multidisciplinary approach that incorporates innovative treatments like ON101 cream alongside established modalities, healthcare practitioners can optimise patient outcomes and potentially reduce the incidence of chronicity in lower limb wounds.

Limitations

Despite the promising results, our study is not without limitations. Firstly, the retrospective design may introduce biases, as it relies on existing clinical data and may not account for all confounding variables. The sample

size of 13 patients, while providing preliminary insights, limits the generalisability of our findings. Additionally, the exclusion criteria, particularly regarding patient compliance with the ON101 cream regimen and off-loading measures, may have influenced the outcomes. Non-compliance can significantly affect healing rates and thus, future studies should incorporate strategies to monitor and encourage adherence to treatment protocols. The assessment of wound healing was based on manual measurements, which may introduce variability; employing digital imaging techniques could enhance accuracy in measuring wound area changes.

Another limitation is the lack of long-term follow-up data to assess the durability of the healing achieved with ON101 cream.

Conclusion

In conclusion, the findings from our study suggest that ON101 *Plectranthus amboinicus*/*Centella asiatica* extract cream is a promising adjunctive therapy for hard-to-heal lower limb wounds, with a mechanism of action that supports wound healing through the modulation of inflammation and enhancement of tissue repair. As chronic wounds remain a significant clinical challenge, integrating innovative treatments like ON101 cream into standard care protocols could improve patient outcomes, reduce the burden of chronicity and ultimately, decrease the incidence of complications such as limb loss. Further research is warranted to validate these findings and explore the long-term benefits of ON101 cream in diverse patient populations. By doing so, we can improve patient outcomes and reduce the burden of chronic wounds in the healthcare system.

Conflict of interest

All authors declare no conflicts of interest related to this manuscript. No author has any financial or personal relationship with Oneness Biotech Co, Ltd, or any other organisation that could inappropriately influence this work.

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Ethical approval statement

As this was a retrospective case series involving analysis of routinely collected clinical data, ethics approval was waived according to institutional policy by the National Healthcare Group Domain Specific Review Board (NHG DSRB), Singapore. Patient consent was not required for this retrospective review under the institutional waiver policy.

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