REVIEW
doi: 10.12032/TMR20190225105

Persian Medicine

Leech therapy indications: a scoping review

Roshanak Ghods[1, 2], Mojtaba Abdi[3], Matineh Pourrahimi[4], Fataneh Hashem Dabaghian[1, 2]

[1]Research Institute for Islamic and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran. [2]School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran. [3]School of Nursing and Midwifery Branch, Iran University of Medical Sciences, Tehran, Iran. [4]Faculty of Allied Medicine Branch, Iran University of Medical Sciences, Tehran, Iran.

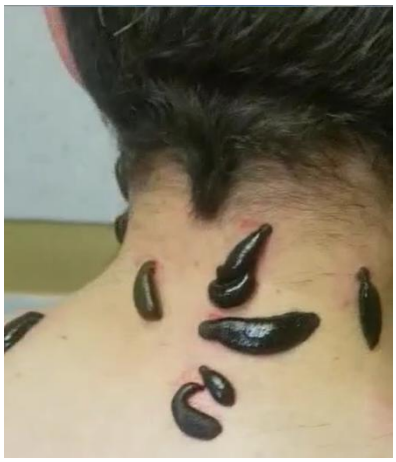
***Corresponding to:** Matineh Pourrahimi, Iran University of Medical Sciences (IUMS), Hemmat Highway, Tehran, Iran. E-mail: matinehpourrahimi@gmail.com.

Highlights

The present scoping review provides evidence for the application of leech therapy in the treatment of plastic and reconstructive surgery, musculoskeletal diseases, osteoarthritis, etc..

Traditionality

The first recorded report of the use of leeches is in a medical poem, Alexipharma, for Nicander of Colophon, born 200 B.C.. There is also evidence of the using leeches by large scholars such as Avicenna in *The Canon of Medicine* and Abd-el-Latif al-Baghdadi in *Al-Mukhtarat fi al-Tibb*. Barbers-surgeons in the middle ages used to use leeches to shed blood for treating some kind of diseases. With the development of modern medicine, the first use of medical leeches occurred in the 1960's, for intravenous congestion after reconstructive surgery. In 2004 the FDA approved leech therapy to accelerate tissue transplantation.



Operational method of leech therapy

doi: 10.12032/TMR20190225105

Abstract

After the developments of modern medicine, leeches were not used as before, but in the late nineteenth century, leeches were still being used in many countries around the world. Until now, leeches have been used to treat a wide range of diseases. The present study, is a scoping review of the evidence of the indication of leech therapy. The results of this study are based on English articles and dissertations published in databases from 2000 up to July 10, 2017. The results showed that leech therapy could be used in different conditions including venous congestion in plastic and reconstructive surgery, osteoarthritis, cardiovascular diseases due to blood coagulation disorders, migraine headache, skin disorders, diabetic foot ulcers, macroglossia, priapism, cancer complications, and wounds. More researches are needed in wider areas with more precise methodologies to ensure the potential therapeutic effects of leech therapy.

Keywords: Leeches, Leech therapy, Review, Plastic and reconstructive surgery, Musculoskeletal diseases, Osteoarthritis

Abbreviations:

DFU, Diabetic foot ulcer; VAS, Visual analog scale; TIA, Transient ischemic attack.

Competing interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

Citation:

Roshanak Ghods, Mojtaba Abdi, Matineh Pourrahimi, *et al*. Leech therapy indications: a scoping review. Traditional Medicine Research, 2019, 4(3): 118-130.

Appendix:

Appendix and video are available at https://www.tmrjournals.com/tmr/EN/10.12032/TMR20190225105.

Executive Editor: Cui-Hong Zhu, Xing Zhao.

Submitted: 1 February 2019, ***Accepted***: 15 February 2019, ***Online***: 24 February 2019.

TMR
doi: 10.12032/TMR20190225105

Background

The word "leech" means a physician, derived from an Anglo-Saxon word (laece) [1]. The leeches are from the ringworm branch (Phylum: Annelida) in Clitellata Class because a genital belt is near their gonads. These worms belong to the Hirudinea sub-class which are bloodthirsty and hermaphrodite and they have suction at their two ends. Their mouth is in the anterior and thinner sections and their connector disk is in the posterior and wider part of their body. Their mouth has three jaws. When the leech bites the body of the host, it leaves a Y shape wound, and in this case, it injects various compounds that were made by its salivary glands [2-4]. The region of leech bites, due to its anticoagulant properties, can bled for hours [5-8].

Medicinal leeches (Hirudo Medicinalis) have a long history. From the cave paintings in ancient Egypt more than 3,500 years ago, until the Persian, Arabic, China, Greek, Byzantine, and Sanskrit writings in the first century A.D.. The first recorded report of the use of leeches is in a medical poem, Alexipharma, for Nicander of Colophon, born 200 B.C. [9-11]. There is also evidence of the using leeches by large scholars such as Avicenna in *The Canon of Medicine* [12] and Abd-el-Latif al-Baghdadi in *Al-Mukhtarat fi al-Tibb* [13]. After the development of modern medicine, the use of leeches was gradually forgotten, but in the late nineteenth century, leeches were still used in many countries of the world [14]. The first use of medical leeches occurred in the 1960's, for intravenous congestion after reconstructive surgery [15]. In 2004 the FDA approved leech therapy to accelerate tissue transplantation [16]. Up to now, the leech has been used to treat a wide range of diseases (Video 1), for its therapeutic properties associated with more than 100 active substances in its salivary glands which injected into the host tissue during sucking [17-24].

Due to the importance of this issue and the need to address a scientific approach to leech therapy, the purpose of this study was to search and review articles related to the common use of leech in various diseases treatment.

Methods

Search strategy

The present study is a scoping review of the evidence of the indication of leech therapy which its proposal was approved by the Institute of Islamic Medicine, Iran University of medical sciences on October 18, 2016, No. 88. The results of this study are based on English articles and dissertation published in databases such as Ebsco Host (All academics Version), Ovid, ProQuest, PubMed, Science Direct, Scopus, Web of Knowledge (Full Access) and Wiley and Google Scholar (as a search engine). The articles were related to our topic gathered and reviewed. The time frame for the search of articles was up to July 10, 2017, and because of using new findings publications below 2000 were omitted from this study.

At first, the standard keyword and its equivalents were extracted from the MESH. Then, in the PubMed, pilot search was performed to discover more keywords for writing search strategy by using Leech, Leeche, Leech Therapy, Leeching, Hirudinea, Hirudineas, Hirudo therapy and their equivalents, along with their expected combined forms, with the help of appropriate operators of the site. After identifying all the equivalent terms and all the combinations of words a search strategy was written and a strategic search was carried out at all of the sites mentioned. The articles were probed independently by two members of the research team for increasing accuracy and precision in the search. Finally, all of the articles were merged into one another. The search strategy is mentioned in the appendix.

Papers selection

This stage was conducted by two members of the research-team work and in case of disagreement, the third person gave the final comment. At the first step, duplicate articles were deleted. Then valid articles were separated from the news, the pages of public journals, newspapers and other non-authoritative sources, as well as articles in the form of posters or lectures because of inability to evaluate the internal validity of the research. Next, valid sources extracted were categorized by subject. In the next step, the abstract part of the articles was reviewed. Then, the full text of the articles with our desired characteristics was extracted through an access to the Central Library of Iran University of Medical Sciences. In order to get the full text of the inaccessible articles through this library, emails were sent to the authors of the articles. Then the entire texts of articles were studied and the final papers which were absolutely related to our study were selected to use in this study. The EndNote Ver.X7 software was used to manage articles. The paper flow is shown in Figure 1.

Data extraction

The findings of the articles and related items together with their reference were collected separately for each category. After reading all the selected articles and searching the citation of each paper, the materials were summarized and used in the text of the article.

Results

Researches showed that leech therapy is used in the following conditions in the world:

Plastic and reconstructive surgery

doi: 10.12032/TMR20190225105

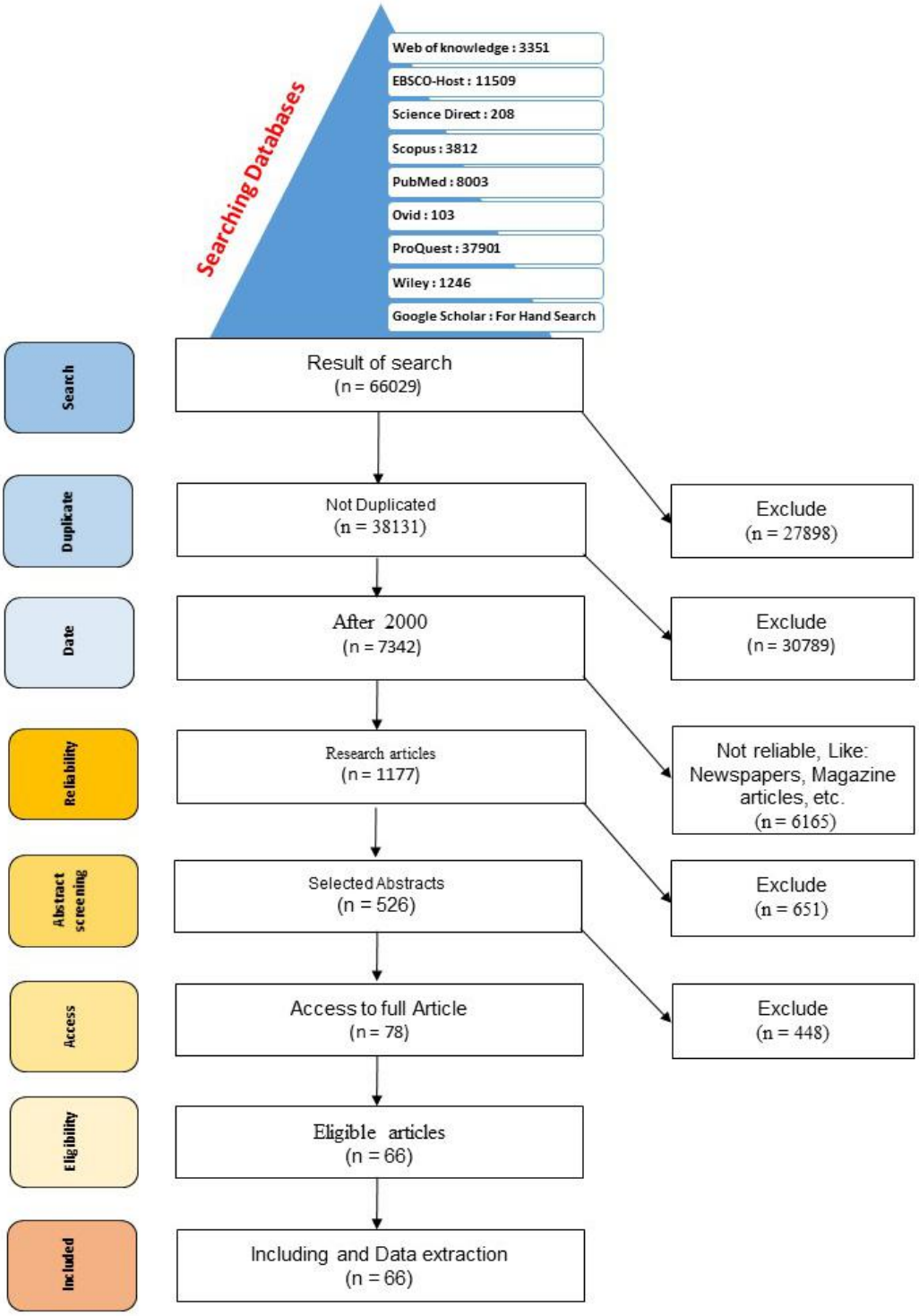


Figure 1 The papers flow chart

TMR
doi: 10.12032/TMR20190225105

Table 1 Plastic and reconstructive surgery

Type of study	First author	Year published	Type of flap	Total	Survived	Failed
Retrospective Studies	Cornejo [25]	2017	Free flaps native tissues pedicled flaps and replantation	87	53	34
	Butt [26]	2016	Venous congested flaps congested replanted or revascularized hand digits	20	13	7
	Gröbe [27]	2012	Local flaps pedicled flaps and microvascular flaps	148	54	94
	Koch [28]	2012	Free flaps and replanted tissues	6	6	0
	Nguyen [29]	2012	Native skin local flaps regional flaps and free flaps	38	29	9
	Agarwal [30]	2010	Thumb replantation	52	48	4
	Riede [31]	2010	Various local flaps	23	20	3
Case Reports	Banihani [32]	2014	Penile replantation	1	1	0
	TarazJamshidi [33]	2014	Finger replantation	3	2	1
	Stemann [34]	2012	Nose replantation	1	1	0
	Kim [35]	2011	Eyebrow transplantation	1	1	0
	Baj [36]	2010	Lip replantation	1	1	0
	Kim [37]	2009	Ear replantation	1	1	0
	Taylor 38]	2009	Lip replantation	1	1	0
	Ward [39]	2008	Pedicled flaps	1	1	0
	O'Toole [40]	2008	Ear replantation	1	1	0
	Flores [41]	2007	Nose replantation	1	1	0
	Kim [42]	2007	Tongue replantation	1	1	0
	Hullett [43]	2007	Replantation	1	1	0
	Lazarou [44]	2006	Penile replantation	1	1	0
	Heckmann [45]	2005	Haematoma	1	1	0
	Yim [46]	2005	Replantation	3	3	0
	Frodel [47]	2004	Avulsed soft tissue segments	4	4	0
	Tuncali [48]	2004	Ring avulsion injuries	2	2	0
	Mineo [49]	2004	Penile replantation	1	1	0
	Duroure [50]	2004	Lip replantation	3	2	1
	Ribuffo [51]	2004	Free flap	1	1	0
	Gideroglu [52]	2003	Pedicled flaps	5	4	1
	Sartor [53]	2002	Various	7	2	5
	Guven [54]	2002	Ring avulsion injury	1	1	0
	Chepeha [55]	2002	Free flap	8	8	0
	Akyurek [56]	2001	Ear replantation	1	0	1
	Talbi [57]	2001	Ear replantation	1	1	0
	Guneren [58]	2000	Nipple congestion	1	1	0
	Total			428	268	160

TMR
doi: 10.12032/TMR20190225105

Venous congestion is known as a common complication after plastic and reconstructive surgery, resulting in tissue loss and failure of the transplant. In this study, 34 articles were found that leech therapy has been used after various reconstructive surgeries (Table 1).

Out of 428 cases, 75 cases were related to the transplant which include ears [37, 40, 56, 57], nose [34, 41], lips [36, 38, 50], eyebrows [35], tongue [42], thumbs and fingers [30, 33], penile [32, 44, 49] and nipple [58]. Of the 428 cases, 62.6 percent (268 cases) achieved treatment success.

Another application of leech therapy in reconstructive surgery is salvage of tissue avulsions. Although the use of leeches in these conditions is unusual, in three studies, leech therapy is used when arterial inflow was adequate yet venous outflow was not and all 7 cases were treated [47, 48, 54].

Musculoskeletal diseases

9 related articles were found (Table 2) and 7 of them focused on the use of leeches in order to treat knee osteoarthritis. One study reported that after application of leeches, rapid relief of pain was observed in all patients. This patients' pain score was reduced from an average score of 4.7 in the Visual Analog Scale (VAS) to 1.3 meaningfully and remained stable for 4 weeks after treatment [59]. A similar study was conducted to compare leech therapy with the use of topical diclofenac in patients with knee osteoarthritis. The mean pain score in the leech therapy group and the diclofenac group respectively reduced 39.9 and 7.7 scores in pain scales of the Western Ontario and McMaster Universities Osteoarthritis Index visual analogue scales [60]. In another study, pain relief was not significantly different with a double application of leeches, but both groups had a significant reduction in pain compared to the control group. The results showed improvement in stiffness and function in a double application with the leeches [61]. Improvement in disease-specific symptoms after leech therapy was reported by other studies that confirming the previous findings [62-65].

There is a research, aimed to treat symptomatic arthrosis of the first carpometacarpal joint. In this study, one application of leeches was compared with topical diclofenac. The mean of pain score in the VAS reduced from 50.6 ± 13.3 to 46.9 ± 18.5 in Topical diclofenac and from 59.6 ± 13.8 to 27.1 ± 20.6 in leech group ($P < 0.0003$) during 7 days. Grip strength of the thumb joint (lateral pintch power) which was performed by an electronic device, significantly increased too [66].

Also, there is a similar article dealt with chronic epicondylitis. During 45 days, the mean scores from 3 visual analog scales for pain during motion, grip, and rest decreased strongly in the leech group comparing with topical diclofenac [67].

Cardiovascular diseases

In the field of cardiovascular disease, there are 2 articles focusing on blood coagulation. The research reported that symptoms in over 50% of chronic heart failure patients improved using standard treatment combined with leech therapy. The diastolic pressure decreased and ejection fraction increased in hypertensive patients. Platelet aggregation reduced and fibrin monomer complexes normalized [68]. In another study, leech therapy was used to treat patients with deep vein thrombosis [69].

Leeches also were applied for neurological disorders caused by ischemia. It was showed that patients with transient ischemic attack (TIA) receiving leech therapy combined with routine treatments, less re-TIA occurs within one year after treatment [70]. Another research also showed that leech therapy caused a significant decrease of ear noise and the maintenance of the tendency toward further improvement of cochlear and vestibular functions in patients with peripheral cochleovestibular disorders [71].

Migraine headaches

There is a non-randomized clinical trial including two groups of patients with migraine headaches. One receiving leech therapy and the other receiving routine drug therapy (Propranolol 80 mg/day and Amitriptyline 50 mg/day). Patients were followed up one week, one month, two months and three months after the intervention. The result indicated leech therapy had the same effect as medication to relieve migraine headaches and it could reduce severity and duration of a headache significantly for at least three months [72].

Skin disorders

2 articles were found related to using of leeches for skin disorders. It is showed that leech therapy can reduce erythema, thickness, scratching and lichenification in patients with dermatitis. The total scores of EASI and SCORAD decreased and the patients' quality of life increased [73]. A case of a patient with Nevus of Ota receiving leech therapy also showed significant improvement in the skin color [74].

Diabetic foot ulcers

3 articles reported using of leech therapy as a treatment for diabetic foot ulcer (DFU). In a case report of a patient with 4 DFUs grade 5 receiving leech therapy caused completely improvement of the pain, wound, and deformity of the patient's leg. The diabetic foot saved from amputation and the patient could walk finally. However antiseptic and deobstruent drugs besides leech therapy and unripe papaya dressing helped in the process of healing [75]. Other cases of DFUs which perfectly improved by leech therapy showed in table 2 [76, 77].

TMR
doi: 10.12032/TMR20190225105

Table 2 Papers at a glance

First author	Year published	Type of study	Diagnosis	Patients	Effect of leech therapy
Michalsen [59]	2002	Non-randomized controlled trial	Knee osteoarthritis	Leech therapy: 10 patients; control: 6 patients	Rapid relief of pain within 24 hours and 10 days later and stable until 4 weeks
Michalsen [60]	2003	Randomized controlled trial	Knee osteoarthritis	Leech therapy: 24 patients; topical diclofenac therapy: 27 patients	Relief of pain within 7 days
Andereya [61]	2008	Randomized controlled trial	Knee osteoarthritis	Single application: 35 patients; double application: 38 patients and a control group: 40 patients	Improvement in stiffness and function in a double application with the leeches until 6 month. Relief of pain has no different in single and double application but has different with the control group.
Zaidi [62]	2009	Randomized controlled trial	Knee osteoarthritis	Leech therapy: 20 patients; control: 27 patients	Improvement in disease-specific symptoms after six weeks of treatment in patients receiving leech therapy like pain level, stiffness, and functional ability, it was significant in comparison to mean scores but it is statistically non-significant.
Rai [63]	2011	Self-control clinical trial	Knee osteoarthritis	32 patients of knee osteoarthritis	Reduction of pain, tenderness, swelling, stiffness, restriction of movement and crepitus after leech therapy
Stange [64]	2012	Randomized controlled trial	Knee osteoarthritis	Leech therapy first: 27 patients; transcutaneous electrical nerve stimulation first: 25 patients	Improvement in pain and functional symptoms with single leech therapy
Shiffa [65]	2013	Randomized controlled trial	Knee osteoarthritis	Leech therapy along with an Unani formulation: 30 patients; Unani formulation only: 30 patients	Improvement in the reduction of pain, other symptoms, and physical functions in the test group
Michalsen [66]	2008	Randomized controlled trial	Osteoarthritis of the first carpometacarpal joint	Leech therapy: 16 patients; Topical diclofenac: 16 patients	Improvement in pain, joint function, quality of life, and grip strength in the leech group
Bäcker [67]	2011	Randomized controlled trial	Chronic lateral epicondylitis	Leech therapy: 20 patients; Topical diclofenac: 20 patients	Reduction of pain score and functional disability
Konyrtaeva [68]	2002	Randomized controlled trial	CHF	Leech therapy: 36 patients; control: 34 patients	In more than 50%: reduction of dyspnea and peripheral edema and increase of physical stress tolerance. In hypertensive patients: decreased of diastolic blood pressure and increased of ejection fraction. Reduce of platelet aggregation and normalizing fibrinogen and SFMC levels.
Hanif [69]	2012	Case report	DVT	1 patient with DVT	Treated

TMR
doi: 10.12032/TMR20190225105

Nargiza [70]	2010	Randomized controlled trial	TIA	55 patients: hypertension; 24 patients: atherosclerosis; 41 patients: atherosclerosis and Hypertension) (leech therapy: 58 patients; control: 62 patients)	The greatest improvement in pain, stiffness, and function in the group treated twice with the leeches
Bakhshi [72]	2015	Non-randomized clinical trial (with individual matching)	Migraine headaches	26 Female patients with primary headache which all reported lack of efficacy in past drug treatments (leech therapy: 13 patients Drug therapy (Propranolol 80 mg/day and Amitriptyline 50 mg/day): 13 patients)	No significant difference in the mean of pain severity and duration between drug therapy and leech therapy until 3-month follow-up after treatment. But reduction in the mean of pain severity and duration in compared with the baseline was significant.
Shankar [73]	2014	Self-control Clinical trial	Dermatitis (Vicarcikā)	27 patients with classic symptoms of Eczema	Reduction of erythema, redness, thickness, scratching and lichenification 54.45% reduction in EASI score 55% reduction in SCORAD score 62.36% improve in quality of life
Rastogi [74]	2014	Case report	Nevus of Ota	1 patient with nevus of Ota	Improvement in the skin color
Ziadi [75]	2016	Case report	Diabetic foot ulcer	1 patients with DFUs in left foot	Complete Healing in 90-150 days
Na [76]	2003	Case report	Diabetic foot ulcer	1 patients with DFU in right foot	Complete Healing in 41 days
Ziadi [77]	2016	Case report	Diabetic foot ulcer	1 patients with DFUs in left foot	Complete Healing in 90-150 days
Ramzan [78]	2010	Case report	Macroglossia	1 patients with Macroglossia	Complete Healing in 1 days
Bumpous [79]	2001	Case report	Macroglossia	1 patients with Macroglossia	Complete Healing in 3 days
Asgari [80]	2017	Case report	Priapism	1 patient with Priapism	After 2 days: reduce of pain 3rd day: discharged from hospital One month later: loss of pain and perineal swelling
Kalender [81]	2010	Case report	Leiomyosarcoma	1 patient with synchronous renal cell carcinoma and leiomyosarcoma was admitted with severe pain in the lumbar region. The pain was refractory to radiotherapy, and systemic and epidural analgesic infusion.	After 2 days in a month reduce of pain from 9/10 in visual analog score to 1/10.
Philip [82]	2003	Case report	Prostate adenocarcinoma	Three men with locally advanced prostate adenocarcinoma presented acutely with penoscrotal edema.	After 3 times use of leeches within 15 days: decrease in the edema with near-normal scrotal size and urinary symptomatic relief
Darestani [90]	2014	Randomized control trial	Wound	15 male Wistar rats (Rattus norvegicus albinus) with 2 cm liner incision (5 rats: Leech Therapy; 5 rats: treated with Topical phenytoin 1%; 5 rats: no treatment)	Leech therapy improved incisional skin-wound healing in rats significantly.

CHF, Chronic heart failure; DVT, Deep vein thrombosis; TIA, Transient ischemic attack; DFU, Diabetic foot ulcer.

TMR
doi: 10.12032/TMR20190225105

Macroglossia

2 articles founded in this issue. They focused on macroglossia caused by edema and hematoma. One case of macroglossia caused by damage and ecchymosis, was treated with leeches, although previously, routine treatment did not work. As the result of the 24-hour treatment process, a significant reduction in the size of the tongue occurred [78]. In another case of a progressive macroglossia after blunt trauma, it rapidly improved by leech therapy [79].

Priapism

Leech therapy was used in order to treat priapism in a 26-year-old patient without a history of certain diseases. After two days, the pain was significantly reduced, although the patient still had cavernosal swelling and tenderness to palpation. Finally, the pain and perineal swelling completely healed after one month [80].

Cancer

2 articles were conducted on the effect of hirudo medicinalis. There was the case of a male patient with synchronous renal cell carcinoma and leiomyosarcoma with severe pain in the lumbar region which was refractory to radiotherapy, and systemic and epidural analgesic infusion. The pain healed completely by using leeches on the lumbar region [81]. Also, leech therapy improved penoscrotal oedema due to hormone-refractory prostate carcinoma in another case [82].

However, there are two other species of leeches were taken into consideration that these articles refer to:

Haementeria ghilianii: The substance in the saliva of this leech called Ghilanten, was considered by researchers in 1995. The results showed Ghilanten or the saliva of this leech had antitumor effects without obvious side effects in vivo and in vitro. This effect involves the inhabitation of cell proliferation and reduction of apoptosis by the individual's own immune system and reducing cell-to-cell binding and inflammation [83].

Haementeria ghilianii: There are 7 patents for the use of a whole, leech saliva extract for cancer treatment but no article has been published to prove the effectiveness of this leech so far, and it is only a scientific claim. These patents claimed the effect of leech saliva on cancer treatment, including lymphoma, melanoma and colorectal, pancreatic, kidney, prostate, ovarian and breast cancer [84-89].

Wound

The effect of leech therapy on linear incisional skin-wound was examined in an experimental study. Wounds of about 2 cm in the same depth were made on dorsolateral region of 15 male rats. They were divided into three groups. The first group was treated daily with topical phenytoin 1% while the second group received leech therapy once at the beginning. The control group had neither medications nor leech therapy. Survey of 3th and 7th days of the experiment pointed out hair growth in the wound area was better in the leech therapy group, and the completely covered it during the 7 days. Also, the wounds completely healed in pathological studies. Generally, the superficial wound appearance represents a significant impact on wound healing in the group of leech therapy [90].

Discussion

This study was designed to provide leech therapy indications. The results of this study showed leech therapy is used in different conditions in the world including venous congestion in plastic and reconstructive surgery, osteoarthritis, cardiovascular diseases due to blood coagulation disorders, migraine headache, skin disorders, diabetic foot ulcers, macroglossia, priapism, cancer complications, and wounds. These findings were extracted from articles published from 2000 up to July 10, 2017. As the results show, articles related to plastic and reconstructive surgery with the quantity of 34, has the highest number of published articles. Subsequently, musculoskeletal diseases with 9 published articles are ranked second in this topic. However, knee osteoarthritis with 7 articles of 9 has more evidence than other musculoskeletal diseases. In the third place, there are articles related to cardiovascular diseases. Articles about diabetic foot ulcers, macroglossia, cancer complication, priapism and Nevus of Ota were case reports.

A noteworthy point in this study is the similarity of some of these indications published in recent decades with those recommended in the traditional medical literature, belonged to more than 10 centuries ago. Leech therapy for the treatment of arthritis pain, types of headache (hot headache) [91], skin diseases such as psoriasis (a kind of eczema commonly known as "Guba" or " Da' Alsdf" in Iranian traditional medicine) and erysipelas (a kind of dermatitis commonly known as "Al-Hamreh" in Iranian traditional medicine), decrease venous congestion in varicose veins of legs and healing of variety of wounds ("Sa'feh" and "Balkhieh") has been mentioned in the Ibn-Sina's book *The Canon of Medicine* [12]. It was found that there is still a large number of well-documented and fully accepted indications for the treatment of diseases in traditional medicine books that have not been investigated. These include visual impairment (placing leeches on temples), spot baldness (Alopecia areata), discolored skin patches, various types of rashes and boils, hemorrhage (placing leech around the anus), etc [12].

The limitations of this research are the lack of randomized controlled trials in humans and few

TMR
doi: 10.12032/TMR20190225105

numbers of samples, case reports on the use of leeches for patients, lack of reliable protocol for leeches, high heterogeneity of articles and lack of a proper checklist to check their quality together.

Conclusion

Due to the few numbers of studies in many of these areas and the inadequate methodological quality of some of them, including the small samples, lack of a control group, and the presence of more articles in the lower levels of the evidence pyramid, it seems that more research is needed in wider areas with more precise methodologies in order to ensure the potential therapeutic effects of this little creature recommended repeatedly to use it in various diseases from the past and in ancient medical texts. Although these numbers of evidence that were similar to those recommended in ancient medical texts which they mostly are successful are incentives for researchers to pay more attention to other leech therapies suggested by older scholars. Maybe we can reach less costly and faster and more effective treatments with leech therapy.

References

1. Isaacs D. The much maligned leech. J Paediatr Child Health. 2014, 50: 661-662.
2. Heukelbach J, Hengge UR. Bed bugs, leeches and hookworm larvae in the skin. Clin Dermatol 2009, 27: 285-290.
3. Mann KH. Leeches (Hirudinea): their structure, physiology, ecology and embryology: Elsevier, 2013.
4. Mehlhorn H. Encyclopedia of parasitology. Springer Science, 2008.
5. Eldor A, Orevi M, Rigbi MJBR. The role of the leech in medical therapeutics. Blood Rev 1996, 10:201-209.
6. Koh CY, KiniRMJEroh. Anticoagulants from hematophagous animals. Expert Rev Hematol 2008, 1: 135-139.
7. Salzet M. Anticoagulants and inhibitors of platelet aggregation derived from leeches. FEBS Lett 2001, 492:187-192.
8. Salzet M. Leech thrombin inhibitors. Curr Pharm Des 2002, 8: 493-503.
9. Papavramidou N, Christopoulou - Aletra H. Medicinal use of leeches in the texts of ancient Greek, Roman and early Byzantine writers. Intern Med J 2009, 39: 624-627.
10. Soucacos PN, Beris AE. Management of venous congestion in trauma and reconstructive microsurgery: the significance of medicinal leeches. In: Advances in Upper and Lower Extremity Microvascular Reconstructions. World Scientific 2002, pp. 34-40.
11. Whitaker IS, Rao J, Izadi D, *et al*. Historical Article: Hirudo medicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history. Br J Oral Maxillofac Surg 2004, 42: 133-137.
12. Ibn-Sina. *Kitab al-qanoun fi al-tib*. Typographia Medicea, Romae. 1593.
13. AI-Baghdadi. *Kitab aI-Mukhtarat fi al-Tibb*. Osmania Oriental Publications, Osmania University, Hyderabad. 1942-1944.
14. Lui C, Barkley Jr TW. Medicinal leech therapy: New life for an ancient treatment. Nursing 2015, 45: 25-30.
15. Deganc M, Zdravic F. Venous congestion of flaps treated by application of leeches. Br J Plast Surg 1960, 13: 187-192.
16. Rados C. Beyond bloodletting: FDA gives leeches a medical makeover. FDA consumer 2004, 38: 9-9.
17. Abdualkader A, Ghawi A, Alaama M, *et al*. Leech therapeutic applications. Indian J Pharm Sci 2013, 75: 127.
18. Ahirrao R, Jadhav J, Pawar S. A review on leech therapy. Pharma Sci Monit 2017, 8:228-237.
19. Barzegar A, Azizi A, Faridi P, *et al*. Leech therapy in Iranian traditional medicine. Forsch Komplementmed 2015, 22: 50-53.
20. Baskova I, Kostrjukova E, Vlasova M, *et al*. Proteins and peptides of the salivary gland secretion of medicinal leeches Hirudo verbana, H. medicinalis, and H. orientalis. Biochemistry 2008, 73: 315-320.
21. Hildebrandt JP, Lemke S. Small bite, large impact – saliva and salivary molecules in the medicinal leech, Hirudo medicinalis. Naturwissenschaften 2011, 98: 995-1008.
22. Lemke S, Müller C, Lipke E, *et al*. May salivary gland secretory proteins from hematophagous leeches (Hirudo verbana) reach pharmacologically relevant concentrations in the vertebrate host? PLOS One 2013, 8: e73809.
23. Wollina U, Heinig B, Nowak A. Medical leech therapy (Hirudotherapy). Our Dermatol Online 2016, 7: 91.
24. Zaidi S, Jameel S, Zaman F, *et al*. A systematic overview of the medicinal importance of sanguivorous leeches. Altern Med Rev 2011, 16: 59-65.
25. Cornejo A, Shammas RL, Poveromo LP, *et al*. Institutional outcomes of leech therapy for venous congestion in 87 patients. J Reconstr Microsurg 2017, 33: 612-618.
26. Butt AM, Ismail A, Lawson-Smith M, *et al*. 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 2016, 28: 219-223.
27. Gröbe A, Michalsen A, Hanken H, *et al*. Leech

TMR
doi: 10.12032/TMR20190225105

therapy in reconstructive maxillofacial surgery. J Oral Maxillofac Surg 2012, 70: 221-227.
28. Koch CA, Olsen SM, Moore EJ. Use of the medicinal leech for salvage of venous congested microvascular free flaps of the head and neck. Am J Otolaryngol 2012, 33: 26-30.
29. Nguyen MQ, Crosby MA, Skoracki RJ, *et al*. Outcomes of flap salvage with medicinal leech therapy. Microsurgery 2012, 32: 351-357.
30. Agarwal JP, Trovato MJ, Agarwal S, *et al*. Selected outcomes of thumb replantation after isolated thumb amputation injury. J Hand Surg 2010, 35:1485-1490.
31. Riede F, Koenen W, Goerdt S, *et al*. Medicinal leeches for the treatment of venous congestion and hematoma after plastic reconstructive surgery. J Dtsch Dermatol Ges 2010, 8: 881-888.
32. 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: 472-474.
33. 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: e6897.
34. Stemann Andersen P, Elberg JJ. Microsurgical replantation and postoperative leech treatment of a large severed nasal segment. Plast Surg Hand Surg 2012, 46: 444-446.
35. Kim KS, Hwang JH, Lee SY. Microvascular eyebrow transplantation. J Plast Reconstr Aesthet Surg 2011, 64: e241-e243.
36. Baj A, Beltramini GA, Laganà F, *et al*. Microsurgical upper lip replantation: a case report. J Oral Maxillofac Surg 2010, 68: 664-667.
37. Kim KS, Kim ES, Hwang JH, *et al*. Microsurgical replantation of a partial helix of the ear. Microsurgery 2009, 29: 548-551.
38. Taylor HO, Andrews B. Lip replantation and delayed inset after a dog bite: a case report and literature review. Microsurgery 2009, 29: 657-661.
39. Ward C, Craw L, Cherian A, *et al*. Medicinal leeches: Taking a bite out of venous congestion. Nursing 2008, 38: 28-30.
40. O'Toole G, Bhatti K, Masood S. Replantation of an avulsed ear, using a single arterial anastamosis. J Plast Reconstr Aesthet Surg 2008, 61: 326-329.
41. Flores RL, Bastidas N, Galiano RD. Successful replantation of an amputated nose after dog bite injury. Otolaryngol Head Neck Surg 2007, 136: 326-327.
42. Kim JS, Choi TH, Kim NG, *et al*. The replantation of an amputated tongue by supermicrosurgery. J Plast Reconstr Aesthet Surg 2007, 60: 1152-1155.
43. Hullett JS, Spinnato GG, Ziccardi V. Treatment of an ear laceration with adjunctive leech therapy: a case report. J Oral Maxillofac Surg 2007, 65: 2112-2114.
44. Lazarou EE, Catalano G, Catalano MC, *et al*. The psychological effects of leech therapy after penile auto-amputation. J Psychiatr Pract 2006, 12: 119-123.
45. Heckmann J, Dütsch M, Neundörfer B, *et al*. Leech therapy in the treatment of median nerve compression due to forearm haematoma. J Neurol Neurosurg Psychiatry 2005, 76: 1465-1465.
46. Yim Y, Kwon H, Oh DY, *et al*. Replantation of Nose Amputation by Use of Medical Leech. J Korean Soc Plast Reconstr Surg 2005, 32: 124-130.
47. Frodel Jr JL, Barth P, Wagner J. Salvage of partial facial soft tissue avulsions with medicinal leeches. Otolaryngol Head Neck Surg 2004, 131: 934-939.
48. Tuncali D, Terzioglu A, Cigsar B, *et al*. The value of medical leeches in the treatment of class IIC ring avulsion injuries: report of 2 cases. J Hand Surg 2004, 29: 943-946.
49. Mineo M, Jolley T, Rodriguez G. Leech therapy in penile replantation: a case of recurrent penile self-amputation. Urology 2004, 63: 981-983.
50. Duroure F, Simon E, Fadhul S, *et al*. Microsurgical lip replantation: evaluation of functional and aesthetic results of three cases. Microsurgery 2004, 24: 265-269.
51. Ribuffo D, Chiummariello S, Cigna E, *et al*. Salvage of a free flap after late total thrombosis of the flap and revascularisation. Scand J Plast Reconstr Surg Hand Surg 2004, 38: 50-52.
52. Gideroglu K, Yildirim S, Akan M, *et al*. Immediate use of medicinal leeches to salvage venous congested reverse pedicled neurocutaneous flaps. Scand J Plast Reconstr Surg Hand Surg 2003, 37: 277-282.
53. Sartor C, Limouzin-Perotti F, Legré R, *et al*. Nosocomial infections with Aeromonas hydrophila from leeches. Clin Infect Dis 2002, 35: e1-e5.
54. Guven H, Akbas H. The use of leeches in the management of a ring avulsion injury. Eur J Plast Surg 2002, 25: 162-164.
55. Chepeha DB, Nussenbaum B, Bradford CR, *et al*. Leech therapy for patients with surgically unsalvageable venous obstruction after revascularized free tissue transfer. Arch Otolaryngol Head Neck Surg 2002, 128: 960-965.
56. Akyürek M, Safak T, Keçik A. Microsurgical ear replantation without venous repair: failure of development of venous channels despite patency of arterial anastomosis for 14 days. Ann Plast Surg 2001, 46: 439-443.
57. Talbi M, Stussi JD, Meley M. Microsurgical replantation of a totally amputated ear without

TMR
doi: 10.12032/TMR20190225105

venous repair. J Reconstr Microsurg 2001, 17: 417-420.
58. Güneren E, Erolu L, Akba H, *et al*. The use of Hirudo medicinalis in nipple-areolar congestion. Ann Plast Surg 2000, 45: 679-681.
59. Michalsen A, Moebus S, Spahn G, *et al*. Leech therapy for symptomatic treatment of knee osteoarthritis: results and implications of a pilot study. Leech 2002, 84: 88.
60. Michalsen A, Klotz S, Ldtke R, *et al*. Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med 2003, 139: 724-730.
61. Andereya S, Stanzel S, Maus U, *et al*. Assessment of leech therapy for knee osteoarthritis: a randomized study. Acta orthopaedica 2008, 79: 235-243.
62. Zaidi S, Jamil S, Sultana A, *et al*. Safety and efficacy of leeching therapy for symptomatic knee osteoarthritis using Indian medicinal leech. Indian J Tradit Knowl 2009, 8: 437-442.
63. Rai P, Singh A, Singh O, *et al*. Efficacy of leech therapy in the management of osteoarthritis (Sandhivata). Ayu 2011, 32:213.
64. Stange R, Moser C, Hopfenmueller W, *et al*. Randomised controlled trial with medical leeches for osteoarthritis of the knee. Complement Therap Med 2012, 20: 1-7.
65. Shiffa M, Siddiqui MA, Sultana A, *et al*. Comparative clinical evaluation of leech therapy in the treatment of knee osteoarthritis. Eur J Integr Med 2013, 5: 261-269.
66. Michalsen A, Lüdtke R, Cesur Ö, *et al*. Effectiveness of leech therapy in women with symptomatic arthrosis of the first carpometacarpal joint: a randomized controlled trial. PAIN 2008, 137: 452-459.
67. Bäcker M, Lüdtke R, Afra D, *et al*. Effectiveness of leech therapy in chronic lateral epicondylitis: a randomized controlled trial. Clin J Pain 2011, 27: 442-447.
68. Kusnetsova L, Lusov V, Volov N, *et al*. Hirudotherapy in complex treatment of chronic heart failure. Russian J Cardiol 2008, 2008: 28-30.
69. Hanif H, Nouri M, Amirjamshidi A. Medicinal leech therapy in neurosurgical practice. J Inj Violence Res 2012, 4: 72.
70. Nargiza E, Mirdjuraev E, Ergasheva N. Leech therapy to prevent ischemic stroke: p1231. Eur J Neurol 2010, 17:170.
71. Morozova S, Aksenova O. Hirudotherapy in the treatment of peripheral cochleovestibular disorders of vascular origin. Vestnik Otorinolaringologii 2009, 4: 51-53.
72. Bakhshi M, Jalalian B, Valian M, *et al*. Can leech therapy be used as an alternative treatment for controlling migraine headache? A Pilot Study. Acta Fac Med Naissensis 2015, 32: 189-197.
73. Shankar KP, Rao SD, Umar SN, *et al*. A clinical trial for evaluation of leech application in the management of Vicarcik ā (Eczema). Anc Sci Life 2014, 33: 236-241.
74. Rastogi S, Chaudhari P. Pigment reduction in nevus of Ota following leech therapy. J Ayurveda Integr Med 2014, 5: 125-128.
75. Zaidi SA. Unani treatment and leech therapy saved the diabetic foot of a patient from amputation. Int Wound J 2016, 13: 263-264.
76. Na HJ. The Effects of live leech (hirudo medicinalis) therapy on diabetic foot: a clinical case report. Korean J Orient Med 2003, 24: 136-138.
77. Amarprakash PD. Case study of leech application in diabetic foot ulcer. Int J Res Ayurveda Pharm 2012, 3: 748-751.
78. Asgari SA, Rostami S, Teimoori M. Leech therapy for treating priapism: case report. Iran J Public Health 2017, 46: 985-988.
79. Kalender ME, Comez G, Sevinc A, *et al*. Leech therapy for symptomatic relief of cancer pain. Pain Med 2010, 11: 443-445.
80. Philip J, Armitage D, Phillips K, *et al*. Leech therapy for penoscrotal oedema in patients with hormone‐refractory prostate carcinoma. BJU Int 2003, 91: 579-580.
81. Brankamp R, Manley G, Blankenship D, *et al*. Studies on the anticoagulant, antimetastatic and heparin-binding properties of ghilanten-related inhibitors. Blood Coagul Fibrinolysis 1991, 2: 161-166.
82. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating cancer with a whole, leech saliva extract. United States patent US 8, 501, 241. 2013 Aug 6.
83. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating prostate, ovarian, or breast cancer with a whole, leech saliva extract. United States patent US 8, 932, 642. 2015 Jan 13.
84. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating pancreatic carcinoma with a whole, leech saliva extract. United States patent US 9, 144, 587. 2015 Sep 29.
85. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating colorectal cancer with a whole, leech saliva extract. United States patent US 9, 265, 802. 2016 Feb 23.
86. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating a melanoma with a whole, leech saliva extract. United States patent US 9, 265, 803. 2016 Feb 23.
87. Ghawi AM, Merzouk A, Abdualkader A, *et al*. Treating a lymphoma with a whole, leech saliva extract. United States patent US 9, 433, 649. 2016 Sep 6.
88. Darestani KD, Mirghazanfari SM, Moghaddam KG, *et al*. Leech therapy for linear incisional

TMR
doi: 10.12032/TMR20190225105

skin-wound healing in rats. J Acupunct Meridian Stud 2014, 7: 194-201.
89. Ramzan M, Droog W, Sleeswijk V, *et al*. Leech got your tongue? Haematoma of the tongue treated with medicinal leeches: a case report. Netherlands J Crit Care 2010, 14: 268-270.
90. Bumpous JM, Byrne PJ, Bernstein PE. The use of medicinal leeches to treat macroglossia secondary to blunt trauma. Otolaryngol Head Neck Surg 2001, 125: 649-650.
91. Zarshenas MM, Petramfar P, Firoozabadi A, *et al*. Types of headache and those remedies in traditional persian medicine. Pharmacogn Rev 2013, 7: 17-26.