



Review

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LITERATURE REVIEW ON THE EFFECTIVENESS OF MEDICINAL LEECH THERAPY IN THE WOUND HEALING

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Abstract

Medical leech therapy, which has a history of thousands of years, is still the subject of many scientific studies today. These studies have shown that medicinal leech therapy has anticoagulant, antimicrobial, anti-inflammatory and analgesic effects, as well as increases blood flow in the bite area. Due to these stated effects of leech therapy, it has potential benefits for patients experiencing wounds of the skin and tissues. This review focused on presenting the studies in which medical leech therapy is used to promote wound healing, particularly in post-traumatic wounds and non-healing chronic wounds. Additionally, this review aims to recognize medicinal leech therapy, introduce the leech species that have therapeutic effects and indicate the effect mechanisms of leech saliva on wound healing. The case series, single case reports and review articles on the use of medicinal leech therapy in wound healing were inspected. The original animal-based studies on wound healing were also investigated in this review for additional information. 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. Medicinal leech therapy has promising potential in the healing of post-traumatic and chronic non-healing wounds. Nevertheless, more studies are needed for the potential effects of medicinal leech therapy in wound healing should be clarified by further studies.

Keywords: Hirudotherapy, medicinal leech therapy, trauma, ulcers, wound healing.

Introduction

The skin, which is the largest organ of the body and surrounds the body as a barrier against the external environment, plays an active role both physically and immunologically. Along with these, the skin, which contains hair and nails, also has functions such as UV protection, hormone and enzyme production, homeostasis, and thermoregulation. ¹ Wound healing is a physical process that is essential for preserving the integrity and function of the skin or tissue by eliminating the defects that occur after an accident, trauma, illness or surgery. Normal wound healing consists of three intertwined stages that cannot be separated from each other with clear lines. ² The usual wound healing consists of three interlocking phases, which include the homeostasis/inflammatory phase, the proliferative phase, and the remodeling phase. ³ Although the wound healing stages after the surgery are similar to the others, the immune response and increased inflammation in the body may cause the wound healing to go beyond its normal course and be delayed. Therefore, the maintenance of wound healing is important. ^{4,5}

Leech therapy is one of the most effective and natural ways of wound healing with its mechanical and biochemical properties. Medicinal leech therapy can be used in post-traumatic wounds to increase tissue salvage in amputated tissue replantation or flap surgery. It can also be used for chronic non-healing wounds, such as for treating diabetic foot ulcers, pressure ulcers, and venous leg ulcers. ⁶ The fact that it is low cost, fast, effective, easy and practical makes medicinal leech therapy preferable.

Medicinal leech therapy, also known as *hirudotherapy*, is one of the rare complementary and traditional treatments in which invertebrates are used for medical purposes. The history of leech therapy goes back to 1500 BC, and the usage of leeches can be seen in the Ancient Egyptian Hieroglyphs. However, known written sources have reached this day from Nicander of Colophon in the first second-century BC. ⁷ Unani physicians, who believe that diseases in the body are caused by humoral imbalance, which is Galen's (130-201 AD) theory influenced by Hippocrates (460-370 BC), have used leech therapy for centuries. Avicenna also recommended leech therapy, especially for skin diseases, in his book *Canon of Medicine*. ⁸ The use of leeches for medicinal purposes continued increasingly until the 19th century when their excessive use was referred to as *leechmania*. The use of *Hirudo medicinalis* in Europe was so excessive that leeches of this species were in danger of extinction. Thus, regulations were created for the leech trade. Therefore, the demand for leech therapy decreased with the decreasing leech populations and the developing new treatment methods. ⁹ Afterwards, research on the content of leech saliva and the FDA's (United States Food and Drug Administration) approval in 2004 to use *Hirudo medicinalis* for therapeutic purposes in plastic and reconstructive surgery drew attention to hirudotherapy again. ¹⁰

In Turkey, the 'Regulation on Traditional and Complementary Medicine Practices' was published in the Official Gazette dated 27.10.2014 and numbered 29158. Thus, criteria for the use of *H. medicinalis* and *H. verbana* for therapeutic purposes were determined. In this way, the way was opened for the use of leeches obtained from sterile medical leech farms approved by the Ministry of Agriculture by the relevant personnel and physicians in treatment and application centers for medical purposes. Leech therapy can be applied in government institutions as well as in approved private institutions. ¹¹

Hirudotherapy is defined as the use of sterilized medical leeches in the treatment. Medicinal leeches belong to the phylum Annelida, class Clitellata and subclass Hirudinea. ¹² Leeches feed on the blood of their hosts, the main benefit of leech therapy is that they deliver various bioactive substances from their saliva into the host's bloodstream during sucking. ¹³ The main purpose of this study is to present the studies in which medicinal leech therapy is used in the treatment of wounds in the form of a review. Additionally, this study aims to recognize medicinal leech therapy, introduce the leech species, which have therapeutic effects and indicate the effect mechanisms of leech saliva on the wound healing.

Materials and Methods

There are various studies on medicinal leeches and medical leech therapy. These studies include *in vitro* cell culture studies ¹⁴ and *in vivo* animal studies, as well as case reports. Since medicinal leeches are used in the treatment of various diseases, we come across case reports for many diseases. In this context, there are researches in which medical leeches are used in various diseases such as rheumatic and joint diseases, hemorrhoids, injuries, and ulcers and also for cosmetic anti-aging purposes.

This is a literature review. The authors searched for data on the medicinal leech therapy published between January 2000 and July 2022. The PubMed, Science Direct, Scopus and Google Scholar databases were investigated. The literature on the effects of leech therapy on wound healing has been reviewed in detail. First, leech therapy and hirudotherapy words were used for searching. Additionally, the substances in the leech saliva that may be responsible for wound healing were also investigated. The keywords were searched with multiple electronic searching in abstracts and titles as follows: leech, leech therapy, hirudotherapy, wound healing, medicinal leech therapy, saliva, bioactivities, *Hirudo medicinalis*, *Hirudo verbena*, *Hirudo orientalis*, and *Hirudo manillensis*, chronic wounds, non-healing wounds, trauma.

Articles published before 2000, articles that are written in a language other than English, articles unopen to full access, articles that are out of the context of the research, the incompatibility of articles, articles with insufficient quality, or articles with similar studies excluded from the study.

After removing all articles except for articles on wound healing, 60 of these articles were published before 2000, 190 of them were not full text, 36 of them were not eligible, and 31 of them were duplicates; thus, they were excluded from the review. As a result, 12 articles were selected as case reports for this review (Case reports only, *in vitro* and *in vivo* studies not included in the number given).

Results

Leech Species with Therapeutic Effects

In leeches, the body is flattened dorso-ventrally. The segments are in the form of an anterior and posterior drawer. Their bodies always consist of a fixed number of 34 segments. In their mouths, there are 300 teeth in total, with floating pieces in each jaw. That's why their bites are Y-shaped. Leeches, which are extremely sensitive to sudden changes such as temperature and amount of chlorine in their living environment, die, especially despite high chlorine content. Leeches use oxygen dissolved in water or atmospheric oxygen by taking it from the body's surface.^{15,16}

Although there are almost 800 leech species in the World, only about 15 of them can be classified as medicinal leeches. The types of medicinal leeches of subclass Hirudinea used for medical purposes are shown in Table 1. The leeches used for medicinal leech therapy generally belong to the genus *Hirudo* of the family Hirudinea. These leeches are accepted as non-poisonous and medicinal. One of the most important things in the choosing of leeches for medical purposes is that leeches should be sterile and not used on another person before. Additionally, only leeches in the medical leech category can be used for treatment.

The Effect Mechanisms of Medicinal Leeches

The therapeutic mechanisms of action of leeches have been extensively interpreted from the earliest times to the present day. Leech therapy includes an initial bite and a bonding period of about 20 to 45 min, during which the leech sucks blood. Formerly, it was believed that the main therapeutic benefits were from the phlebotomy when the feeding of leeches with the blood of their host, but in fact, it is shown the benefits caused by the bioactive substances found in the leech saliva that secreted into the host's bloodstream during sucking.¹⁷ The bioactive compounds found in leech saliva and their functions are given in Table 2.

Table 1. The types of medicinal leeches most commonly used for medical purposes

Hirudinea	<i>Hirudo medicinalis</i>
	<i>Hirudo verbana</i>
	<i>Hirudo orientalis</i>
	<i>Hirudo sulukii</i>
	<i>Hirudo nipponia</i>
	<i>Hirudo troctina</i>

Leeches cling to their prey with their suction cups located in the head and tail regions of their body. When the leech begins to feed, it releases chemicals that expand the vessels and increase the fluidity of the blood and analgesics. After the leech bite, it creates a suction pathway (extracellular matrix degradation), inhibits adhesion, aggregation and coagulation (inhibition of platelet function and anticoagulant effect), increases blood flow, protects itself (antimicrobial activity) and avoids detection (analgesic and anti-inflammatory effects).¹² After the feeding period, the leeches drop out from the attachment area as a result of complete satiation. Within the digestive system of leeches, blood is protected by endoenzymes. Endosymbiotic bacteria such as *Aeromonas hydrophilave* and *Pseudomonas hirudinia* play a role in the digestion of blood after feeding and prevent its putrefaction.¹⁸

Although more than 100 bioactive substances in protein and peptide structures with different molecular masses have been observed in leech saliva, some with an important active role have been identified.

Animal-based Studies on the Effects of Medicinal Leeches on Wound Healing

Animal studies have investigated the effects of hirudotherapy on wound healing and flap survival in rats and mice. These studies showed that leeches decrease necrosis via increased blood flow in the bite area and increase wound healing and flap salvage.

In a study, the researchers investigated the effect of leech therapy and topical phenytoin (PHT) application on incisional skin wound healing in an animal model (Wistar albino). The wound healing process of the rats in the group treated with medical leech (*H. orientalis*) was significantly faster than that in the group treated with topical phenytoin (PHT).²⁴ In another study, the scientists conducted a study on the effectiveness of hirudotherapy and ischemic preconditioning in flaps exposed to ischemia for a long time in a mice model. Especially when the hirudotherapy group was compared with the control group, the rate of necrosis decreased satisfactorily, and the flap survival rate increased to an average of 88%.²⁵

Table 2. The Bioactive Compounds Found in Leech Saliva and Their Functions. ^{12,19-23}

Modes of Action	Substance	Target or Function
Analgesic and Anti-Inflammatory Effects	Bdellins	Inhibits trypsin, plasmin, and sperm acrosin
	Hirustasin	Inhibits tissue (but not plasma) kallikrein
	LDTI (leech-derived tryptase inhibitor)	Inhibits tryptase
	Eglins	Inhibits α -chymotrypsin, chymase, subtilisin, and the neutrophil proteinases elastase and cathepsin G
	LCI (leech carboxypeptidase Inhibitor)	Inhibits Carboxypeptidase A
	Complement C1 Inhibitor	It can bind to complement-fixing sites of antibodies (IgG and IgM)
	Guamerin from <i>Hirudo nipponia</i>	Inhibits Leukocyte-elastase specifically
Anticoagulant Effects	Piguamerin from <i>Hirudo nipponia</i>	Inhibits kallikrein, and trypsin
	Hirudin	Inhibits thrombin
	Factor Xa Inhibitor	Inhibits Factor Xa
	Destabilase	Dissolves stabilized fibrin
Extracellular Matrix Degradation	Gelin	Inhibits elastase, cathepsin G, and chymotrypsin
	Hyaluronidase	Targets endoglucoronidic linkages of hyaluronic acid
Anti-Platelet Effects	Collagenase	Dissolves the collagen particles
	Apyrase	Targets Adenosine 5' Diphosphate, arachidonic acid, platelet-activating factor (PAF), and epinephrine
	Calin	Inhibits collagen-induced platelet aggregation (directly) or von-Willebrand factor collagen binding (indirectly)
The Effects on Blood Flow	Saratin	Inhibits the binding of α_2 integrin subunit I domain to collagen
	Acetylcholine	Targets blood vessels
Antimicrobial Effects	Histamine-like Substances	Targets blood vessels
	Destabilase	The β 1-4 bonds of the peptidoglycan layer in the bacterial cell wall
	Chloromycetin	Bacterial protein synthesis
	Theromacin	The bacterial membrane
	Theromyzin and Peptide B	-

The researchers investigated the effects of medical leech application on flap survival. They created ischemic random skin flaps on the rat dorsum. The study consisted of three groups: the control group, the group with one leech applied on the flap and the group with three leech-applied on the flap eight hours apart. While they found a significant decrease in flap survival in the group with three leech-applied flaps compared to the control, there was no significant difference between the group with one leech-applied flap and the control. ²⁶

Clinical Effects of the Medicinal Leech Therapy on Wound Healing

Post-traumatic Wounds

Some numbers of reports show the effectiveness of leech therapy on the salvage of organs damaged by traumatic injuries.

Leech therapy was applied to the patient with a laceration of the right ear after a vehicle accident to reduce venous congestion in this region. At the early stage of wound healing, the ear exhibited marked improvement, and signs of adequate revascularization began to appear in this area after the medicinal leech therapy. At the late stage of wound healing, the ear exhibited signs of complete revascularization.²⁷ When we look at the literature, there are various studies showing that medical leech therapy is used to salvage venous drainage in ear reconstruction.²⁸

In one case, microsurgical lip replantation was performed on a female patient who had traumatic lip amputation because of a dog attack. After the signs of venous congestion in the lip area were observed on the first postoperative day, medical leech treatment was performed. Medicinal leech therapy supported venous drainage and revascularization in the replanted lip. As a result, lip replantation was successful without any complications.²⁹ In the literature search, there are many cases in which leech therapy is used for revascularization, wound healing and survival of the damaged lip and surrounding structures after traumatic injury.³⁰

Flaps, which are one of the reconstructive procedures used to close soft tissue defects formed for any reason, are also generally used for post-traumatic wounds.

In a case report, a nasal flap was applied to a patient who had a nasal laceration after a weapon injury. Medical leech therapy, once daily for five days, was applied to increase flap survival in the patient who showed signs of venous congestion after the operation. Although revision surgery has been recommended after the scar tissue has matured, the fact that the flap remains infection-free and viable during the treatment, thanks to leech therapy, has been considered quite positive for the researchers.³¹

Because of crushing, the fingers of the 25-year-old patient, whose three fingers were at the level of rupture, were surgically replanted in place. Leech therapy, a total of 15 leeches, was applied to the patient to increase blood circulation in the finger area. The result was gratifying. Venous congestion decreased thanks to leech therapy. On the seventh day after the operation, the patient lost the fifth finger, but the third and fourth fingers were salvaged. The patient was able to return to work after three months.³²

Medical leeches were applied for treating ring avulsion in two cases, in which the arterial circulation was healthy, but only the venous supply was impaired. These cases were treated successfully with leeches, in addition to micro venous reconstruction was achieved by means of leech therapy.³³

In a case series evaluating the efficacy of Leech Therapy, patients with traumatic Soft Tissue Avulsions were included in this study. Medical leech therapy was applied to four patients after reconstruction and microvascular flap. Their study confirmed the excellent and positive effects on healing after medical leech therapy for flaps in the case of venous congestion. Additionally, the researchers stated that medicinal leeches might play a critical role in salvaging the soft tissue segment in such cases.³⁴

When we look at the literature, it is possible to come across studies in which the positive effects of medical leech application on patients suffering from gangrene are observed. In one case, a male patient with gangrene of his right toe complained of severe pain and sores upon untreated injury. Doctors applied leeches on the wounded toe to prevent amputation for 30 days. As a result of the treatment, the pain and blackness caused by gangrene in the finger area decreased.³⁵

Chronic Non-Healing Wounds

One case describes a 73-year-old patient who complained of a persistent and non-healing large-scale ulcer in the lower leg area due to scratching after a mosquito bite. After the proper debridement of the wound and a total of five sessions of leech therapy once a week, the healthy granulation tissue started to emerge, and healing started gradually. The wound began to improve significantly, and proper epithelialization was achieved. Slowly the discharge was reduced and the wound healed completely.³⁶

The 85-year-old patient had difficulty walking due to a large wound in the leg area, which caused pain and difficulty in walking. No matter what treatment was applied to the woman who had the chronic wound, it could not be healed and the patient whose leg was recommended to be amputated. The researchers applied bark paste of *Pongamia pinnata* along with medicinal leech therapy to achieve wound healing in this patient. At the end of the treatment protocol, all complaints of the patient were reduced and showed significant healing in the wounded area.³⁷

In a case series evaluating the efficacy of leech therapy, four patients with varicose ulcers were included in this study. Medical leech therapy was applied to four patients of different ages, being affected by different diseases and who had ulcers on their legs. In this case series, out of four cases, three cases of the ulcers were completely healed and also showed remarkable improvement in other variables such as pain, discomfort on walking and itching.³⁸

A 34-year-old female patient was suffering from a non-healing and necrotizing ulcer on her lower leg caused by systemic cutaneous sclerosis. The physicians applied a combination of leech therapy and Ayurvedic medicines to the patient's leg. After one month of treatment and three months of follow-up, the wound area got healed.³⁹

Medical leech therapy, in addition to antiseptic drugs and unripe papaya dressing, was applied to a 60-year-old female patient who was at risk of below-knee amputation due to a diabetic foot ulcer. Successful healing was achieved due to increased vascularization and decreased congestion of the wound after leech therapy. At the end of the 3-month treatment period, necrotic areas disappeared, the patient could walk comfortably, and the wound was completely healed. Thus, the patient was discharged in good condition without losing any of her limbs.⁴⁰

In diabetic foot ulcers that have become worse that may cause a limb amputation, some traditional treatments have been used along with medical leech therapy. Pain decreased immediately after leech therapy, and there was no wound on the toe after three weeks. Here, medical leech therapy had positive effects on wound healing.⁴¹

The case reports on leech therapy for the treatment of non-healing chronic wounds are given in Table 3, cases in which medicinal leech therapy was used.

Complications with Leech Therapy

Leech therapy has positive effects on people who are suitable for this treatment, and it is not possible to apply medicinal leech therapy to every individual (Table 4).

Different complications may be encountered in medical leech applications. The occurrence of infection after the leech application is a common situation with a rate of 2-36%. Bleeding, allergic reactions and bacterial infections are most common. Bacteria in the leech digestive tract can cause pneumonia, septicemia or gastroenteritis. It has been reported that the use of leeches without antibiotic treatment can cause bacterial infection at a rate of 20%.⁴² Some studies show the infections caused by *Aeromonas hydrophila* because of the use of leeches in venous congestion of flaps and replantation. While some of these infections are acute and mild, infections that cause partial flap loss, have also been encountered.^{43,44}

Bleeding is one of the most frequently reported complications. When the publications in the literature are examined, it has been reported that the bleeding due to leech therapy can be serious and excessive. In particular, Hirudin and histamine-like substances cause prolonged bleeding conditions.⁴⁵ A 25-year-old female patient who received leech therapy for varicose vein arrived in the emergency room 24 h after the leech

application because of the prolonged bleeding and received the necessary treatment. As the bleeding continued for 24 h, the physicians had to apply vein ligation under local anesthesia to the patient. ⁴⁶

Table 3. Cases in which medicinal leech therapy was used

The Cases of Traumatic Injuries					
Author(s)	Year	Indication(s)	Number(s)	Treatment(s)	Efficacy
Hullet et al. ²⁷	2007	Ear Laceration	n = 1	Ear Replantation + Medicinal Leech Therapy	Salvaged
Tachi et al. ²⁹	2018	Lip Amputation	n = 1	Lip Replantation + Medicinal Leech Therapy	Salvaged; venous drainage and revascularization
Jose et al. ³¹	2013	Nose Laceration	n = 1	Nasal Flap + Medicinal Leech Therapy	The nasal flap remained viable without infection
TarazJamshid et al. ³²	2014	Finger Crush	n = 1	Finger Replantation + Medicinal Leech Therapy	The patient lost the fifth finger, but the third and fourth fingers salvaged
Frodel et al. ³⁴	2004	Traumatic Soft Tissue Avulsion	n = 4	Flaps + Medicinal Leech Therapy	Decreased venous congestion, increased healing
Lari et al. ³⁵	2021	Gangrene	n = 1	Medicinal Leech Therapy	The pain and blackness decreased
The Cases of Chronic Non-Healing Wounds					
Dhule et al. ³⁶	2022	The Cases of Chronic Non-Healing Wounds	n = 1	Medicinal Leech Therapy + Antiseptic Dressings	Proper epithelialization and complete wound healing was achieved
Balasooriya et al. ³⁷	2021	Ulcerated Wound	n = 1	Medicinal Leech Therapy + the Bark Paste of <i>Pongamia pinnata</i>	Healing was achieved: pain, itching, and smells were no longer present
Zarnigar, Md. ³⁸	2011	Ulcerated Wound	n = 4	Medicinal Leech Therapy	Three out of four cases healed completely
Sharma et al.	2020	Ulcerated Wound	n = 1	Medicinal Leech Therapy + Ayurvedic Medications	Achieved wound healing
Zaidi, S.A ⁴⁰	2016	Ulcerated Wound	n = 1	Medicinal Leech Therapy + Antiseptic Drugs & Unripe Papaya Dressing	Successful healing: increased vascularization and decreased congestion
Laila et al. ⁴¹	2019	Diabetic foot Ulcer	n = 1	Medicinal Leech Therapy + Honey Curcumin Dressing	Decreased pain and increased wound healing

Table 4. Situations in which the application of medical leech therapy is not recommended¹⁰

Hematological Parameters	Patients receiving anticoagulant drug therapy	
	Patients with hemorrhagic disease, especially patients with hemophilia	
	Patients with severe anemia (Hb < 10)	
	Patients with an active bleeding focus	
Diseases	Patients with active tuberculosis or hypotension	
	Patients with advanced chronic disease:	Delayed wound healing
		Diabetes
		Arterial insufficiency
The acute phase of mental illness.		
Pregnant or Lactating Women	Since there is not enough data on the use of medical leeches in pregnant or lactating women, it should not be applied to these people.	
Immunological Parameters	Patients with acquired immune deficiency	
	Patients who are taking immunosuppressive therapy	
Others	Patients who will undergo surgical intervention	
Not recommended for children under the age of 18 years old		

Discussion

There are various review articles on the therapeutic effects, the effect mechanisms and indications of medical leech therapy and the content of medicinal leech saliva.^{12,47,48} We have reviewed the studies in which medical leech therapy is used to promote wound healing, particularly in post-traumatic wounds and non-healing chronic wounds.

Because of the continuous bleeding caused by the anticoagulant substances in the leech saliva, the capillary network is relieved, and tissue congestion is greatly reduced. That also causes an increase in lymph flow, positive changes in local hemodynamics, ease of hemorheology, an increase in oxygen supply, improvement of tissue metabolism, and elimination of tissue ischemia. Thus, the survival rate of the affected area is increased.

Post-traumatic wounds and chronic non-healing wounds carry the risk of various complications. One of the most common complications is necrosis due to insufficient perfusion developing in the affected areas. Also, delayed or impaired wound healing can lead to limb amputation. For this reason, many methods have been sought in the scientific community to increase wound healing and perfusion rate.

The results of our literature review indicate that medicinal leech therapy has promising potential in the healing of post-traumatic and chronic non-healing wounds. Medical leech therapy, which has a history of thousands of years, is still the subject of many scientific studies today. Nevertheless, more studies are needed for the potential effects of medicinal leech therapy in wound healing should be clarified by further studies.

Conflict of Interest: The authors declare no conflict of interest.

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