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Medicinal leech therapy in venous congestion and various ulcer forms: Perspectives of Western, Persian and Indian medicine

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ABSTRACT

The use of medicinal leech therapy (MLT) is the subject of many articles describing basic pharmacological principles, application procedures, or efficacy and safety of the broad range of therapeutic indications.

This review is focused on the information gap between Eastern and Western medicine when medicinal leech therapy is used in wound healing.

Impaired wound healing has serious consequences for patients' health in a variety of clinical conditions. Western, Persian and Indian medicine seem to apply different therapeutic approaches when using medicinal leech therapy for healing wounds.

A range of review articles, single case reports and case series on the use of medicinal leech therapy in wound healing have been inspected.

The various reports indicate that medicinal leech therapy has potential benefits for patients experiencing venous congestion of the skin and tissues, as well as varied types of ulcers. Such therapy is proven to have thrombolytic, anti-coagulant, blood and lymph enhancing, anti-inflammatory and pain-relieving effects.

The specifics of these approaches are expected to stimulate further research on the use of medicinal leech therapy in wound healing.

Although the use of medicinal leech therapy to relieve venous congestion following reconstructive and plastic surgery is well-known in Western medicine, its use in promoting wound healing in various ulcer forms, in the context of Ayurveda/Unani/Persian medicine, seems largely restricted to Asian- and Arabic spheres. The true value of medicinal leech therapy in wound healing should be elucidated by further investigations applying modern, evidence-based research methods.

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1. Introduction

Chronic wounds such as pressure sores, leg ulcers and diabetic foot ulcers, which heal by secondary intention, are common in both acute and community settings. The strategies used to prevent and

treat such wounds commonly include the application of various wound dressings, bandages and antimicrobial agents, as well as the use of footwear, physical therapies and educational strategies.¹ Less conventional approaches include allogeneic micro grafting, allogeneic skin cell transplantation² and medicinal leech therapy (MLT).

Wound healing is a dynamic, sequential process involving exudative, proliferative and extracellular matrix remodeling phases. These phases are regulated by signaling molecules produced by a wide range of cells present in the extracellular matrix. The early stages of this process (hemostasis, inflammation and proliferation) prepare the tissues for the final, remodeling stage which can last for

Abbreviations: MLT, Medicinal Leech Therapy; VC, Venous catheterization; FDA, Food and Drug Administration; PUSH, Pressure Ulcer Scale for Healing; PAOD, Peripheral Arterial Occlusive Disease.

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one year or more.^{3,4} Various factors affect wound healing. Most chronic wounds are ulcers associated with ischemia, venous stasis or pressure.³ The therapeutic measures used to promote and treat wound healing must be adjusted to the states of the various wound healing phases.⁵

MLT is a multi-faceted therapeutic concept. It comprises the biting stimulus, blood drawing and the injection of pharmacologically-active substances found in leeches' saliva into patients' blood and tissues.⁶ Its therapeutic effects include anti-coagulation, blood and lymph flow stimulation and the reduction of both inflammation and pain.⁷ The pharmaceutical profile of MLT means that this therapy must be restricted to the late, remodeling phase of wound healing.⁷

This article compiles evidence from review articles and case reports on the use of MLT for wounds that result from acute venous congestion and chronic ulcer-related wounds.

2. Materials and methods

In this cross-sectional study, the authors searched for data on MLT published between January 1985 and April 2018. The main search engines used were Scopus, PubMed, ScienceDirect and Google Scholar. Sources cross-referenced in the articles thus found were also investigated. The search terms used included: leech, leech therapy, hirudotherapy, wound healing, ulcer(s) and venous congestion. Available peer-reviewed articles on MLT, published in English, German or Persian with at least an abstract were included. Articles with an incomplete explanation of the data and/or the use of therapeutic methods for wound healing, besides MLT, were excluded. The selected articles were reviewed by one of the authors (MP). The data was then gathered for final group review.

3. Results

3.1. Pharmacological actions of medicinal leeches

Animal-based pharmacological studies have investigated the effects of leech application on blood supply in ischemia induction models in mice, rats, rabbits and pigs. These studies showed that leeches increase blood flow velocity, improve microcirculation and accelerate anastomosis.^{8–13}

A controlled study of wound-healing in rats, using an electric wound model, showed that leeching decreased local necrotic and inflammatory reactions, accelerated epithelization and granulation, increased the amount and balance of macrophage activity and enhanced the synthesis of new blood and lymphatic vessels.¹⁴

Darestani et al.¹⁵ conducted a randomized controlled study, also in rats, comparing leeching with the use of a standard treatment (the application of topical phenytoin) and a control for incisional skin wound healing. This study found significantly faster effects, on wound closure, hair growth and histological findings, from the application of leeches than in either the standard treatment or the control group.

In a patient-based study, Chmiel et al.¹⁶ found significant and long-lasting rheological reductions in the viscoelasticity of their blood samples following the application of leeches.

Rothenberger et al.¹⁷ went on to investigate the pharmacological effects of MLT on patients experiencing venous congestion. The results indicated distinct changes in patients' blood microcirculation, with significant increases in the levels of blood flow and oxygen saturation found and a reduction in the amount of hemoglobin.

3.2. Clinical effects of medicinal leech therapy in wound healing

3.2.1. Venous congestion

The use of MLT in **reconstructive and plastic surgery** has been reported in many review articles to date (e.g. 18–21). These articles show salvage rates of 65%–80% in cases of congested skin flaps, avulsed digits, ears and noses, with a degree of risk of loss due to post-operative venous congestion.

In a controlled case series study, Riede et al.²² reported the use of medicinal leeches in reconstructive surgery for 23 patients with necrotic skin flaps and hematomas. MLT was started an average of 2.6 days following these patients' surgical interventions. On average, 2.6 leeches were applied to patients' wounds, with a mean of 1.7 treatment sessions per patient. The authors reported that 87% of these patients (20/23) showed restitution and integration of their skin flaps after their MLT. Clinical improvement was noticed after 1.1 days on average. Although prolonged bleeding occurred, lasting up to two days, no further adverse reactions or complications were observed.

Another clinical trial by Mozafari et al.²³ compared MLT and venous catheterization (VC). These authors found VC to be more effective than MLT in treating venous congestion in distally-based sural flaps, but this difference did not prove statistically significant in terms of the study's primary outcome; partial flap necrosis. In this study, safety parameters such as blood loss, infection and wound dehiscence showed better results with VC as compared to MLT.

In addition to the above, individual case reports give an overview of the potential applications of MLT for venous congestion following varied types of reconstructive and plastic surgery, as follows:

Banihani et al.²⁴ describe the case of a 7-day-old baby with the reattachment of a complete penile amputation. Venous congestion developed on the first post-operative day; for which a week's MLT was immediately undertaken. A follow-up assessment, conducted nine months later, showed satisfactory results.

In a case report by Tarazjamshidi et al.,²⁵ a young man with a traumatic near-amputation of three fingers was referred to a hospital in Mashhad/Iran. In the absence of an available vascular surgeon, a meticulous wound debridement was performed at the time and his bone and soft tissue were later repaired. MLT was started 12 h after the surgery, in order to achieve acceptable capillary refilling. A total of 15 leeches were used over seven days and the patient left the hospital after two weeks. The treatment delivered saved two of his damaged fingers, but failed to save the third. A three-month follow-up showed that his saved fingers were functionally active although their range of motion was decreased.

A case report by Hajtalebi et al.²⁶ describes the use of leech treatment in a 12-year-old boy who sustained right lower limb trauma in a motorcycle accident. Following orthopedic surgery, his leg remained swollen, with severe venous congestion. When the patient did not respond to conventional treatment, MLT was initiated, with 10 leeches used every three days for 10 treatment sessions. The patient's venous congestion and severe swelling were significantly decreased after four sessions of MLT. Two months later, the boy had made a full recovery, following successful skin-grafting surgery. Many case reports provide further evidence of MLT's efficacy in the treatment of venous congestion (e.g. 27–29).

Major adverse reactions to be considered, in using medicinal leeches, are blood loss requiring transfusion and the risk of infection necessitating prophylactic antibiotic treatment.

In 2004, the United States (US) Food and Drug Administration (FDA) granted market approval for medicinal leech therapy as "An adjunct to the healing of graft tissue when problems of venous congestion may delay healing, or to overcome problems of venous

congestion by creating prolonged bleeding.”

3.2.2. Non-healing chronic wounds

Leech therapy is a traditional remedy used in Ayurveda/Unani/Persian medicine; mainly for bloodletting and in cases of inflammation, thrombosis, phlebitis, varicosity and pain³⁰.

3.2.2.1. Ulcerated wounds. In this context, Bapat et al.³¹ evaluated medicinal leeches' effectiveness in treating 19 patients with **venous leg ulcers**. The number of leeches applied in this prospective non-randomized open study ranged from one to four, with between two and twenty leech sessions being delivered per patient, depending on the area and severity of their ulcers. At the end of the study, all of the patients' ulcers showed complete epithelization. Potential complications noted by the authors, from the use of MLT in treating venous ulcers, included wound infection from the leeches' gut flora, excessive bleeding and leeches' wandering from the target tissues. None of these complications were observed in this study.

A case report of a patient with a history of a six-month leg ulcer is described by Prakash et al.³² The authors undertook baseline assessments of the wound's color and discharge, the extent of the pain and burning sensations felt and the diameter of the ulcer's inflammation. MLT was then used to treat the ulcer once a week for three weeks. A post-treatment assessment was completed one week after the MLT treatment ended. Following the MLT treatment, the authors found that pain was only present with strong pressure, that the patient's skin color had almost returned to normal and that neither discharges nor burning sensations were present. The diameter of the wound was reduced from 3.8 cm × 2.5 cm × 1.2 cm–1.3 cm × 0.8 cm × 0.3 cm. In their conclusion, the authors suggested that this study's three-week treatment period might have been too short to assess MLT's true clinical value in treating chronic ulcers.

Zarnigar³³ went on to report the cases of four patients with foot and leg ulcers. These wounds, which had developed over the previous eight months to 3 years, had not responded to a variety of treatments. The author conducted baseline observations of patients' symptoms, followed by examinations every 15 days for two months. The length, width and depth of patients' ulcers, and the extent and nature of any wound exudates, were measured using the Pressure Ulcer Scale for Healing (PUSH). Patients were also asked to rate their pain on a 10-point analogue scale. Leeches were applied on alternate days, during this study, for two months. At the end of patients' treatment (Day 60), three of the four cases showed complete wound healing. The last patient experienced improvement, but incomplete healing (PUSH score: 15 at baseline, 10 at Day 60).

Mahanta et al.³⁴ described a patient with severe pain and intermittent fever, as well as swelling and ulceration of the dorsum of the foot, following an unidentified insect bite two weeks before visiting. Local examination revealed an ulcer covered with necrotic tissue. The patient's wound was dressed daily with *Securinega Leucopyrus* powder, mixed with sesame oil. After three sessions of additional MLT, the ulcer healed completely within two months. The authors concluded that the treatment regimen “had a significant role in controlling inflammation and promoting healing of infected wounds without any adverse events.”

Another case of MLT for foot ulceration was reported by Saranya & Kanesalingam.³⁵ This case related to a patient with a 12 cm × 7 cm wound from a snake bite sustained four years earlier. Multiple therapies had failed in the interim. Leech treatment was accordingly instituted, with one leech being applied to the edge of the wound once a week. This procedure was carried out for a total of twenty weeks; at which point the wound became dry. One year later, the wound was completely cured.

A recent article describes the use of MLT in a rare case of chronic

thumb ulcer related to Peripheral Arterial Occlusive Disease (PAOD) Stage IV in the left hand.³⁶ Three to five leeches were applied the first 15 days on alternate days, the next 15 days twice a week, and then once a week for one month. The wound was completely healed by the 13th setting (Photographic documentation).

3.2.2.2. Diabetic foot ulceration. Diabetes affects more than 150 million people worldwide, with increasing estimates of its future prevalence.³⁷

About five percent of the patients who have diabetes go on to develop foot ulcers. With standard care (i.e. antidiabetic medications, podiatric care, wound debridement and the management of infection) approximately a third of these ulcers heal within 20 weeks.³⁷ The recurrence rate is, however, high (66%), with amputation proving necessary in some twelve percent of cases. More than four fifths (84%) of all diabetes-related lower leg amputations are preceded by foot ulcers.³

Dwiwedi³⁸ describes a single observation-based case study of a patient with persistent **diabetic ulcers** on both feet, despite two months of wound-healing treatment and five years' use of antidiabetic medications. MLT was delivered once a week for four weeks. Three leeches were placed, per wound, around the edges of the lesions. Weekly assessments of the ulcers' resulting pain, size, smell, discharge, edge and floor were undertaken. The MLT induction of complete healing, over time, was documented photographically.

Hajtalebi et al.³⁹ went on to report on the leech treatment of a 74-year-old female patient with a diabetic foot ulcer. Her diagnosis and treatment progress were documented according to the Wagner and Texas Diabetic Wound Classification systems. This patient had a 20-year history of type II diabetes, with consistent use of oral antidiabetics. The patient was then hospitalized with infected diabetic foot ulcers on her right foot. The latter did not respond to antidiabetic and anti-infective treatments, leading an orthopedic surgeon to recommend amputation. Guided by an acquaintance, the patient was referred to a complementary medicine unit. MLT was initiated, along with nutritional advice and the use of medicinal herbs. The patient underwent ten sessions of MLT every three days for a month. The leeches were applied both inside and around the wounds. After the first week, granulation tissue began to appear and inflammation, infection and gangrenous conditions within the wound had resolved after four treatment sessions. The wound was completely healed in a month. The healing progress was documented photographically. The patient was monitored for a further two months, with no recurrence being observed during that time or thereafter.

Another patient with a 25-year history of diabetes was referred to the hospital by Hajtalebi et al.⁴⁰ for counseling due to a diabetic foot ulcer. Once again, the latter had not responded to conventional treatments and the surgeons recommended amputation. This patient had two wounds on his right foot, diagnosed clinically as Stage D/Grade III on the Texas University Diabetic Wound Classification System (equivalent to Grade 4 on the Wagner diabetic foot ulcer classification system).

Pharmaceutical measures included the use of conventional anti-hyperglycemic medications and medicinal herbs. A total of sixteen sessions of MLT were delivered with 10–12 leeches being placed inside and around the wound every two to four days. The authors reported that the ulcer was completely healed within sixty days.

Hajtalebi et al.³⁷ compiled a retrospective review of ten patients with diabetic foot ulcers who had undergone MLT in 2015–2016. Each of these patients had had a history of sequential foot ulcers, which had failed to respond to previous common treatments. As a result, all were candidates for amputation on orthopedic advice. The patients' wounds were infected and severely inflamed. The

researchers' treatment regime consisted of antidiabetic medications, the use of medicinal herbs and MLT. Ten to twelve leeches were applied inside and around the patients' wounds once every three to seven days, for a total of ten sessions. All of the patients' diabetic foot ulcers were completely cured following 40–60 days of this treatment.

The avoidance of imminent amputation is also reported by Zaidi.⁴¹ The patient concerned presented with a non-healing diabetic foot ulcer assessed as Grade 5. The wound was extremely painful (rated as 80/100 mm on a visual analogue scale), gangrenous and foul-smelling. Following wound dressing with unripe papaya, MLT was initiated. The author reported that the patient's pain score decreased to 0–10 mm within 20 days and no further analgesics were required. After four months, the necrotic areas had disappeared and the wound was completely healed.

A final patient with a non-healing diabetic ulcer was treated with leeches by Rampure et al.⁴² The authors noted that the ulcer on this patient's left ankle joint had not responded to two months of conventional therapy. The patient had had diabetes for 15 years and had continuously taken antidiabetic medications since his diagnosis. The ulcer was assessed and followed-up during the patient's leech treatment with respect to its size, pain, edge, floor, discharge and smell. Four leeches were applied around and on the wound once a week for thirty days, at which time the ulcer was completely healed. The healing progress was documented photographically.

3.2.2.3. Traumatic hand injury. Kenari et al.⁴³ reported the case of a 44-year-old in-patient presenting with **trauma to his right hand** following a car accident. During his hospitalization, this patient received conventional medical care, including three orthopedic operations and a vascular transplantation for his hand. Seventeen days post-admission, his doctors decided to amputate his second to fifth fingers due to the failure of these treatments. The patient did not consent to these amputations and was discharged from hospital at his own request. The patient was subsequently referred to a Persian medicine clinic.

There, the patient was recommended a strict diet. Debridement of the necrotic tissues was achieved by washing the patient's wounds with a mixture of thyme, chamomile and pennyroyal distillates. A poultice consisting of extracts of cabbage, spinach and marshmallow roots was then used to cover the wounds. The patient also received various Persian medicine medications (e.g. Aloe Vera capsule, St. John's Wort oil, Aloe Vera cream).

Leech therapy was delivered alongside the above; one of the most important interventions used, according to the study authors. The leech therapy was delivered once daily for ten days, with eight leeches being applied in each treatment session. The researchers reported that, after three to four days' treatment, the patient's fingers and wounds became significantly less edematous. After two weeks, the movement in his fingers was greatly improved. Within one month, the damaged ligaments, nerves, muscles and skin were gradually restored; enabling hand function to be regained and amputation avoided.

3.2.2.4. Buerger's disease (Thromboangiitis Obliterans). **Buerger's disease** (Thromboangiitis Obliterans) is a rare inflammatory disease of the arteries and veins in the arms and legs which can lead to skin tissue damage and gangrene. The disease is more prevalent in the Middle East and Far East than in North America and Western Europe. The prevalence of this disease among all patients with peripheral arterial diseases varies from 0.5 to 5.6% in Western Europe to as high as 16–66% in Japan and Korea, and 45–63% in India.⁴⁴

Choudhary⁴⁵ reported a case of Buerger's disease in a hospital

in-patient. The patient was in severe pain to the extent that he was unable to put his foot to the ground. Conventional opioids and non-opioid analgesics had not proven effective. The patient's toe was black in color, with signs of dry gangrene and an ulcer bordering the gangrenous area. MLT was carried out twice a week, for a total of ten sessions, with three to four leeches being used per session. The leeches were applied around the affected area. At the end of leech treatment, the patient showed a marked improvement. His pain was very much lessened and the swelling reduced; such that he could walk without a stick. The patient came for follow-up examinations after six months and two years, but remained free of the symptoms of Buerger's disease. A color Doppler scan, performed after two years, confirmed normal blood flow and velocity.

In their review article, Kumar et al.⁴⁶ included photographs illustrating the successful use of MLT in the treatment of Buerger's disease and wound healing. A further review article, by Rajeev et al.⁴⁷ also recommended MLT as an effective treatment for Buerger's disease.

3.2.2.5. Cutaneous leishmaniasis. Another disease leading to skin and tissue damage is **cutaneous leishmaniasis**. This disease is transmitted by parasites and mainly occurs in tropical and subtropical countries. It affects about 12 million people worldwide,⁴⁸ with annual incidence rates of 0.7–1.2 million new cases.⁴⁹

Hamidzadeh et al.⁵⁰ mention a prevalence rate of 20,000 people in Iran. They reported on two cases of cutaneous leishmaniasis that had not responded to conventional medications. The male patient presented with a wound to his left hand despite four months of conventional medication. MLT was initiated, with five leeches being placed on the wound. The leech treatment sessions were repeated four times at one, two, three-and-four-week intervals. The wound was completely recovered within four months and a follow-up examination found no relapse.

The other, female, patient described by Hamidzadeh et al.⁵⁰ had an ulcer on her face for six months. She had received no medication during this time. This patient was also treated with five leeches. On this occasion, two treatment sessions were delivered, at two week and four-week intervals. The patient's wound had completely healed within six months, with no relapse seen at a follow-up visit after 18 months. The authors documented both cases photographically.

Table 1 summarizes the efficacy and safety data of exemplary case reports and studies investigating the use of MLT in venous congested tissue and various ulcer forms.

4. Discussion

In contrast to previous review articles referring to history, pharmaceutical characteristics and the broad range of therapeutic applications of MLT (e.g. ^{51–55}), we have reviewed the different ways MLT is used in wound healing by Eastern and Western medicine. There might be some more non-accessible articles in this field. However, our review had revealed a consistent message.

The above sources show that medicinal leech therapy (MLT) can heal wounds. To a Western European audience, the therapeutic use of this approach is strange and counter-intuitive.

On the other hand, MLT has a long history of use, for this indication, as part of both Persian/Iranian (Ayurveda) and Greek/Arabic (Unani) medical traditions.^{30,56}

Modern explanations for the principles of this therapeutic concept are found in leeches' capacity to drain blood, to reduce venous congestion, and more than twenty bioactive substances found in leech saliva. Such substances have been shown to have thrombolytic, anti-coagulant, anti-inflammatory, antimicrobial and pain-relieving effects, with an associated increase in blood flow and

Table 1
Efficacy and safety of medicinal leech therapy in venous congestion and various ulcer forms.

Indication	Efficacy	Complications	Comments	Reference
Venous Congestion	Complete healing (N = 13/20 = 65%)	Amputation, defect closure, flap removal	Venous congestion in flaps, digital replants and revascularizations	Butt 2016/UK ¹⁸
Venous Congestion	Complete healing (N = 20/23 = 87%)	Prolonged bleeding	Clinical case series study	Riede 2010/Germany ²²
Venous Congestion	Complete healing (N = 26)	Blood loss, wound infection, dehiscence	Clinical trial comparing MLT with venous catheterization	Mozafari 2011/Iran ²³
Venous Congestion	Complete healing (N = 1)	Safe and well tolerated	Amputation of penis in a ritualistic circumcision	Banihani 2014/USA ²⁴
Venous Congestion	Complete healing (N = 1)	Safe and well tolerated	Traumatic-near-amputation of fingers	Tarazjamshidi 2014/Iran ²⁵
Leg Ulcer	Complete healing (N = 19)	No complications observed	Clinical case series study	Bapat (1998)/India ³¹
Leg Ulcer	Near to complete healing (N = 1)	Not stated	Short treatment period	Prakash 2015/India ³²
Leg and Foot Ulcer	Complete healing (N = 3) Near to complete healing (N = 1)	Safe and well tolerated	None	Zarnigar 2011/India ³³
Foot ulcer	Complete healing (N = 1)	No complications observed	Insect bite sequelae	Mahanta 2017/India ³⁴
Foot ulcer	Complete healing (N = 1)	Not mentioned	Snake bite sequelae. Extended treatment time	Saranya & Kanesalingam 2017/ Sri Lanka ³⁵
Thumb ulcer	Complete healing (N = 1)	Not mentioned	Ulcer related to PAOD Grade IV	Kapadiya 2018/India ³⁶
Diabetic Foot Ulcer	Complete healing (N = 1)	Not mentioned	Observation single case study	Dwiwedi 2012/India ³⁸
Diabetic Foot Ulcer	Complete healing (N = 1)	Not mentioned	Leech therapy combined with medicinal herbs	Hajtalebi 2016/Iran ⁴⁰
Diabetic Foot Ulcer	Complete healing (N = 1)	Not mentioned	Leech therapy combined with nutrition advice and medicinal herbs	Hajtalebi 2017/Iran ³⁹
Diabetic Foot Ulcer	Complete healing (N = 10/10)	Not mentioned	Leech therapy combined with medicinal herbs	Hajtalebi 2017/Iran ³⁷
Diabetic Foot Ulcer	Complete healing (N = 1)	Not mentioned	Pain relief	Zaidi 2016/India ⁴¹
Diabetic Foot Ulcer	Complete healing (N = 1)	Not mentioned	None	Rampure 2017/India ⁴²
Traumatic hand injury	Complete healing (N = 1)	Not mentioned	Leech therapy combined with Persian medication and diet	Kenari 2018/Iran ⁴³
Buerger's Disease	Complete healing (N = 1)	Not mentioned	Two years follow-up using Doppler fluorimetry	Choudhary 2015/India ⁴⁵
Cutaneous Leishmaniasis	Complete healing (N = 2)	Not mentioned	Follow-up for 18 months	Hamidzadeh 2017/Iran ⁵⁰

an inhibition of platelet functions. The impact of leech saliva on wounds' local blood and lymph microcirculation appears an essential feature of wound healing, although details of the processes involved await further exploration.⁷

Despite the published evidence supporting medicinal leech therapy's effectiveness in treating chronic wounds, this therapy appears to have been largely neglected in the Western world to date. The fact that almost all of the existing case reports come from India and Iran is unsurprising; given that these countries are major sources of Ayurveda and Persian medicine. This does not mean superiority of one therapeutic concept to the other. Currently no data is available to support either approach as the more favourable one.

Proof of MLT's clinical efficacy in the above-mentioned indications of wound healing, using evidence-based standards, is outstanding. Additional information on the successful use of MLT for venous congestion and the treatment of various ulcer forms, from pharmacological results and clinical reports, would also bear further investigation using the standards of modern Western medicine.

There is some evidence of minor (and occasionally major) side effects with MLT, including allergic reactions, bleeding and infections. Such complications should not be neglected during MLT/hirudotherapy.^{57,58}

Clinicians who use MLT must ensure that they are entirely familiar with the treatment procedures involved. Comprehensive instructions are needed if leech therapy is to be used effectively in wound healing. Such instructions must encompass detailed information about the preparations needed at the start of therapy, the precise treatment approach/ regime to be adopted and the provision of accurate aftercare. Each of these elements is vital to the delivery of successful MLT. Existing references suggest that MLT for the wound-healing warrants further investigation in order to

determine its potential as part of the modern therapeutic armamentarium.

The same holds true for other indications where MLT is used, such as osteoarthritis of knee and thumb, epicondylitis, lower back pain, haematomas, or haemorrhoids.

5. Conclusions

Pharmacological experiments and clinical reports indicate that medicinal leech therapy (MLT) has convincing potential in healing varied types of chronic wounds. The therapy appears to work through by venous decongestion, thrombolysis, blood and lymph flow enhancement and the suppression of inflammation.

MLT has a long history in the healing of chronic wounds in the context of traditional Ayurveda/Unani/Persian medicine. Further research in this area is essential. Investigating these effects, using modern evidence-based standards, is a demanding and promising challenge.

Conflicts of interest

The authors declare that there is no conflict of interest.

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References

- O'Meara S1, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: antimicrobial agents for chronic wounds; diabetic foot ulceration. *Health Technol Assess.* 2000;4(21). 1-237.
- Kruse CR, Sakthivel D, Sinha I, et al. Evaluation of the efficacy of cell and

- micrograft transplantation for full-thickness wound healing. *J Surg Res.* 2018 Jul;227:35–43.
3. Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res.* 2010;89(3):219–229.
 4. Oliveira Gonzales AC, Costa TF, Andrade ZA, Peixerto ARA. Wound healing – a literature review. *An Bras Dermatol.* 2016;91(5):614–620.
 5. Kujath P& Michelsen A. Wunden – von der Physiologie zum Verband. *Dtsch Ärzteblatt.* 2008;105(13):239–248.
 6. Hildebrandt JP, Lemke S. Small bite, large impact – saliva and salivary molecules in the medicinal leech, *Hirudo medicinalis*. *Naturwissenschaften.* 2011;98:995–1008.
 7. Sig AK, Guney M, Uskudar Guclu A, Ozmen E. Medicinal leech therapy—an overall perspective. *Integr Med Res.* 2017;6(4):337–343.
 8. Anthony JP, Lineaweaver WC, Davies JW, Buncke HJ. Quantitative fluorimetric effects of leeching on a replanted ear. *Microsurgery.* 1989;10(3):167–169.
 9. Conforti ML, Connor NP, Heisey DM, Hartig GK. Evaluation of performance characteristics of the medicinal leech (*Hirudo medicinalis*) for the treatment of venous congestion. *Plast Reconstr Surg.* 2002;109(1):228–235.
 10. Cottler PS, Gampper TJ, Rodehaever GT, Skalak TC. Evaluation of clinically applicable exsanguination treatments to alleviate venous congestion in an animal skin flap model. *Wound Repair Regen.* 1999;7(3):187–195.
 11. Kashiwagi K, Hashimoto I, Abe Y, et al. Quantitative analysis of hemodynamics of congested island flaps under leech therapy. *J Med Invest.* 2013;60:213–220.
 12. Lozano DD, Stephenson LL, Zamboni WA. Effect of hyperbaric oxygen and medicinal leeching on survival of axial skin flaps subjected to total venous occlusion. *Plast Reconstr Surg.* 1999;104(4):1029–1032.
 13. Moosavian HR, Mirghazanfari SM, Moghaddam KG. Effect of ischemia preconditioning and leech therapy on cutaneous pedicle flaps subjected to prolonged ischemia in a mouse model. *Aesthet Plast Surg.* 2014;38(5):1024–1029.
 14. Gilyova OS, Korobeinikova GA, Gibadullina NB. Experimental studies on the healing and anti-inflammatory effects of leeching. *Int Biother Soc.* 2007;1.
 15. Darestani KD, Mighazanfari SM, Moghaddam KG, Hejazi S. Leech therapy for linear incisional skin-wound healing in rats. *J Acupunct Meridian Stud.* 2014;7(4):194–201.
 16. Chmiel H, Anadare I, Moser K. Hemorheological changes under blood leeching. *Clin Hemorheol.* 1989;9:569–576.
 17. Rothenberger J, Petersen W, Schaller HE, Held M. Determining the appropriate number and duration of leech therapy in congested tissues using tissue spectrophotometry and Laser Doppler flowmetry. *Wound Repair Regen.* 2016;24(6):1023–1029.
 18. Butt AM, Ismail A, Lawson-Smith M, Shahid M, Webb J, Chester DL. Leech therapy for the treatment of venous congestion in flaps, digital Re-plants and revascularizations – a two-year review from a regional centre. *J Ayub Med Coll Abbottabad : JAMC (J Assoc Med Can).* 2016;28(2):219–223.
 19. Herlin C, Bertheuil N, Bekara F, et al. Leech therapy in flap salvage: systematic review and practical recommendations. *Ann Chir Plast Esthetique.* 2017;2(2):1–13.
 20. Knobloch M, Gohritz A, Busch K, et al. *Hirudo medicinalis* – anwendungen in der plastischen und rekonstruktiven Mikrochirurgie – eine Literaturübersicht. *Handchir Mikrochir Plast Chir.* 2007;39(2):103–107.
 21. Whitaker IS, Oboumarzouk O, Rozen WM, et al. The efficacy of medicinal leeches in plastic and reconstructive surgery: a systematic review of 277 reported clinical cases. *Microsurgery.* 2012;32:240–250.
 22. Riede F, Koenen W, Goerdts S, et al. Der Einsatz medizinischer Blutegel zur Therapie der venösen Stase und von Hämatomen bei Lappenplastiken. *JDDG J der Deutschen Dermatol Gesellschaft.* 2010;8:1–9.
 23. Mozafari N, Ghazisaidi MR, Hosseini S, et al. Comparisons of medicinal leech therapy with venous catheterization in the treatment of venous congestion of the sural flap. *Microsurgery.* 2011;31(1):36–40.
 24. Banihani OI, Fox JA, Gander BH, et al. Complete penile amputation during ritual neonatal circumcision and successful replantation using postoperative leech therapy. *Urology.* 2014;84(2):472–474.
 25. Tarazjamshidi M, Bagheri F, Mirkazemi M, et al. Leech therapy in nearly total amputation of fingers without vascular repair: a case report. *Iran Red Crescent Med J.* 2014;16(5), e6897.
 26. Hajtalebi H, Lurigh HK, Hajtalebi HR. Treatment of leg venous congestion using Iranian leech therapy after orthopedic surgery in a 12-year adolescent with double and open fracture of distal of right leg and ankle dislocation. *Trad Integr Med.* 2017;2(2):83–89.
 27. Elyassi AR, Terres J, Rowshan HH. Medicinal Leech therapy on head and neck patients: a review of literature and proposed protocol. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116(3):167–172.
 28. Mamelak AJ, Jackson A, Nizamani R, et al. Leech therapy in cutaneous surgery and disease. *J Drugs Dermatol JDD.* 2010;9(3):252–257.
 29. Mumcuoglu KY, Pidhorz C, Cohen R, et al. The use of the medicinal leech, *Hirudo medicinalis*, in the reconstructive plastic surgery. *Internet J Plast Surg.* 2007;4(2):1–20.
 30. Vaibhav A, Antiwal M, Singh JP, Singh OP. Leech therapy (Jalaukavacharan) in Ayurveda medicine: a scientific review. *Int J Pharm Pharm Res.* 2016;6(4):503–515.
 31. Bapat RD, Acharya BS, Juvekar S, Dahanukar SA. Leech therapy for complicated varicose veins. *Indian J Med Res.* 1998;107:281–284.
 32. Prakash J, Singh M, Kumar M, et al. Effect of leech therapy in chronic ulcer – a case study. *Indian J Res.* 2015;4(9):169–170.
 33. Zarnigar AA. Clinical efficacy of leech therapy in varicose ulcer – a case series. *Unani Res.* 2011;1(1):31–38.
 34. Mahanta VD, Foram J, Dudhamal TS, Gupta SK. Jalaukavacharana (Leech application) and adjuvant therapy in the management of infected wound. *J Ayurveda Case Rep.* 2017;1(1):13–17.
 35. Saranya U, Kanesalingam M. Wound healing activity of leech therapy on Dhusta Virnam: a case study. *Shalaky Sandipani.* 2017;68. International Conference of the Shalaky Tantra.
 36. Kapadiya M, Shresta M, Dudhamal TS. Efficacy of leech application in the management of peripheral arterial occlusive disease (PAOD) – a rare case report. *Int Ayurv Med J.* 2018;2(6):1382–1387.
 37. Hajtalebi H, Lurigh HK, Hajtalebi HR. Investigating the treatment status of 10 patients with second and third degree diabetic foot ulcers based on the therapeutic protocols of Iranian traditional medicine in Bojnurd from 2015–2016. *Asian J Clin Case Rep Trad Alter Med.* 2017;8(2-3):55–64.
 38. Dwiwedi AP. Case study of leech application in diabetic foot ulcer. *Int J Res Ayurveda Pharm.* 2012;3(5):748–751.
 39. Hajtalebi H, Lurigh HK, Hajtalebi HR. Treatment of diabetic foot ulcer in a 74-year-old female patient based on Iranian traditional medicine in Bojnurd. *Asian J Clin Case Rep Trad Alter Med.* 2017;1(1):1–10.
 40. Hajtalebi H, Lurigh HK, Hajtalebi HR. Treatment of diabetic foot ulcer in a 58-year old Turkman patient. *Trad Integr Med.* 2016;1(4):151–159.
 41. Zaidi SM. Unani treatment and leech therapy saved the diabetic foot of a patient from amputation. *Int Wound J.* 2016;13(2):263–264.
 42. Rampure N, Channabasavanna BM, Mallikarju. Jalaukavacharana in diabetic foot ulcer – a case study. *J Ayurveda Integr Med Sci.* 2017;2(3):271–278.
 43. Kenari HM, Kordafshari G, Aghighi S, Moghimi M. Treatment of a traumatic injury of hand with Persian medicine. *Archiv Clin Biomed Res.* 2018;2(2):59–67.
 44. Rivera-Chavarria JJ, Brenes-Gutierrez JD. Thromboangiitis obliterans (Buerger's disease). *Ann Med Surg.* 2016;7:79–82.
 45. Choudhary PK. Leech therapy in thromboangiitis obliterans (Buerger's Disease). *J Ayurveda Holist Med.* 2015;3(6):130–134.
 46. Kumar S, Dobos GJ, Rampp T. Clinical significance of leech therapy in Indian medicine. *J Evid Based Compl Alter Med.* 2012;18(2):152–158.
 47. Rajeev K, Chandramohan A, Sarita V. Buerger's disease – where is the relief?: a critical review. *Int J Rec Adv Multidiscip Res.* 2016;3(6):1544–1547.
 48. Bessat M, Shanat SE. Leishmaniasis: epidemiology, control and future perspectives with special emphasis on Egypt. *J Trop Dis.* 2013;3(1):1–10.
 49. Alvar J, Velez D, Bern C, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One.* 2012;7(5), e35671.
 50. Hamidzadeh N, Azizi A, Zarshenas MM, Ranjbar S. Leech therapy in treatment of cutaneous leishmaniasis: a case report. *J Integr Med.* 2017;15(5):407–410.
 51. Herlin JM, Bertheuil N, Bekara F, et al. Leech therapy in flap salvage: systematic review and practical recommendations. *Annales de Chirurgie Plastique et Esthétique.* 2017;2(2):1–13.
 52. Khan BA, Khan R, Chaudhari AH, et al. Leech therapy (Irsal-el-Alaq) in Unani system of medicine: a review. *Int J Unani Integr Med.* 2018;2(1):17–19.
 53. Sha A, Sha S, Khan T. Irsal-el-Alaq (Leech therapy) in Unani system: a review. *Res Rev: J Unani Siddha Homeopathy.* 2018;5(1):27–31.
 54. Sig AK, Guney M, Guclu AU, Ozmen E. Medicinal leech therapy – an overall perspective. *J Integr Res.* 2017;6(4):337–343.
 55. Yagici AK, Durmus M, Tanyukzel M, et al. *Hirudo medicinalis* – historical and biological background and their role in microsurgery. *Hand Microsurg.* 2017;6(1):34–38.
 56. Barzegar A, Azizi A, Faridi P, Mohagheghzadeh A. Leech therapy in Iranian traditional medicine. *Complementary Med Res.* 2015;22(1):50–53.
 57. Schnabl SM, Kunz C, Unglaub F, et al. Acute postoperative infection with *Aeromonas hydrophila* after using medical leeches for treatment of venous congestion. *Arch Orthop Trauma Surg.* 2010;130(810):1323–1328.
 58. Pietrzak A, Kanitakis J, Tomasiewicz K, et al. Cutaneous complications of improper leech application. *Ann Agric Environ Med.* 2012;19(4):790–792.