International Journal of Medicine Research
ISSN: 2455-7404; Impact Factor: RJIF 5.42
www.medicinesjournal.com
Volume 1; Issue 4; September 2016; Page No. 23-27

Irsal-e-Alaq (Leech Therapy/ Hirudo therapy) in Surgical Diseases: A review

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Abstract
The *Unani* system of medicine founded by Hippocrates (460-377 BC) is based on the concept of equilibrium and balance of natural body humors (blood, bile, black bile and phlegm). If imbalance occurs in these four types of humors, diseases appear and if these four types of humors remain balanced then health is present in the body. The treatment modalities of the diseases in Unani system are based on the four modalities i.e *Ilaj-bit-Tadbeer* (Regimental therapy), *Ilaj-bil-Ghiza* (dietotherapy), *Ilaj-bil-Dawa* (pharmacotherapy) and *Ilaj–bil-Yad* (Surgery). Leech therapy or *Irsal-e- Alaq* is one of the most widely practiced therapies in *USM. Irsale alaq* is the method of evacuation of morbid humors from the body and thereby balancing the four humors and hence regaining the health. Ancient Egyptian, Indian, Greek and Arab physicians used leeches for a wide range of diseases starting from the conventional use for bleeding to systemic ailments, such as skin diseases, nervous system abnormalities, urinary and reproductive system problems, inflammation, and dental problems. Recently, extensive researches on leech saliva unveiled the presence of a variety of bioactive peptides and proteins involving antithrombin (hirudin, bufrudin), antiplatelet (calin, saratin), factor Xa inhibitors (lefaxin), antibacterial (theromacin, theromyzin) and others. The commonest indication of leech therapy as mentioned in unani classical literature are *dawali* (varicose vein), *quroohe khabeesa* (septic wound), *khanazeer* (lymphadenitis), *bawaseer* (piles), *nawaseer* (fistula in ano) and *da-ul-feel* (elephantiasis) etc.

Keywords: *Irsal-e-Alaq* (leech therapy)/ Hirudo therapy, Humors, *Ilaj-bil-yad* (surgery)

Introduction
According to Unani system of Medicine, bloodletting is based on concept of Humoral imbalance. Their imbalance causes diseases, whereas restoration of the balance leads to health. According to USM majority of diseases are caused by endogenous factors by excessive accumulation of morbid humors.[2] Bloodletting in the form of venesection, leech therapy and cupping with scarification is an essential part of USM for surgical diseases. It has been utilized for preventive as well as therapeutic measures for thousands of years by ancient *Unani physicians* [1].

Leeches are carnivorous or blood sucking annelid worms with pronounced ability to extend or contract their bodies. In India, about 45 species belonging to 22 genera are present [3] The common Indian species are *Hirudinaria granulosa*, *H.viridis*, *H.javanica*, and *H. manillensis*.[4] The medicinal leech (*Hirudo medicinalis*) is a European species while among Indian leeches; *Hirudinaria granulosa* has got medicinal properties. The saliva of the leech contains about 100 pharmacologically active biological substances like hirudin, hyaluronidase, vasodilators, anesthetics, antibacterial, fibrinase and collagenase etc. These substances are injected into the human body while sucking the blood and are responsible for the anti-inflammatory, vasodilators and analgesic and various other effects [3].

For the purpose of therapeutic application, *Unani* scholars have classified leeches into poisonous leeches and nonpoisonous (useful) leeches on the basis of specific characteristics. The features of therapeutically useful leeches are leeches with thin tiny head, emerald green color, tiny and rounded like rat's tail and leeches found in moist rich places where frogs are in abundance. Leeches with long head, black, grey or green color are described as poisonous [3, 5, 6].

Historical review
The importance of leech in clinical therapy can be simply represented from the Anglo-Saxon word of physician "*laece*''. The usage of leech for various medical applications can be traced back thousands of years ago. Before the Christian era (BC), medicinal leeching was mentioned in the 18th dynasty Pharaohs paintings (1500 BC) [7, 8]. Talmud, Bible, and other Jewish manuscripts outlined the medical indications of leeching. The Greek poets, Nicader of Colophain (200-130 BC) mentioned leeches in his medical poems. Greek physicians used leeches for bloodletting and for treating rheumatic pains, gout, all types of fever and hearing loss. The usage of leeches during that time depended upon the humor concept of Galen (130-201 AD), which was an inspiration from Hippocrates (460-370 BC) hypothesis about body fluids imbalance-related illnesses. Galen believed that illnesses alleviation can be achieved by restoring the balance between the body fluids when a leech withdraws blood from patients [7, 9]. Galen would prescribe bloodletting by leech for almost all illnesses such as simple inflammatory conditions, mental disorders and hemorrhoids [10]. Moreover, Themission of Laodice, a Syrian doctor, outlined that removing blood from the patient will evacuate the evil spirits, which can cause diseases [7]. Avicenna (980-1037 AD) delineated in his book "Canon of Medicine" that leech can suck blood from deep veins which cannot be reached by the conventional wet cupping and he recommended leeching for skin diseases [7, 9]. In 12th century, *Abd-el-latif al-Baghdadi* mentioned in his texts the beneficial usage of leech application after surgical operations. Thereafter, *Ibn Maseehi-al-Quf* (1233-1286 AD) in his book "*Umda Fi Jarahat*" differentiated the medical leeches from the non-medical (poisonous) ones according to their shape and color [7].

By the end of 19th century, leeching gradually fell into disrepute, and almost stopped by the early twentieth because Hirudo therapy did not match the new requirements of the modern medical regulations and the great advancement in all medical fields [7]. After the recession period of leech therapy, it has resurged after the mid-20th century with new applications in many medical fields including surgical and reconstitution procedures, vascular diseases, arthritis and migraine [7, 9]. This novel therapeutic utilization of leeches resulted in more interest in isolation and characterization of the active constituents of leech saliva [7, 11]. In 2004, the Food and Drug Organization (FDA) approved leeches for medicinal purposes [7, 9].

Procedure for leech therapy

Ibne Sina narrated that leeches should be collected one day prior to their use. Patient is advised to take light semi-solid diet prior to the leech therapy. The affected part to be treated is thoroughly washed with distilled water or with a solution of borax and rubbed until redness appears. If the leech fails to attach, a few drops of blood may be smeared on the part to be treated and then leech is applied. Normally, one or more leeches are applied to the affected part and left for about half an hour. Once the leech is attached, it will likely remain safely in place until fully distended but it is necessary to observe the site continuously to insure that the leech hasn′t separated. Thereafter, the leeches are detached by pulling them off or by loosening their grip with table salt, borax or heat but sometimes leeches detach spontaneously. The used leeches are then killed and disposed off [2, 3, 12, 13].

Mechanism of action

According to USM, leech therapy works on the principles of *Tanqiya-e- mawad* (Evacuation of morbid humors) and *Imala-e-mawad* (Diversion of humors). *Tanqiya-e-Mawad* means the resolution and excretion of morbid humors and excess fluids from the body, thereby maintaining the homeostasis in the quality and quantity of four body humors, which is actually responsible for the maintenance of normal health. *Imala-e-mawad* refers to the diversion of the morbid fluids from the site of affected organ to the site where from it is easily expelled from the body tissues. Based on this holistic approach, *Unani* physicians have been widely using this therapeutic regimen for a number of diseases. The effectiveness of this therapy may also be attributed to the *Mussakin* (sedative) and *Muhallil* (anti-inflammatory) actions of saliva of leeches [2, 3, 14].

Table 1: The saliva of the leech contains various pharmacologically active biological substances as follows [1].

1.	*Hirudin*	Inhibits blood coagulation by binding to thrombin.
2.	*Calin*	Inhibits blood coagulation by blocking the binding of von-Willebrand factor to collagen-Mediated platelet aggregation.
3.	*Destabilase*	Monomerizing activity. Dissolves fibrin. Thrombolytic effects.
4.	*Hirustasin*	Inhibits Kallikerin, Trypsin, Chymotrypsin, Neutrophilic Cathepsin G.
5.	*Bdellins*	Anti- inflammatory, Inhibits trypsin, Plasmin, and Acrosin.
6.	*Tryptase inhibitor*	Inhibits Proteolytic enzymes of host mast cells.
7.	*Eglins*	Anti- inflammatory. Inhibits activity of alpha- Chymotrypsin
8.	*Ghilanten*	Anti metastatic.
9.	*17-kDa protein (Antistasin)*	Prevent lung cancer colonization
10.	*Bufrudin*	Thrombin inhibitor
11.	*Theromin*	Thrombin inhibitor
12	acetylcholine and carboxipeptidase	Vasodilator
13	Complement inhibitors	May possibly replace natural complement inhibitors, if they are deficient.

Indications

Varicose Vein

Dawali (varicose vein) is a disease in which veins of the lower limbs becomes dilated, tortuous, prominent and greenish in color. The etiology of the varicose vein is still not cleared. Greeko-Arab physicians postulated that is caused by accumulation of non-purulent *Balghami* (phlegmatic), *Saudawi* (atrabilious) or *Damwi* (sanguinous) matters in leg veins or by weakness of the veins. *Zakaria Razi, Ibn Sina, Ismaiel Jurjani* etc have mentioned *fasad* in *dawali* but *M. Azam Khan and A. Arzani* mentioned *Taleeq* in varicose vein [31].

The effect of leech therapy in varicose vein is due to the biochemical present in the saliva of the leech which contains anticoagulant, thrombolytic, anti-inflammatory, antibiotic, anesthetic and analgesic properties. *Hirudin* and *calin* are anti-coagulants. Enzyme *Destabilase* has thrombolytic effect. Histamine like substances, acetylcholine and carboxipeptidase has vasodilator effect. Anticoagulant, thrombolytic and vasodilators present in saliva of leech produce prolonged bleeding and hypovolumic haemodilution of the blood which reduces pressure at the vessels and excretion of metabolites at the site of microcirculatory units [9].

Non Healing Ulcers

Quruhe Asratul Indamal/Non healing ulcers are those which do not heal by conservative treatment within six weeks. The clinically most significant chronic wound in terms of epidemiology and health economics are venous stasis ulcer, wound and wound healing disorders in diabetes mellitus and pressure ulcers in immobile patients with reduced general condition [32, 33]. According to the *Unani* literature non healing ulcers are those ulcers whose healing is delayed and associated with more damage and destruction of the local part having different types of causes [34].

Leech application has peripheral vasodilator effect due to presence of vasodilator constituents in the saliva of leech which improves blood circulation and corrects the ischemia around the wound thus promotes wound healing. Leech application has ani inflammatory action on nerves due to presence of substances like *Bdellins* and *Eglins* which prevents leucocytic accumulation in the surrounding vessels, thus inhibits release of inflammatory factors which causes chronic wound formation [35].

Hemorrhoids

Bawaseer/Hemorrhoids are dilated veins within the anal canal

in sub epithelial region formed by radicles of the Superior, Middle and Inferior rectal veins [36].

Hemorrhoid was first described by *Buqrat* (Hippocrate), a renowned *Unani physician*. According to *Unani system of medicine*, it is a disease of rectum in which there is an accumulation of black bile in the venules of rectum to form a polyp like growth in it. *Bawaseer* (hemorrhoid) is of two type, *Bawaseer zahira* (external hemorrhoids) and *Bawaseer Ghaira* (internal hemorrhoid). Another classification of *Bawaseer* is *Bawaseer damiya* (bleeding hemorrhoid) and *Bawaseer asm* (non- bleeding hemorrhoid) [37, 38, 39]. According to the *Unani* doctrine, leech therapy works on the principles of *Tanqiyae Mawad* (Evacuation of morbid humors) and *Imalae Mawad* (Diversion of humors) [3].

In this condition application of leech helps to improve the circulation by sucking the liquid blood and interstitial fluids from inflammatory swelling and releasing some important bio chemicals such as anti-inflammatory, anti-coagulants and analgesic substances at the site. Hence there will be an immediate reduction in the size of the swelling, pain and tenderness.

Deep vein thrombosis

This condition commonly occurs after the operation under general anesthesia, when the calf muscles remain idle and fail to maintain the normal flow of blood within the deep veins, thus causing thrombosis. It also occurs following child birth, immobility or any debilitating diseases. The condition is asymptomatic, only 1/4th of the patients produce symptoms and signs [32].

Avicenna (980-1037 AD) delineated in his book "Canon of Medicine" that leech can suck blood from deep veins which cannot be reached by the conventional wet cupping and he recommended leeching for skin diseases [7, 9]. Recent scientific study showed that the effectiveness of leech saliva is the results of specific thrombin inhibitors, *hirudin*, which was first isolated from *H. medicinalis*. [7, 15, 16, 17]. Furthermore, other thrombin inhibitors were identified from different leech species. For instance, *bufrudin* was isolated from *H. manillensis* with a chemical structure closely similar to *hirudin* [7, 18]. A tight-binding thrombin inhibitor named *haemadin* was identified from the whole body extract of the leech species *Haemadipsa sylvestris*.[19] Another anti thrombin named *granulin-like* was isolated from the leech species *H. nipponia* [20]. Finally, a human granulocyte and monocyte protein inhibitor known as *theromin* was characterized from the head extract of *Theromyzon tessulatum* leech species with an anti-thrombin activity [21]. Many studies revealed that *hirudin* is more effective than heparin in preventing deep venous thrombosis. Furthermore, and unlike heparins, *hirudin* has a promising prophylactic activity in patients who are at a high-risk of developing cardiovascular events because it can hinder thrombus growth due to its ability to block thrombin-fibrin binding [31, 32].

By the year 1997, a novel antithrombotic and anticoagulant pharmaceutical preparation was released to the Russian markets under the trade name "Piyavit", which consisted of the medicinal leech saliva extract. The product was prescribed as thrombolytic and anti-platelet [3].

Reconstructive and microsurgery

Microsurgery is a type of surgical operations carried out using the micro instruments under the microscope aiming to anastomose small blood vessels, veins and arteries during the replantation of tissues or amputated digits [8]. Arterial thrombosis is not common while venous occlusion is a serious threat in newly transplanted tissues and may lead to thrombus formation, stasis, and eventually tissue necrosis. Thus, physicians argued that relieving venous congestion is a vital step in order to mitigate this risk and to salvage this transplanted tissues [7, 8].

The long-acting anticoagulants in leech saliva motivated medics to use leech to alleviate venous congestion [8, 24]. The relieving effect is the accumulated result of the leech bite-induced blood oozing, which is a consequence of many factors, including bleeding wound, secreted bioactive enzyme, anticoagulants, and vasodilators [25]. Leeches were also used to decongest completely amputated ears. Another study shows a 4 day leeching course for the treatment of eight individuals who received replantation and revascularization operations after amputation injuries. It was reported that more than half of the treated cases were completely salvaged. Others outlined that bloodletting by leeches in combination with vascular endothelial growth factor may improve flap survival [7].

Malignancy and metastasis

In 2008, cancer was responsible for about 13% of all global deaths. These alarming rates are expected to increase during the next two decades to reach up 13.2 million deaths by the year 2030 [26]. It was presumed that the extraordinary combination of many anticoagulants, protease inhibitors, and other components in leech saliva could be more powerful as an anti-metastatic drug. It was outlined that the salivary gland extract from *H. ghilianii* and *Haementeria officinalis* inhibited the metastatic colonization of lung tumor cells, which were injected intravenously into the experimental animals [7] later, an anti-metastatic and anticoagulant protein named *ghilanten* was purified from the salivary gland secretion of the proboscis leech, *H. ghilianii*. It was reported that *ghilanten* could suppress metastasis of melanoma, breast cancer, lung cancer, and prostate cancer [7, 27]. The Mexican leech *Haementeria officinalis* was subjected to many studies, which eventually led to unveil the anti-metastatic activity of its salivary gland secretion. It was observed that its saliva contains a 17-kDa protein, called *antistasin*, having the capability to prevent lung cancer colonization [28, 29].

By the year 2010, other scientists delineated for the first time that a 2 month treatment by topical application of *H. medicinalis* can completely cure the local lumbar pain in patients with advanced stages of renal cancer and leiomyosarcoma [7].

Diabetic gangrene

The peripheral vascular complications in diabetic patients can lead to less blood flow to the distal parts of the body resulting in ischemic diseases of limbs like gangrene. The control of gangrene is very crucial to diabetic patients by lowering both blood pressure and lipidaemia, along with increasing blood circulation in the peripheral blood vessels [7]. The wild leech species *Whitmania pigra* (Family: *Hirudinidae*) has been used by the traditional Chinese therapists to augment blood flow to the distal parts of the body and to alleviate coagulation disorders. It was reported that the aqueous and alcoholic extracts of the whole body of this leech species possessed a potent anticoagulant activity [7, 30].

The commonest indications other than mentioned above

are *Jarabul Ajfaan* (Blephritis), *Darde pindali* (Painful Calf muscle), *Malankhoolia* (Mania), *Qooruhe khabisa* (septic wound, non-healing ulcer), *Warm* (inflammation) of organs, *Khanaazeer* (Lymphadenitis), *Warme Tajaweful Anaf* (sinusitis), *Warme halq* (Pharyngitis), *Nawaseer* (Fistula in ano), *Daaul feel* (Elephantiasis), at the biting site of poisonous animals, skin disorders like *Qooba* (Ringworm), *Saa'fa* (*Tineacorporis*), *Namash* (Chloasma), *kalaf* (Warts), *Nar-e-farsi* (eczema), *Da-us-sadaf* (psoriasis), *Bars* (Vitiligo), *Waja-ul-Mufasil* (Osteoarthritis), hypertension etc. Nowadays use of leeches in *thromboembolic diseases* (coronary artery thrombosis and Ischemic heart diseases), plastic surgery, replantation and other reconstructive surgeries is very famous all over world [3].

Complications of leech therapy

Infection is the most common complication of leeching and occurs in 2-36% of the patients. Several bacterial strains have been encountered in these infections involving *Aeromonas* spp., *Pseudomonas* spp. and *Vibrio* spp. agent is the Gram-positive rod, *Aeromonas hydrophila*, which can cause pneumonia, mascular necrosis, flap failure and even septicaemia [3]. A hydrophila can infect the bite or surrounding skin during feeding, such an infection presents itself as a local abscess. The infection is not reactive to penicillin but to chloramphenicol and amino glycoside. Other complications are allergic reactions such as itching followed by burning and blister formation and ulcerative necrosis due to toxins present in leech saliva have also been reported after leech therapy. Transmission of certain infections from one subject to the other is another probable complication of leech therapy [1].

Conclusion

To conclude, leeching has been a popular therapeutic practice for a long period of time for a wide range for diseases and it was applied as an unscientific way by classical therapists. Nowadays, leech came back to the contemporary medicine with fewer applications, which has been proven and supported by a large number of scientific studies and case reports. Leech therapy in the field of plastic and reconstructive surgery is expected to be of paramount importance due to the ease of leech application and reduced side-effects. Leech therapy as indicated by *Unani* physicians can be safely and effectively used to evacuate the blood and morbid humors from deeper structures. On the other hand, surgeons who practice plastic operations consider leeching as a promising remedy, since they observed that the Y-shaped wounds caused by leech bites usually heal without scars or complications Furthermore, modern biochemistry has been able to point out so many substances in the leech saliva as well as their mode of action. On the basis of these findings, it may be suggested that leech therapy can produce better results either single or as an adjuvant with drug therapy in diseases like external hemorrhoids, deep vein thrombosis, atherosclerosis, varicose vein, diabetic gangrene, non-healing ulcers and in various surgical traumatic conditions such as re-attachment of severed extremities, fingers, toes and ears.

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