

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

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ABSTRACT

Diabetic gangrene, characterized by the pathophysiological triad of neuropathy, ischemia, and infection, remains a principal etiology of lower extremity amputation. Classical Unani medical literature, extending from Hippocratic observations through Avicennian systematic nosology, conceptualized chronic ulceration as a manifestation of humoral temperamental dyscrasia (*su-e-mizaj*) with subsequent accumulation of morbid matter (*mawad-e-fasida*), necessitating both restorative and evacuative therapeutic strategies. This case documents the successful limb salvage of extensive diabetic gangrene through an integrative Unani protocol in a patient presenting with multifactorial wound chronicity peripheral neuropathy, arterial insufficiency, polymicrobial infection, anemia, uncontrolled hyperglycemia, and protein-energy malnutrition. The therapeutic regimen comprised crushed unripe papaya providing papain-mediated selective enzymatic debridement of necrotic tissue, medical-grade honey conferring broad-spectrum antimicrobial activity with osmotic wound conditioning and granulation promotion, and *Hirudo medicinalis* therapy enhancing microcirculation through hirudin anticoagulation and vasoactive peptide release. Complete wound epithelialization was achieved without surgical amputation, demonstrating synergistic mechanisms of proteolytic necrotic tissue dissolution, antimicrobial coverage, angiogenic stimulation, and perfusion optimization. This outcome substantiates the therapeutic validity of traditional Unani pharmacological interventions in refractory diabetic foot pathology, challenging conventional amputation-centric approaches and warranting systematic investigation through controlled clinical trials to establish evidence-based protocols integrating ethnomedical modalities with contemporary wound management paradigms for limb preservation in high-risk diabetic populations.

Keywords: Diabetic foot gangrene, Unani medicine, papain debridement, hirudotherapy, limb preservation, integrative wound management

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Introduction

The prevalence of non-healing ulcers all over the world are in between 1.51 to 2.21 per 1000 people and 13.1% of the general population in developed countries is estimated to be around 1–2%. In the Indian community, the reported prevalence in 2004 was 4.8 cases per 1,000 people [1,2].

The occurrence of chronic ulcers dates back to the earliest records of medical history. Hippocrates, often regarded as the father of medicine, reportedly suffered from a leg ulcer himself. During his time, knowledge of anesthesia, anatomy, and physiology was nearly nonexistent. He managed varicose veins by puncturing them at various points to prevent chronic, non-healing

ulcers. Around 400 BC, he wrote that standing was not advisable for patients with leg ulcers. Centuries later, Avicenna (982–1027 AD) provided an extensive description of diabetes and was the first to identify diabetic gangrene. Between the 10th and 18th centuries, physicians such as Hali Abbas, Avicenna, Falopio, and Pare attributed leg ulcers to the accumulation of black bile or harmful humors, believing that such ulceration played a beneficial role in expelling these noxious substances from the body [3].

In Unani medicine, the term *Qarha* (ulcer) is closely related to *Jarahat* (wound), both of which involve the presence of pus. *Jarahat* (wound) is defined as *Tafarruk-e-ittehal*, the separation or damage of

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

lahem (muscular tissue). The causes of *Jarahat* may be *berooni* (external) or *androoni* (internal). When a *Jarahat* is accompanied by pus formation, it is referred to as a *Qarha* (ulcer).

Unani scholars classify ulcers (*Qurooh*) into three main categories:

1. *Qurooh-e-baseet* (Simple ulcers): These are uncomplicated ulcers not affected by factors that delay the healing process.
2. *Qurooh-e-murakkab* (Compound ulcers): These ulcers are characterized by tissue blackening, pain, and suppuration.
3. *Qurooh-e-Usratul Indamaal* (Non-healing ulcers): These are chronic ulcers with delayed healing, accompanied by progressive tissue damage and localized destruction due to various underlying causes [4].

According to Rabban Tabri, each organ of the body possesses its own *mizaj* (temperament) and performs its functions optimally as long as this *mizaj* remains within normal limits. A core principle of the Unani system of medicine states that when *hararat* (heat) and *ratubat* (moisture) exceed their normal levels, they lead to *ufoonat* (putrefaction) by creating a favorable environment for it. Therefore, it is essential to adopt measures that help in restoring the normal *mizaj* [5].

Wound healing is a complicated process that happens in several stages: stopping the bleeding, reducing inflammation, forming new tissue, and rebuilding the skin. A wound is called chronic when it does not heal properly within about three months and the normal repair process slows down. These wounds can easily get hurt again and may become larger. Chronic wounds cause pain and stress for patients and put a heavy load on healthcare systems. As the population grows older, the number of such wounds is likely to increase. More than half of chronic wounds occur on the feet and include diabetic foot ulcers, pressure sores, and arterial or vein-related ulcers. Injuries caused by explosions or fast-moving projectiles can also lead to long-lasting wounds that are difficult to treat. Today, treatments for chronic wounds include removing dead tissue, using negative pressure therapy, and applying dressings like hydrogels, hydrocolloids, or foam. Because many chronic wounds do not heal easily, there is growing interest in natural and herbal medicines. The World Health Organization notes that more people around the world are using herbal and traditional treatments. In fact, about 80 percent of the world's population uses traditional medicine for basic healthcare. Many medicinal plants have shown the

ability to work with regular antibiotics to fight bacteria and help wounds heal more effectively [6].

Diabetic foot gangrene represents one of the most devastating complications of diabetes mellitus and continues to be a major cause of morbidity and mortality worldwide. It is estimated that approximately 15-25% of diabetic patients develop foot ulcers during their lifetime, with 14-24% of these cases requiring amputation [7].

The pathophysiology of chronic non-healing ulcers is multifactorial and complex. Unlike acute wounds that follow a predictable healing trajectory through hemostasis, inflammation, proliferation, and remodeling phases, chronic wounds remain trapped in a prolonged inflammatory state [8,9]. These wounds characteristically demonstrate elevated levels of matrix metalloproteinases and other proteases that degrade the extracellular matrix, high inflammatory markers including persistent neutrophil infiltration, diminished growth factor activity due to protease degradation, senescent cells with reduced proliferative capacity, and impaired angiogenesis leading to inadequate tissue perfusion [8,10,11]. Multiple contributing factors typically converge to impair wound healing, including bacterial infection and biofilm formation, tissue ischemia from peripheral arterial disease, metabolic disturbances particularly uncontrolled diabetes mellitus, immunosuppression from various causes, neuropathy leading to loss of protective sensation, repeated trauma and pressure, malnutrition and micronutrient deficiencies, and iatrogenic factors including inappropriate wound management [7,9,12].

The development of diabetic foot gangrene involves a complex interplay of three critical pathophysiological factors: peripheral neuropathy (sensory, motor, and autonomic), peripheral arterial disease with critical limb ischemia, and immunological dysfunction predisposing to severe infections [7,9,14]. This triad creates a perfect environment for rapidly progressive tissue necrosis. Minor trauma, often unnoticed due to neuropathy, initiates a cascade of events bacterial invasion leads to local infection, impaired immune response fails to contain the infection, ischemia from arterial disease prevents healing and tissue oxygenation, and progressive tissue necrosis ensues with potential for limb-threatening and life-threatening sepsis [7,12,13]. Young diabetic patients with poor glycemic control, particularly those with lifestyle risk factors such as chronic alcohol consumption, tobacco use, and occupational factors requiring prolonged standing or walking, are at

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

heightened risk for developing severe lower limb complications [15].

The management of advanced diabetic foot gangrene requires a comprehensive multidisciplinary approach [9,10,14]. The fundamental principle involves debridement of necrotic tissue, as it is well established that removal of eschar and dead necrotic tissue from the wound floor enhances granulation and healing by reducing bacterial load, eliminating the physical barrier to healing, decreasing protease activity in the wound, allowing assessment of viable tissue, and stimulating growth factor release [10,16,17,18]. Debridement can be achieved through various methods including surgical/sharp debridement for rapid removal of large amounts of necrotic tissue, enzymatic debridement using commercially available agents, autolytic debridement utilizing the body's own enzymes, mechanical debridement, and biological debridement using medical-grade larvae or leeches [16,17,18,19].

Enzymatic debridement has gained recognition as a valuable adjunct in wound management [16,17]. Collagenase, an enzyme isolated from *Clostridium histolyticum*, possesses the unique ability to selectively digest collagen in necrotic tissue while sparing healthy tissue, making it particularly useful in wounds with adherent eschar [20]. Papain, a proteolytic enzyme naturally found in papaya fruit, requires activation by urea and similarly digests proteins in nonviable tissue while preserving healthy granulation tissue [16,17]. Some papain formulations include chlorophyllin for odor control [16]. While the general consensus indicates that enzymatic and autolytic debridement are slower than surgical methods and most effective in wounds with minimal necrosis, they offer significant advantages as adjuncts to surgical debridement, particularly in patients who cannot tolerate surgery, for wounds in anatomically sensitive areas, and for continuous debridement between surgical sessions [16,17,19,21].

Leeches have proven to be highly effective in treating non-healing ulcers and were recommended by ancient physicians for this purpose [23]. Medicinal leech therapy, also known as hirudotherapy, is a traditional method that has been used since ancient times to treat various diseases. Among the different species of leeches, *Hirudo medicinalis* is the most commonly used. Leeches secrete more than 20 bioactive compounds in their saliva, including hirudin, antistatin, bdellins, eglins, and carboxypeptidase inhibitors. These substances exhibit anti-inflammatory, analgesic, and anesthetic properties,

along with vasodilatory, anticoagulant, platelet-inhibitory, and thrombin-regulatory activities. They also contribute to extracellular matrix degradation and possess antimicrobial effects [22]. One or more leeches are applied to the affected area of the skin to harness the therapeutic properties of their saliva, which is released during feeding. Medicinal leeches have been used for centuries, and the word "leech" is derived from the term "laece," meaning physician. The earliest recorded use of leech therapy dates back to ancient Egypt [23].

This case presentation from Majeedia Unani Hospital, Jamia Hamdard University, New Delhi, documents a challenging clinical scenario that required comprehensive assessment and an intensive treatment approach to attempt limb salvage in a patient with extensive lower limb gangrene.

CASE PRESENTATION

A 38-year-old male professional driver from Sambhal, Uttar Pradesh, working in Dubai, presented to the Surgery OPD of Majeedia Unani Hospital, Jamia Hamdard University, New Delhi, on 31st January 2023, brought on a stretcher due to inability to walk. He complained of blackish discoloration of the right lower limb extending from below the knee to the entire foot, foul-smelling discharge for 1.5 months, severe pain, inability to bear weight, intermittent fever with chills, loss of appetite, and general weakness. The patient reported that about 6 weeks earlier, he had sustained a minor injury to his right great toe while working in Dubai, which initially appeared as a small superficial wound but rapidly worsened despite using over-the-counter antiseptics and oral antibiotics. The condition progressed to involve discoloration and necrosis of the toe, extending to the entire foot and lower leg, accompanied by purulent and foul-smelling discharge. Prior to arriving at Majeedia Unani Hospital, he had consulted several hospitals where limb amputation was advised, but he refused and opted for Unani management instead.

He had a two-year history of Type 2 Diabetes Mellitus managed with Glimepiride-Metformin (Gepride M-2) with poor compliance and irregular monitoring. The patient was also a chronic alcoholic but had quit from 1.5 month (6 weeks). His lifestyle included irregular meal timings, high carbohydrate and fried food consumption, occasional tobacco use, polyuria over the past six months, and minimal physical activity. He was also anaemic and transfused of blood two times. On examination, he appeared acutely ill and distressed. Vital signs showed blood pressure 134/88

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

mmHg, pulse 104/min (regular), respiratory rate 22/min, temperature 101.2°F, and SpO₂ 96% on room air. He had pallor, mild dehydration, and significant pedal edema of the right lower limb. Cardiovascular examination revealed absent dorsalis pedis and posterior tibial pulses on the right side and a weakly palpable popliteal pulse, while all pulses were normal in the left leg. Respiratory, gastrointestinal, and CNS examinations were unremarkable except for peripheral neuropathy in the right lower limb with diminished to absent sensations below the knee.

Local examination revealed extensive gangrene extending from all toes to about 2–3 cm below the knee (30–32 cm in length) with black necrotic tissue, mottled dry black eschar, yellowish-green slough, and profuse seropurulent discharge emitting a strong foul odor suggestive of anaerobic infection. The calf circumference measured 38 cm compared to 30 cm on the contralateral side, and areas of skin breakdown exposed tendons. The affected areas were cold, leathery, and insensate, while the viable–nonviable junction showed severe tenderness and warmth. The grading of ulcer prognosis was done according to Wagner’s classification (Table 1).

Table 1: Gradation criteria for assessment of ulcer

Parameters for Assessment	0	+	++	+++
Size	No discontinuity of skin/mucous membrane	¼ of previous area of the ulcer	½ of previous area of the ulcer	>½ of previous area of the ulcer
Pain	No pain	Localized pain during movement but relieved on rest	Localized pain even during rest	Localized pain even during rest and also towards other side
Discharge	No discharge/dry dressing	Scanty, occasional discharge/Little wet dressing	Often discharge needs daily dressing	Profuse, continuous discharge needs frequent dressing
Smell	No smell	Bad smell	Tolerable, unpleasant smell	Foul and intolerable smell
Edge	Adhere edge	Smooth, even and regular edge	Rough, irregular edge	Angry look
Floor	Smooth, regular with granulation tissue/No need for dressing	Rough, regular, mild discharge, less granulation tissue/needs dressing	Unhealthy, less granulation tissue/needs daily dressing	Unhealthy, no granulation tissue

1. CBC: Hb-8 gm%
2. Blood Sugar -Fasting-103mg/dl, post-prandial-150mg/dl,
3. LFT- S. Bilirubin Total-0.7mg/dl, S. Bilirubin Direct 0.3mg/dl, S. Bilirubin Indirect-0.4mg/dl, SGOT- 26 IU/L, SGPT- 30 IU/L, S. Alkaline Phosphatase-162 IU/L
4. KFT- Blood Urea-18mg/dl, S. Creatinine- 0.9 mg/dl, S. Uric Acid-5.8mg/dl, S. Protein Total-6.9mg/dl, Albumin- 3.8g/dl, Globulin- 3.1g/dl
6. Pus Culture- gram negative bacilli seen
7. HbsAg- Non-Reactive
8. HIV- non-reactive
9. Color doppler: diffuse atheromatous wall thickening with luminal narrowing in all major arteries of right lower limb, negligible blood flow in tibial arteries, no blood flow in DPA.

TREATMENT METHOD (Unani Medicines)

Oral Medication

- *Qurs Kushta Faulad* once a week
- *Qurs Kushta Khubsul Hadeed* twice a day
- *Arq Murakkab Musaffi Khoon* 30ml twice a day
- *Iksir Jigar* twice a day

INVESTIGATION

Local treatment

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

- Cleaning of the wound by neem water/normal saline.
- Application of honey on the floor of ulcer
- Unripe mashed papaya dressing was placed over the wound.
- Application of leeches (4-5 leeches) twice a week.
- Papaya and honey along with the debridement of the tissue was done in operation theatre Majeedia Unani Hospital.
- Patient was educated about ulcer care and prevention.

Results

The treatment course was carefully documented from the initial presentation on 31 January 2023 to the final follow-up, showing a gradual transformation from extensive gangrene to complete healing with successful limb salvage as shown in **Table 2** and **Figure 1**.

Initial Presentation

At presentation, the right lower limb exhibited extensive dry gangrene extending from all toes to approximately 2–3 cm below the knee joint. The affected tissues appeared mummified, desiccated, and leathery, with uniform black to brownish-black discoloration. A well-defined line of demarcation was observed below the knee, clearly separating necrotic from viable tissue. Despite the dry character of the lesion, a strong foul odor indicated underlying putrefactive changes. The limb showed marked atrophy and loss of normal anatomical contours.

One month response

After one month of intensive treatment, significant improvement was seen. The dead tissue had mostly separated, revealing bright red, healthy granulation tissue covering about 60–70% of the wound bed, especially on the top of the foot and lower leg. The

wound looked clean and well-supplied with blood, and tendons were visible over the front of the ankle and foot. The remaining dead tissue was limited to the toes and front of the foot, which showed clear signs of natural separation. A small amount of slough remained in a few deep areas. The surrounding skin looked healthy, with no redness or swelling, and the bad odor had completely disappeared.

After 6-month response

The wound bed showed healthy, well-vascularized granulation tissue with minimal necrotic remnants. The toes exhibited progressive auto-amputation with clear separation lines. Granulation tissue had proliferated extensively, nearly covering all exposed areas, while the adjacent skin displayed re-epithelialization advancing from the periphery toward the center.

After 15 months response

Final documentation confirmed complete epithelialization and wound closure of the entire right lower limb. The skin appeared intact, dry, and free of ulceration or infection. Mild post-inflammatory pigmentation and mature scar tissue were visible, along with slight toe deformity and atrophy, consistent with sequelae of severe gangrene. Functionally, the patient was able to bear weight and walk independently. Hair growth was noted over the proximal leg, indicating restored vascular health. Overall, the outcome represented complete wound healing with excellent cosmetic and functional recovery, despite the severity of initial tissue loss.

Table 2: Observation of prognosis of ulcer as per assessment criteria

Sign and symptoms	Before treatment	After 1 month	After 6 months	After 15 months
Size	+++	+++	++	-
Pain	++	++	-	-
Discharge	+++	++	-	-
Smell	+++	+++	-	-
Edge	+++	+++	++	-
Floor	+++	+	+	-

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report



Figure 1: Prognosis of ulcer over the course of treatment

Discussion

This case illustrates the successful healing of extensive diabetic gangrene using a conservative, integrative Unani approach incorporating crushed unripe papaya, honey, and leech therapy. Chronic non-healing ulcers have been recognized since antiquity, from the early observations of Hippocrates to the comprehensive descriptions by Avicenna and other Unani scholars, who conceptualized ulceration as a consequence of deranged mizaj (temperament) and accumulation of morbid matter. In the present patient, the persistence and progression of the ulcer were attributable to the classical triad underlying diabetic foot pathology peripheral neuropathy, critical ischemia, and infection further exacerbated by systemic factors including anemia, poor glycemic control, and nutritional deficiency.

According to Unani principles, such ulcers correspond to *Qarha-e-Asratul Indamaal* (non-healing ulcer) arising from a *Sue Mizaj Haar Yabis* (hot and dry temperament) and *ufunat* (putrefaction) due to excessive *hararat* and *ratubat*. The therapeutic approach, therefore, emphasized *Tanqiya-e-Mawad* (evacuation of morbid matter), *Tadeel-e-Mizaj* (correction of temperament), and *Imala-e-Mawad* (diversion of morbid material from the affected site).

The use of unripe papaya in this case served as a natural enzymatic debriding agent due to the presence of papain, which breaks down necrotic tissue while preserving viable granulation tissue. This enzymatic debridement accelerated the removal of slough, promoted granulation, and reduced bacterial load, an outcome consistent with modern wound healing principles [24].

Honey acted synergistically by maintaining a moist wound environment, providing antimicrobial activity, and facilitating epithelial regeneration. It was used as a local wound-healing agent due to its broad-spectrum antimicrobial and tissue-regenerative properties. Its antibacterial activity, which may be bacteriostatic or bactericidal, is primarily mediated by glucose oxidase-derived gluconic acid and low levels of hydrogen peroxide, creating an acidic wound environment (pH 3.5–4.0) that inhibits microbial growth, reduces protease activity, enhances oxygen release, and stimulates fibroblast and macrophage function. Hydrogen peroxide further promotes angiogenesis via VEGF signaling, while the high osmotic potential of honey, augmented by invertase activity, reduces wound exudate and bacterial proliferation. These combined effects facilitate infection control, granulation, and epithelialization, supporting the favorable wound-healing outcome observed in this case [25].

Leech therapy (*Irsaal-e-Alaq*), a time-honored Unani practice, played a complementary role in improving local circulation, reducing venous congestion, and enhancing perfusion in ischemic tissue. The bioactive compounds in leech saliva—such as hirudin, bdellins, and eglins exhibit anticoagulant, anti-inflammatory, and analgesic properties, thereby supporting both debridement and tissue repair. Together, these modalities represent a blend of ancient wisdom and contemporary wound care principles, addressing both the local pathology and systemic imbalance [26].

Over the 15-month course, the patient's wound healing followed a clear progression from necrosis and foul discharge to healthy granulation and complete epithelialization, without surgical amputation. The gradual auto-amputation of gangrenous toes indicated natural demarcation and selective tissue separation, minimizing trauma. Concurrent use of Unani oral formulations *Qurs Kushta Faulad* [27], *Khubsul Hadeed* [28] and *Arq Murakkab Musaffi Khoon* [29] corrected anemia, purified blood, and improved hepatic and systemic functions, contributing to the restoration of *tabiyat* (vital force).

Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

The complete limb salvage and functional recovery underscore the efficacy of this integrative method in managing chronic diabetic ulcers. It aligns with both Unani and modern understanding that wound healing requires systemic correction, infection control, adequate debridement, and promotion of vascularity. The findings also reaffirm WHO's advocacy for incorporating traditional medicine into modern healthcare frameworks for chronic and refractory diseases.

While the results were highly encouraging, limitations included the prolonged treatment duration and the absence of objective biochemical monitoring of inflammatory and angiogenic markers. Nonetheless, this case exemplifies how the evidence-based integration of Unani therapeutics with modern scientific wound-care strategies can provide a viable and cost-effective alternative for limb preservation in advanced diabetic ulcers. The findings suggest that a holistic approach, combining Unani therapies with preventive measures, plays a significant role in reducing diabetic foot morbidity, improving overall quality of life, and consequently contributing to a reduction in disability-adjusted life years (DALYs).

Conclusion

This case highlights the successful limb salvage of a 38-year-old man with extensive diabetic foot gangrene who was previously advised for amputation. Through an integrated Unani and modern medical approach involving enzymatic debridement with papaya, regular leech therapy, Unani medicines for anemia and metabolic correction, honey and neem-based wound care, and strict glycemic control, complete healing was achieved over 15 months. The outcome shows that even in severe diabetic gangrene with poor circulation, conservative management can succeed when systemic factors are corrected and patients remain compliant. This case demonstrates the potential of combining traditional Unani treatments with modern wound care to achieve effective outcomes in complex conditions, thereby improving quality of life and reducing disability-adjusted life years (DALYs) and encourages further research into such integrative approaches.

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Beyond Surgery: Papain-Leech Synergy for Limb Salvage in Advanced Diabetic Foot Gangrene - A Case Report

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1. **Author 1:** supervision, clinical management, revision of manuscript.
2. **Author 2:** Patient management, clinical management, wound care, manuscript revision.
3. **Author 3:** Patient care, wound dressing, literature review, manuscript writing, editing.
4. **Author 4:** Manuscript editing, proof reading.
5. **Author 5:** formatting, final proofreading, and submission-related requirements.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Declaration

Ethics declaration: Not applicable

Consent to Participate: Written informed consent was obtained from the patient.

Consent to Publish: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.