

An Interdisciplinary Critical Review of Leech Therapy; Evolution, Indications, Salivary Gland Secretions and Mode of Action– The Scientific Way

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Abstract: Leech therapy can be correlated to Jaloukavacharana in Ayurveda, which is the best tool of Raktamokshana curing many diseases like abscess, cysts, tumors, cellulites, and blood borne diseases. It is a parasurgical procedure which can be done in children, delicate people, ladies, and in those who are afraid of surgery. *Hirudomedicinalis* (European Medicinal Leech) is the most frequently used species of leech that is not native to the Indian subcontinent. In India the species used traditionally for therapeutic purposes is *Hirudinariagranulosa*. Besides these, *Macrobdelladecora* (American medicinal leech), *Hirudomichaelseni*, *Hirudonipponia*, *Hirudo verbena*, and *Hirudoorientalis* are also being used for therapeutic purposes. Scientific research reveals that the beneficial effect of leeching occurs via blood decongestion and injection of a cocktail of several medicinally useful bioactive molecules present in their saliva. This article elaborates the indications, contraindications, types of leeches in a very candid way, and throws light on the review of various salivary gland secretions in its pharmacological action point of view after reviewing certain articles on this subject.

Keywords: Leech Therapy, Salivary gland secretions, leeching, Jaloukavacharana, raktamokshana

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I. INTRODUCTION

Leech therapy is becoming increasingly popular among practitioners of Ayurveda, which is also called as complementary and alternative medicine. Many studies are currently under way to evaluate its various medicinal effects, all around the globe and thousands of patients have been healed using leech therapy. Many traditional medical systems, for example, the Greek, Arab, and Russian, mention leech usage. [1] The origins of traditional Indian medicine ie, Ayurveda, is said to date back some 3000 years. Leech therapy has been an active part of traditional Ayurvedic medicine throughout its history. Acharya Sushruta has described Leech as Jalouka in the area of para surgical toolsie, Anushastra, which means the tool which can be used in the absence of surgical instruments. [2] The word 'leech' is supposed to be derived from an old English word for physician, laece [3]. According to Sushruta, the leech is called as 'jalouka' or 'Jalayuka' meaning that which dwells in 'jala' or water [4]. Leech is a freshwater amphibious worm, usually black or brown and about 10 cm in length. With a very simple etymology and a very tiny appearance, this soft slimy parasite hails in more than 650 known species in the *Hirudo* genus, and the most often used is *Hirudomedicinalis* in medical therapy [5].

Leeches were named *Hirudomedicinalis* by Linnaeus in 1758 [6]. During the seventeenth and eighteenth centuries, leech therapy played a pivotal role in therapeutic practices, which involved bloodletting and purification, a practice employed to treat many ailments, from gout to headaches [7]. In India the species used traditionally for therapeutic purposes is *Hirudinariagranulosa*. Besides these, *Macrobdelladecora* (American medicinal leech), *Hirudomichaelseni*, *Hirudonipponia*, *Hirudo verbena*, and *Hirudoorientalis* [8] are also being used for therapeutic purposes.

'Attaivald' (leech therapy) is one of the way of bloodletting which comes under the external therapies of *Siddha*. Leeches have been used for therapeutic purposes before 2000 years by ancient renowned '*Siddhars*' which state that speckled leech has many active compounds in their saliva. Thus, remove toxins and impure blood and cures many diseases efficiently [9].

Leeches play a major role in Unani medicine as one of the most important regimential therapy as 'Irsal-e-Alaq'. Eminent Unani physicians have described and practiced the use of non-poisonous (medicinal) leeches in

a number of diseases like joint diseases, chronic non healing ulcers, and various skin disorders like eczema, psoriasis etc. [10]

The US FDA has approved medicinal leeches for commercial marketing, not as drugs, but as medical devices. According to FDA, the agency announced that leeches meet the definition of a device because they are considered to be articles intended to diagnose, cure, treat, prevent, or mitigate a disease or condition, or to affect a function or structure of the body, that do not achieve their primary effect through a chemical action and are not metabolized. If used judiciously, leeches can get blood flowing in regions that even a skilled surgeon cannot. [11].

1.1 The objectives of writing this article are;

By going through this article, the readers will be able -

- 1] To elaborate the legacy of Leech Therapy in ancient Ayurveda texts and around the globe
- 2] To highlight the indications of leech therapy from interdisciplinary point of view
- 3] To describe the pharmacological properties of Salivary gland Secretions of Leech
- 4] To understand the mode of action of Leech Therapy
- 5] To generate data for validation

II. REVIEW OF LEECH THERAPY IN AYURVEDA:

Sushruta, the father of surgery has described Leech Therapy as Jaloukavacharanawhich has been an established therapy of Raktamokshana by Anushastrasor parasurgical tools. Raktamokshana can be stated as bloodletting which is performed by various tools such as Shringa (Horn), Alabu (Gourd), Jalouka (Leech), and ghatiantra (Cupping therapy). It is stated by Acharyas that, in the field of Shalyatantra, bloodletting deserves supreme importance. Acharya Vagbhata has rated raktamokshana to the highest degree stating that all the other curative procedures in Ayurveda if put aside, raktamokshana alone is equivalent to them. For cessation of progress of the disease as well as for cure of the disease one has to aim at removal of vitiated blood i.e. Raktamokshana therapy. In Sushruta Samhita, the procedure of Raktamokshana has been hailed as one of the most effective therapies of Vranashopha. [12] Raktamokshana is considered as half of the whole treatment of any disease in Shalyatantra [13] Among various methods for Blood Letting, Jalloukavacharana is described as the supreme therapy because of its safety and high efficacy in the disorders involving the vitiation of blood. [14]

2.1 Types of Leeches;

Leeches vary from terrestrial, marine, land to aquatic type. Some are found in alluvial soil, some in flowing water. Leeches are generally small and range from 10 to 15 cm long. But fully grown specimen may be 30 to 35 cm long [15]. The ectoparasite, leech range in size from tiny species that are 5 mm long to varieties such as Haemopsis, which have been reported to be as long as 45 cm when extended and swimming. The body of the leech is brightly coloured with characteristic markings and the dorsal surface is olive green [16]. Limnatis nilotica (horse leech) is 8-12 cm long and its body is soft, Leeches classified under the phylum Annelida to the class Hirudinea, are of worldwide distribution and are extremely abundant both in species and in the number of individuals. Around 650 species of leeches is found worldwide. [8]

The terrestrial, or land varieties of leeches are found in the tropical regions of the world, particularly, South East Asia, the Pacific Islands, the Indian sub continents, and South America. Land leeches are found on the surface of trees and grasses and under stones in damp places. One terrestrial leech, Haemopisterrestris, has been plowed up in fields in the mid-western United States [17]. Haementeria officinalis, which is found in South America have proboscis instead of jaws. Placodellacatenigera, occurring in the Mediterranean region, also attacks man and domestic animals. Limnatis nilotica is found in North Africa, and Southern Europe. Haemadipsazeylanica, found in Asia lives on land attacking all vertebrates and many different species of mammals have been killed by them through sheer loss of blood. Throughout the Mediterranean area and the middle and Far East regions, certain leeches are injurious to animals and humans [18].

In Ayurveda, leeches are classified into poisonous and non-poisonous types, depending on their toxicity symptoms. The application of poisonous leeches can cause swelling and itching in the bitten area, as well as fainting, fever, burning sensations, vomiting, intoxication, and myalgia [19]. The use of nonpoisonous leeches causes no complications during bloodletting. In India, Phylum-Annelida, class-Hirudinea, Hirudomedicinalis are used for bloodletting. These leeches are dark in color and marked with 6 longitudinal stripes. Their bodies are 2 to 3 inches long, convex and wrinkled transversely, tapering at each end. These leeches are classified into 12 types, with each type bearing Sanskrit names [20]

2.2 Table 1 & 2 Types of Savisha Jalouka and Nirvisha Jalouka-

Sr. No	Savisha Jalouka	Features of Savisha Jalouka
1	KRISHNA	Resemble in black colour, Thick

2	KARBURA:	Resemble the fish of vermin type. Ventral surface is convex (Ayata).
3	ALAGARDA:	Thick Hairy Round at sides Black at the mouth
4	INDRAYUDHA	Having different colours like rainbow Number of linings on the body
5	SAMUDRIKA	Blackish yellow with dotted skin
6	GOCHANDANA	Narrow mouth Marked by bifurcating lines. Bottom (end Part) like the scrotal sac on a bull.
	NirvishaJalouka	Features of NirvishaJalouka
1	KAPILA	Colour like Manashila at the sides Dorsal surfaces are slimy and colored like Mudga pulse
2	PINGALA:	Colour – Reddish Shape – Round Locomotion – Speedy
3	SANKUMUKHI:	Colour – blackish red like that of liver. Provided with the greatest swiftness
4	MUSHIKA:	Colour – like the common blind moles Emit a foetid smell from the body
5	PUNDARIKAMUKHI:	Colour – like Mudga pulse. Presence of resemblance of the mouth of the full blown lotus lilies
6	SAVARIKA	Marked with impressions like lotus leaves. Measured eighteen fingers in length. Directed to apply only in the lower animals.

III. INDICATIONS FOR RAKTAMOKSHANA (BLOODLETTING) FROM ANCIENT AYURVEDA TEXTS:

Vranashopha(Cellulites), Kushtha(Skin Diseases), Visarpa(Erysipelas), Pidaka(Skin eruptions), Raktapitta(Bleeding disorders), Gudapaka(Proctitis), Pleeha(Splenomegaly), Vatarakta(Gout), Arsha(Haemorrhoids), Vidradhi(Abscess), Arbooda(tumour), Shwitra(Leucoderma), Dadru(ring worm) [21]

3.1 Complications of Jalloukavacharan (Leech Therapy) according to SushrutaSamhita:

- Shotha(swelling),
- Kandu(SevereItching),
- Murcha(Shock),
- Jwara(fever),
- Daha(local Burning),
- Chardi (Vomiting).[22]

3.2 Indications for Leech therapy according to modern science:

Indications cited by medical practitioners of leech therapy are as follows:

Inflammatory Reactions [23, Passive congestions and spastic conditions [24,25], Plastic and reconstructive surgery [26,27,28], Cardiovascular diseases [29,30,31,32], Hypertension [32,33], Varicose Veins. [32,34], Hemorrhoids [35], Arthrosis, osteoarthritis, periartthritis and rheumatoid arthritis [36,37], Thrombophlebitis, thrombosis and embolism [38], Hematomas [39], External ear and chronic ear infections [33]. Eye diseases, including cataracts, glaucoma, traumatic injuries and inflammation [36], Dental problems, like gingivitis, paradontitis, gingival edema and stomatorrhagia [36, 33]. Skeletal Pain syndromes Pain Syndromes [36], GI tract – hepatitis, cholecystitis, pancreatitis, stomach ulcers [37,33], Chronic skin diseases,

like scabies, psoriasis, eczematous dermatitis, and chronic ulcers [38]. Respiratory disorders - Asthma, acute rhinopharyngitis and spasmodic coryza [39, 55], Gynecological disorders - male and female sterility, endometriosis, para-metritis, mastitis, fibro-mastopathy [36,33]

3.3 Experimental and Investigational Role of Leech Therapy:

Some areas are considered as experimental and investigational for treatment by medicinal leech therapy due to lack of randomized control trials on these clinical areas-

1. Cancer pain,
2. Epidermoid cysts,
3. Knee osteoarthritis,
4. Inadequate arterial supply or tissue ischemia,
5. Priapism
- 6 Rheumatoid arthritis and other musculoskeletal diseases[40]

3.4 Contraindications of Leech Therapy according to some citations:

Leech Therapy is not given under the following conditions:

1. Hemophilia
2. Anemia
3. Leukemia
4. Hypotonia
5. Pregnancy[41]

3.4 Complications of Leech Therapy according to certain citations –

1. Itching on the application area.
2. bleeding on the application area
3. Orthostatic hypotension
4. vasovagal symptoms
5. Regional lymphadenopathy.
6. Scar formation [42]
7. In very rare cases, thrombotic microangiopathy and renal failure have been reported when leeches were applied in patients with arterial insufficiency[43]

IV. THE PHARMACOLOGICAL PROPERTIES OF SALIVARY GLAND SECRETIONS OF LEECH

As mentioned earlier, scientific research reveals that the beneficial effect of leech therapy occurs via the blood suction and blood decongestion and injection of a cocktail of several medicinally useful bioactive molecules present.

Calculation of Jacquard's coefficient showed that *H. medicinalis* and *H. orientalis* are closest to each other in SGS [salivary gland secretions] composition, which is consistent with data in the literature on the phylogenetic relationship between these two species of medicinal leech.[44]

The judicious description of Leech salivary gland secretions is as follows:

4.1. **Hirudin**-In 1950, Fritz Marquardt of Germany isolated a protein from *Hirudo medicinalis* that he termed "Hirudin" and demonstrated its thrombin inhibitory effect. As a heparin-like substance, it is the most potent known natural inhibitor of thrombin..[43]

4.2. **Hyaluronidase**- Hyaluronidase is a spreading substance that modifies the permeability of connective tissue, through the hydrolysis of endoglucuronidic linkages of hyaluronic acid - a polysaccharide found in the intercellular ground substance of connective tissue.[34] Hence, hyaluronidase from leech saliva helps increase the spread of all salivary secretions..[44]

4.3. **Calin**- Calin has a rapid (1-10 min.) effect on collagen that is reflected in its ability to suppress collagen induced platelet aggregation as well as adhesion of platelets to collagen coated micro-carrier beads[45]

4.4 **Destabilase**- Destabilase possesses glycosidase activity. Destabilase lysozyme is the first invertebrate lysozyme with combined enzymatic and non-enzymatic antibacterial action[46] and it also dissolves blood clots [46]

4.5. **Apyrase** (adenosine 5'-diphosphate di-phospho-hydrolase) is a nonspecific inhibitor of platelet aggregation by virtue of its action on adenosine 5'-diphosphate, arachidonic acid, platelet-activating factor (PAF), and epinephrine. Two apyrases (isoenzymes) have been isolated from the saliva of medicinal leeches.[47]

4.6. **Eglin**-Eglins (elastase-cathepsin G leech inhibitors) are small proteins present in Hirudomedicinalis that have strong inhibitory activity against chymotrypsin and subtilisin-like serine proteinases acting on non-cationic substrates. One leech contains approximately 20 µg of eglin.[48]

4.7. **Bdellins**- inhibitors of trypsin, plasmin, and sperm acrosin were first discovered in 1969. A similar proteinase inhibitor, bdellin B-3, was isolated from extracts of Hirudomedicinalis. Bdellins were named after the Greek word for leech.[49]

4.8. **Decorsin**- Decorsin is a protein isolated from American medicinal leech *Macrobdelladecora*. It acts as an antagonist of platelet glycoprotein II b-III a and is a potent inhibitor of platelet aggregation.[50]

4.9. **Hirustasin**- Hirustasin (Hirudoantistatin) belongs to a class of serine protease inhibitors. It was first isolated from the salivary glands of the Mexican leech, *Haementeria officinalis*, but has recently been prepared from *Hirudomedicinalis*. [51]

4.10. **Piguamerin**- Piguamerin is a serine protease inhibitor of plasma kallikrein that has been screened and purified from the Korean leech, *Hirudonipponia*. The peptide potently inhibits plasma and tissue kallikrein and trypsin [60]

4.11. **Gelin**- Gelin is a potent thrombin inhibitor analogous to eglin, and is isolated from the saliva of the *Hirudinaria manillensis*, a leech belonging to the same family as *Hirudomedicinalis*. Like eglin, gelin inhibits elastase, cathepsin G, and chymotrypsin. [52]

4.12. **Gamma-Glutamyl Transpeptidase**- This compound has been isolated from salivary gland secretion of *Hirudomedicinalis*. [53]

4.13. **Platelet Activating Factor Antagonist (PAFA)** and an Ornithine-Rich Peptide has been isolated from lyophilized dilute leech saliva. It is identified as a phosphoglyceride, which may prove to be an important compound for the treatment of thromboembolic disorders and inflammation. In addition, two specific factor Xa inhibitors from diluted leech saliva have been isolated. [54]

4.14. **Vasodilatation Effect**- Besides, leech saliva contains acetylcholine, histamine like vasodilators that prolong bleeding time. [55]

4.15. **Fibrolytic Activity**: It also contains enzymes that reduce scar tissue and adhesions. Two types of **fibrinases** and a **collagenase** that are also present reduce the density of scar tissue and help reduce fibroblast formation in hypertrophic scars and keloids [56]

4.16. **Antithrombotic effect**: Anticoagulant complex isolated from lyophilized medicinal leeches exerted pronounced antithrombotic, thrombolytic, and hypotensive effects in experimental animals after intravenous injection and showed antithrombotic activity after oral administration in combination with hirudin. [57]

4.17. **Antifungal activity**: Antifungal activity of recombinant medicinal leech destabilase-lysozyme was investigated by using fungi: *Botrytis cinerea*, and *Verticillium lateriticum*, and was found to be potent. [58]

4.18 **Antibacterial activity**: Its antibacterial activity was investigated on gram-negative bacteria *Pseudomonas fluorescens* and was found to be potent. [59]

4.19. **Analgesic and anti-inflammatory activity**: The anti-inflammatory and analgesic properties of leeches are subjects of modern hirudobiochemistry and hirudopharmacology and in many aspects are associated with the blockage of amidolytic and kininogenase activities of plasma kallikrein, resulting in prevention of pain or pain relief during leech sessions [60]

4.20 **Inhibition of platelet functions**: Destruction of the blood vessel wall for sucking blood causes activation of platelets and the coagulation cascade, which are fatal for the leech. For this reason, leech secretions contain many bioactive molecules to locally inhibit these actions. In a normal host, wall destruction causes spread and release of collagen particles and they are targets of free von Willebrand factor (vWF). This complex strongly binds to glycoprotein (GP) Ib on platelets as vWF works like a bridge. With this binding, up regulatory mechanisms occur, platelets bind to each other to make a plug and stop any bleeding. [61]

4.21 **Other possible actions**: Many in vitro studies have indicated the anticancer effects of leech saliva extracts. Since coagulation is related to metastasis and tumor progression, blocking the cascade can have an antitumor effect. In addition, other anticoagulant derivatives are claimed to have similar effects, as well as reducing cell growth and tumor angiogenesis. Effects against cell degeneration have also been reported. Eglin C, bdellastatin, destabilase, bdellins, and hirudin are cytoprotective and exert positive stimulatory actions, especially on neurons, but these studies are only at the preliminary stage [62]

In reference to the said context, a search for relevant topic was done through ancient Ayurveda texts, but there is no description found related to the salivary secretions of *Jalouka* or any other matter which could be correlated for discussion.

V. MODE OF ACTION OF LEECH THERAPY

Leech Therapy depends on the following main steps of medicinal leeching:

1. The blood-letting action during active suction of blood,
2. Passive oozing of the wound, and

3. Injection of biologically active substances with the saliva into the host.

The saliva of *H. medicinalis* contains more than 100 bioactive substances, including coagulation inhibitors, platelet aggregation inhibitors, vasodilators, and anaesthetizing, antimicrobial and anti-inflammatory agents [45]

A. One of the most important ingredients is hirudin, which is the principal anticoagulant responsible for enhanced bleeding and prevention of coagulation. In addition to hirudin, leeches secrete two inhibitors of Factor Xa responsible for the conversion of prothrombin to thrombin [47] Furthermore, leech saliva is an effective platelet aggregation inhibitor due to the presence of active ingredients such as calin, apyrase, platelet activating factor (PAF-) antagonist, collagenase, and prostaglandin. Their main function is preventing the ingested blood from congealing within the leech's gut. The medical benefit to the patient is a sustained local bleeding that can last several hours after the end of each leech session.

B. The saliva of the medicinal leech also contains proteinase inhibitors, such as bdellins [46], eglin, inhibitors of α -chymotrypsin, subtilisin, and the granulocytic neutral proteases-elastase and cathepsin G [63], responsible for the anti-inflammatory effect of leeching.

C. Medicinal leeches also secrete hirustasin, which selectively inhibits tissue kallikreins that are largely responsible for the maintenance of a normal level of blood pressure. Hirustasin can also play a role in the intrinsic coagulation process [50]

D. The anti-inflammatory and analgesic properties of leeches are subjects of modern hirudo-biochemistry and hirudo-pharmacology and in many aspects are associated with the blockage of amidolytic and kininogenase activities of plasma kallikrein, resulting in prevention of pain or pain relief during leech sessions [48]

E. Leeches may also secrete a vasodilative, histamine-like substance, which increases the inflow of blood after a leech bite and reduces local swelling [53]

F. Hyaluronidase, which is known as the "spreading factor," can degrade tissue hyaluronic acid, thus facilitating the infiltration and diffusion of the remaining ingredients of leech saliva into the congested tissue. Tissue permeability, restored with the help of hyaluronidase, promotes the elimination of tissue- and circulatory-hypoxia as well as local swelling [47]

G. The persistent bleeding largely potentiates tissue decongestion and leads to loss of blood, relief of capillary net, decrease in venous congestion, decompression of the nerve trunks and endings, increase in lymph flow, positive changes of local hemodynamics, amelioration of hemorheology, increase of oxygen supply, improvement of tissue metabolism, and elimination of tissue ischemia [64]

VI. DISCUSSION

In the 18th and 19th centuries, medicinal leeching was popular for treating a variety of human illnesses, including mental disorders, whooping cough, gout, tumors, headaches and obesity. A lack of documented success led to a sharp decline in the use of leeches in the 20th century that is, until its application in managing a common postoperative complication of micro-vascular surgery became evident. Medicinal leech therapy should be considered an exciting new tool in your medical toolbox for treating challenging conditions like woundcare and reconstructive surgeries. No complications were seen with this therapy. Provided specific recommendations regarding the handling of leeches, monitoring during leeching and patient management after leeching should be followed. Specifically, prophylactic antibiotics must be instituted, and depending on the number and length of leeching treatments, blood transfusions should be expected. The salivary gland secretions are a cocktail of proteolytic enzymes of tremendous medicinal value. These have got wide range of therapeutic actions ranging from anti-inflammatory, anesthetic, to anti-bacterial and fibrolytic and many more. Mode of action is dependent upon the actual time of leech-therapy. This is the time required to apply the leeches, the blood sucking period, the detachment of leech, and the capillary oozing period which may range from 6 to 24 hours, and in some extreme cases up to 48 hours.

VII. CONCLUSION

The majority of studies on leeches are related to: internal and external morphology. Fewer research projects focus on the indications and the pharmacological aspects of the salivary gland secretions. In the past, leeches were used for a variety of applications; their mechanism of action behind this therapy was obscure, and all that mattered was curing or relieving the problem. Today, the research studies concerning the active substances in leeches have given us a better understanding of how the therapy works and have increased their therapeutic use. Leech therapy may be applied to various diseases known nowadays, due to its anticoagulant, vasodilator, and thrombolytic, anti-inflammatory and anaesthetizing qualities. But with further studies, the spectrum of effects may widen. The technique is cheap, effective, easy to apply, and its modes of action have been elucidated for certain diseases. In conclusion, for treatment of some diseases, Leech Therapy is not an alternative, but is a complementary and/or integrative choice. It is a part of multidisciplinary treatments, and secretes various bioactive substances. These substances vary among species and different species should be

evaluated for both treatment capability and their particular secreted molecules. There is huge potential for the invent of novel substances and these could be future therapeutics. After the study of SGS it can be stated with élan that used judiciously, leeches can get blood flowing in regions that even a skilled surgeon cannot. Compared to other techniques of complementary and natural therapy, Leech therapy can be learned relatively quickly and can reduce the complications arising from the excessive use of synthetic drugs. This article is a sincere attempt to highlight the relatively important areas of leech therapy with more clinical areas to be covered under the research domain on this wonder parasite.

Conflict of interest- The Author doesn't have any conflict of interest.

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