Leech Therapy (Hirudotherapy): A Comprehensive Systematic Review of Pharmacological Constituents, Mechanisms of Action, Therapeutic Applications, and Safety

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ABSTRACT

Background: Hirudotherapy, the medicinal use of leeches, has evolved from traditional healing practices into a scientifically recognized therapeutic modality. The renewed interest in leech therapy arises from the identification of a wide spectrum of pharmacologically active molecules in leech saliva, many of which exhibit potent anticoagulant, anti-inflammatory, antithrombotic, analgesic, and vasodilatory effects.

Objective: This systematic review aims to critically analyze the pharmacologically active compounds present in leech saliva, their mechanisms of action, preclinical and clinical evidence, pharmacokinetic and pharmacodynamic aspects, safety concerns, and future potential in drug discovery.

Methods: A systematic literature search was performed across PubMed, Scopus, Google Scholar, Experimental, preclinical, and clinical studies relevant to pharmacology were included. Data extraction focused on bioactive molecules, mechanisms, therapeutic outcomes, and adverse effects.

Results: Leech saliva contains over 100 bioactive molecules, including hirudin, calin, destabilase, bdellins, and Eglins. These compounds exert synergistic effects on coagulation pathways, inflammatory mediators, and microcirculatory dynamics. Clinical studies support its use in venous congestion, osteoarthritis, and reconstructive surgery, though standardization remains a challenge.

Conclusion: Leech therapy represents a biologically rich source of pharmacologically valuable compounds. Despite promising evidence, further large-scale, standardized clinical trials and molecular studies are essential for its integration into mainstream pharmacotherapy.

Keywords*:* Leech therapy, Hirudotherapy, Hirudin, Anticoagulants, Pharmacology, Bioactive peptides

INTRODUCTION

One of the earliest known therapeutic methods is leech therapy, sometimes referred to as Hirudotherapy. Evidence points to its use in Ancient Egypt as early as 1500 B.C. In the graves of Egyptian from the 18th dynasty (1567–1308 B.C), Leech therapy was widely used in ancient India, as evidenced by Sanskrit literature from circa 1300 B.C. Leech therapy was frequently utilized in ancient civilizations like Greece, China, India, and Pre-Columbian America. Leeches are thought to have been used in medicine for the first time· Using blood-sucking leeches, medicinal leech therapy (MLT) or Hirudotherapy is a type of complementary and integrative treatment. The name "leech" comes from the word "laece" (physician), and MLT has been in use for centuries. The earliest known uses were noted in ancient Egypt.In addition, Chinese, Arabic, Anglo-Saxon, MLT has become an important part of much scientific research. They are sensitive to touch, light, heat, sound, water movements, and a variety of substances. They are divided into several segments, including "brain parts," and each segment contains distinct organs like testicles and ganglions. For adhesion and creeping, two sucker pieces are used; the anterior one contains three jaws with many teeth. They often use rhythmic contractions to bite heated areas of the host and draw blood.A leech digests 10–15 mL of blood with each feeding, which typically takes about 40 minutes like Aeromonas hydrophila and Pseudomonas hirudinia, facilitate digestion. Following plastic, reconstructive, and microsurgical procedures, as well as cardiovascular conditions, deep vein thrombosis, postphlebitic syndrome, complications from diabetes mellitus, tinnitus, acute and chronic otitis, and the alleviation of osteoarthritis pain, MLT has been extensively tested. Hirudo medicinalis, Hirudo

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troctina, Hirudo nipponia, Hirudo quinquestriata, Poecilobdella granulosa, Hirudinaria javanica, Hirudinaria manillensis, Haementeria officinalis, and Macrobdella decora are the most often used leech species globally There are still numerous compounds that need to be investigated, but more than 20 have been found along with their mechanisms of action. These compounds have antibacterial and extracellular matrix degradative properties in addition to analgesic, anti-inflammatory, platelet inhibitory, anticoagulant, and thrombin regulating actions. Due to recently clarified effect mechanisms, it is thought that further indications may surface with additional research. Our goals in this paper are to compile data on MLT, offer a comprehensive overview, and examine various approaches.

Definition of leech therapy:

Parasitic worms include leeches. Applying leeches to a wound in order to stimulate blood flow, boost circulation, and encourage healing is known as leech therapy. Although its application has changed over time, it is still utilized during modern surgery.

Historical Background:

- Jalinoos (1st century AD): Prescribed leech bloodletting for many illnesses, including inflammatory conditions, mental disorders, and haemorrhoids.
- Zakariya Razi (10th century AD): Recommended leech use for various skin diseases.
- Ibn Sina (980-1037 AD): Noted in "Al-Qanoon" that leeches can draw blood from deep veins unreachable by wet cupping; advised leeching for skin diseases. Leech therapy was widely practiced in the 18th and 19th centuries
- The practice became so popular it sparked a "leech-mania" across Europe and America
- This period marks a significant historical phase for leech therapy use

Description of Leech:

Figure: 1 Leech

- Leeches are carnivorous or blood-sucking annelid worms with a strong ability to extend or contract their bodies.
- Their body has many segments: two pre-oral nonmetameric segments and 32 post-oral metameres, usually up to 20 cm long.
- Leeches are olive-green with lighter stripes and can grow up to 30 cm in length.
- They typically suck 2-20 ml of blood in 10-30 minutes, then drop off once fully engorged, showing no immediate urge to feed again.
- Leeches absorb blood via a proboscis that punctures skin or by biting with jaws.
- Mouth is tri-radiate with three jaws, each having 80 to 100 teeth.
- Leech bites resemble mosquito bites and are painless due to anaesthetic saliva.

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- Two suckers: anterior sucker (with mouth) for feeding and attachment, posterior sucker for attachment and movement.

Lee ch Classification in Unani Tib b:

two main categories based on their characteristics and effects: non-poisonous and poisonous.

- **Non-poisonous Leeches:** These leeches are typically small in size, with both their heads and bodies being relatively diminutive. Their coloration ranges from yellowish red to brown or a shade resembling liver, which aids in their identification.

- **Poisonous Leeches:** In contrast, poisonous leeches are distinguished by their larger head size and darker coloration, including dark grey, black, or green hues. Their bodies feature noticeable elevations or bumps, which can serve as a visual cue for identification

Scientific Classification of Medicinal Leeches:

Medicinal leeches belong to a fascinating group of segmented worms known for their unique biological features and therapeutic uses. In addition to this species, other medicinal leeches found in India include *Hirudo granulosa*, *Hirudo viridis*, *Hirudo javanica*, and *Hirudo manillensis*, each contributing to traditional and contemporary healing practices.

- Kingdom: Animalia.
- Phylum: Annelida.
- Class: Clitellata.
- Order: Hirudinida • Family: Hirudinidae
- Genus: Hirudo.
- Species: medicinalis
- Binomial Name: Hirudo medicinalis Linnaeus.

Procedure of Leech Therapy:

The procedure of leech therapy can be divided into several key stages to ensure safety and effectiveness:

- **Pre-Leeching:**

I. **Preparation of Patient:** This involves assessing the patient's medical history, ensuring there are no contraindications such as bleeding disorders or allergies, and preparing the skin area where the leech will be applied by cleaning and possibly numbing it.

II. **Preparation of Leech:** Leeches must be healthy and properly stored. They are usually kept in a clean, temperature-controlled environment and may be rinsed before application to remove any contaminants.

- **Leeching:**

This is the actual application of the leech to the prepared site. The leech attaches and begins to draw blood, releasing beneficial enzymes that promote healing and improve blood flow.

- **Post-Leeching:**

I. **Control of Bleed**: After the leech detaches, bleeding is controlled to prevent excessive blood loss. This may involve applying pressure or using haemostatic agents.

II. **Care of Leech:** Used leeches are handled carefully to prevent infection and are disposed of or stored according to medical guidelines to avoid cross-contamination.

- Each of these stages is crucial for the success of leech therapy, ensuring patient safety and maximizing therapeutic benefits.

Prerequisites:

- Prerequisites refer to the essential conditions, knowledge, skills, or resources that must be in place before beginning a particular task, project, or learning module. Examples of prerequisites might include prior coursework, specific technical skills, necessary software installations, or access to certain tools and materials.

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Preparation of Patient for Leech Therapy:

- **Skin Cleansing and Stimulation:** The targeted area of the skin should be thoroughly cleansed using Normal Saline (NS) to remove any dirt or contaminants. Following this, this redness indicates increased blood flow, which helps in the effective attachment and feeding of the leech.

- **Localization and Treatment Planning:** Clearly specify the exact localized area that requires treatment. Additionally, determine and document the frequency of leech application based on the patient's condition and therapeutic goals.

- **Pre-Treatment Investigations:** Before proceeding, ensure all relevant investigations are within normal limits (WNL). Recommended tests include Haemoglobin percentage (Hb%), Complete Hemogram to assess overall blood health, Random Blood Sugar (RBS) to check glucose levels, Bleeding Time (BT) and Clotting Time (CT) to evaluate coagulation status, and serological tests such as VDRL (for syphilis), HIV, and Hepatitis B surface antigen (HbsAg) to rule out infectious diseases.

- **Vital Signs Assessment:** Conduct a thorough examination of vital signs including pulse rate, body temperature, and blood pressure. Stable vitals are essential to safely proceed with the therapy.

- **Patient Education and Consent:** Educate the patient comprehensively about the procedure, potential benefits, risks, and aftercare requirements. This ensures the patient is well-informed and comfortable.

Obtain informed consent formally, documenting the patient's agreement to undergo leech therapy.

Preparation of Leeches:

- **Pre-application Conditioning:** One day before using the leeches, it is important to encourage them to vomit out any previously ingested blood. Turmeric not only stimulates the leech's activity but also has mild antiseptic properties, which can help maintain the leech's health.

- **Fasting and Storage:** Leeches should be kept fasting in fresh, clean water to ensure they are ready for the next application. Use a wide-mouthed bottle or a bowl filled with water that is free from contaminants and chlorine, as these substances can harm the leeches. The water should be changed regularly to maintain optimal conditions.

- **Selection of Active Leeches:** Before application, select only the active and healthy leeches from the storage container. Transfer these leeches carefully into a kidney-shaped tray filled with clean water. This setup facilitates easy handling and application of the leeches while keeping them comfortable and hydrated.

Leeching Procedure:

- **Preparation of the Treatment Area:** The area to be treated should first be thoroughly cleaned using Normal Saline (NS) and Betadine. This cleansing helps to reduce the risk of infection. After washing, gently rub the area until it becomes slightly red, which helps stimulate blood flow and encourages the leech to attach.

- **Encouraging the Leech to Bite:** If the leech is hesitant to bite, a small droplet of blood can be drawn from the wound site using a sterile needle prick. This fresh blood acts as an attractant, making it easier for the leech to latch on.

- **Identifying Successful Attachment:** When the leech attaches to the skin, it will lie flat with its mouth protruding, resembling the shape of a horse's hoof. Additionally, the leech's neck will appear swollen, indicating that it has begun to suck blood effectively.

- **Post-Leech Removal Care:** Once the leech detaches naturally or is removed, it is beneficial to apply suction using cups to draw out any residual blood. This helps prevent blood pooling and promotes better healing.

- **Application of Medicinal Substances:** After bloodletting, apply topical agents such as Haldi (turmeric) which possess astringent and antiseptic properties. These substances aid in preventing infection and assist in wound healing.

• **Additional Considerations:** Throughout the procedure, ensure that all instruments and materials are sterile to minimize infection risk. Monitor the patient for any adverse reactions, such as excessive bleeding or allergic responses, and be prepared to manage these if they occur.

MOJAR BIOACTIVE COMPOUNDS IN LEECH SALIVA :

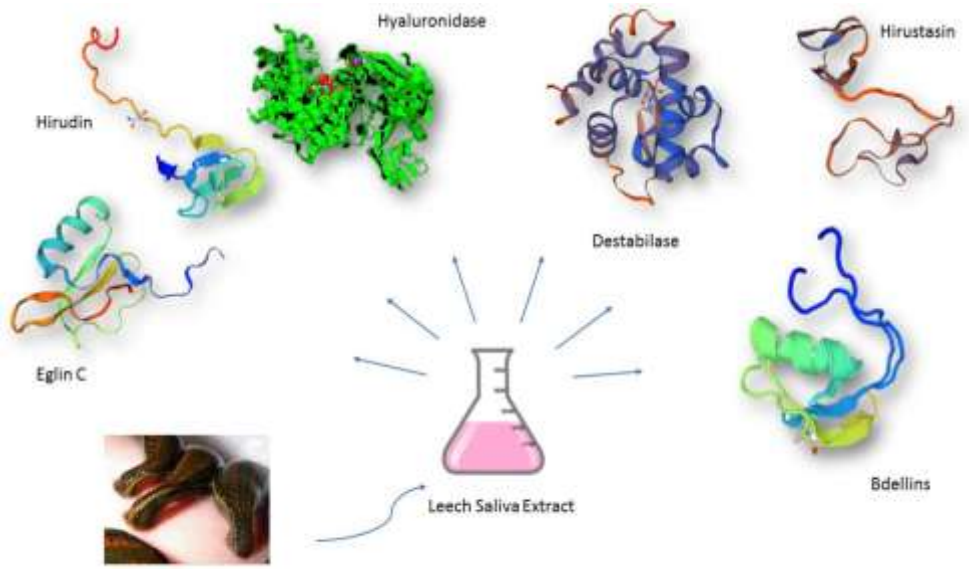

Figure: 2 Medical leech saliva contains wide range of proteins and enzymes which have multifunctional effect in diseases.

Table 1 Isolated chemical compounds from different leech species

leech species	Isolated compounds
Hirudo medicinalis	hirudin, destabilase, bedellin B, Calin, factor Xa inhibitor, Bedellastain, Hirustatin, Leech-derived tryptase inhibitor (LDTI), Hyaloronedase, Eglins, Apyrase, Collagenase, Leech carboxy peptidase inhibitor, Lipase (triglyceridase), Cholesterol-esterase, Steroids, Histamine, and Serotonin.
Hirudinaria manillensis	Bufrudin HM1, HM2 Hirullin P6, Hirullin P18 Manillase, Geli
Hirudo nipponia Theromyzon tessulatum	Leech granulin, Guamerin ,Piguamerin ,Theromin Therostasin Cytin ,Therin, Tessulin ,Theromacin and Theromyzin , Renin-like
Haementeria officinalis	Leech antiplatelet protein (LAPP) , Antistasin
Haementariaghilianii	Hementin ,Tridegin ,Ghilantin , Saratin
Haementeria depressa	Hementerin ,Lefaxin
Haementarealutzipintu	Hementerin
Haemadipsa sylvestris	Haemadin
Macrobdella decora	Decorsin
Placobdella ornate	Ornatins
Leech in general	100++ unidentified proteins

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Hirudin: Hirudin is a very potent polypeptide that stands out from other peptides with comparable roles due to its remarkable effectiveness as a thrombin inhibitor. It has 64–66 amino acids and was first extracted from Hirudo medicinalis saliva. the N-terminus of natural hirudin consists of five neutral aquaphobic amino acid sequences, while the C-terminus contains 25 amino acid residues. Additionally, Tyr63' is a sulfated amino acid that increases the number of negatively charged amino acids. Hirudin exhibits a high affinity and specificity in binding to thrombin, thereby neutralizing its enzymatic activity[15]. the inhibition of thrombin obstructs the conversion of fibrinogen to fibrin, preventing clot formation. Moreover, by inhibiting thrombin, hirudin also impedes thrombin-induced platelet activation through Protease-Activated Receptors (PARs), leading to a reduction in platelet aggregation at sites of vascular injury Thrombin, acting downstream of factor Xa, is essential for converting prothrombin to thrombin. By blocking thrombin, hirudin indirectly impacts the activation of factor Xa, as thrombin generation is a pivotal step in the propagation phase of coagulation involving factor Xa .Hirudin is the most commonly treating patients with disseminated intravascular coagulation syndrome and platelet abnormalities. Recent studies have significantly expanded the understanding and applications of hirudin and its derivatives. These include its roles in wound repair, antifibrosis, antidiabetic medication, antithrombotic agent, anti-hyperuricemia, and treatments for cerebral hemorrhage, IgA nephropathy, acute lung injury, and myocardial infarction

Furthermore, hirudin has demonstrated anti-tumor effects in various cancers, including liver, lung, breast, laryngeal, malignant glioma, and prostate cancer.

Antistasin: Antistasin was first isolated from the salivary glands of the Mexican leech Haementeria officinalis with 119-amino acid. However, recently identified in the saliva of the leech species Helobdella austinensis by. Antistasin includes five conserved cysteine residues and two glycine residues or six cysteines and two glycine residues. exerts anticoagulant effects by inhibiting the conversion Antistasin is a crucial component of leech saliva extract, known anti-inflammatory properties. The presence of platelet aggregation inhibitors, anticoagulants, and anti-proteolytic enzymes in the Haementeria officinalis saliva made it antistasin have antimetastatic activity. Beyond its role alongside hirudin, antistasin has been demonstrated to have antimetastatic effects, as well as anti-platelet and anti-thrombin effects.

Saratin: Saratin is a protein 103 amino acids and three disulfide bridges, extracted from the saliva of the leech Hirudo medicinalis .This bioactive molecule prevents thrombocyte aggregation by disrupting the initial binding stage of thrombocytes to the von Willebrand factor (vWF). It achieves this by binding to exposed type I and II collagen, thus preventing platelet aggregation. Consequently, Saratin reduces thrombocyte aggregation to vessel walls and subsequent thrombus formation [22] Saratin is a potent therapeutic agent that locally prevents coagulation without affecting normal hemostatic functions. He demonstrated saratin's have antithrombotic effect on human atherosclerotic plaques. Additionally, animal studies suggest that recombinant saratin could be a promising treatment option.

Tryptase Inhibitor: The leech-derived tryptase inhibitor (LDTI), originally isolated from the European medicinal leech Hirudo medicinalis, consists of 46 amino acids. Tryptase inhibitors have been shown to counteract the effects of various proteolytic enzymes, including chymosin, mast cell chymotrypsin, subtilisin protease, human blood neutrophil proteases, elastase, and cathepsin The tryptase inhibitor holds promising effects for allergic and inflammatory diseases, including alleviating allergic reactions and anaphylaxis symptoms such as itching, swelling, and respiratory distress; and managing conditions like asthma, arthritis, and inflammatory diseases .It is also important for wound healing and tissue repair processes and for alleviating associated pain from various conditions .

Hyaluronidase: A hyaluronidase activity was first described in Hirudo medicinalis. Its primary function involves the degradation of hyaluronan, a multifunctional polysaccharide found in the extracellular matrix of connective tissue demonstrated that hyaluronidase acts as a spreading factor by digesting tissue hyaluronic acid and exhibiting antimicrobial activity, thereby increasing the viscosity of interstitial walls and leading to antibiotic effects. Consequently, this facilitates the infiltration and diffusion of other leech components into deep or congested tissues Hyaluronic acid, a polymer associated with tumor metastasis, may be influenced by hyaluronidase, potentially exerting anticancer activity by inhibiting tumor-promoting substances and slowing cancer progression. Furthermore, hyaluronidase facilitates the diffusion and penetration of pharmacologically active substances into tissues, particularly in joint pain management, and possesses antibiotic properties. Additionally, it is utilized to decrease venous congestion and exhibits antithrombotic, thrombolytic, hypotensive, anti-inflammatory, and bacteriostatic activities .

Collagenase: Collagenase, a well-known bioactive compound extracted from the saliva of the medicinal leech Hirudo medicinalis. As an enzyme, it exerts inhibitory effects on platelet functions and the coagulation cascade, with a specific target on collagen. Its primary function lies in facilitating tissue penetration and the dispersion of other bioactive molecules secreted by the leech. Collagenase aids in removing dead tissue from chronic wounds like ulcers, promoting healing by cleaning the wound bed.

Calin: Calin, an enzymatic protein secreted by the salivary glands of the medicinal leech Hirudo medicinalis,functionally analogous to saratin, this bioactive substance primarily binds to type I collagen thereby impeding von Willebrand factor (vWF) from binding to exposed collagen and inhibiting platelet aggregation. alin likely contributes significantly to inhibiting platelet aggregation as well as regulating blood clotting, improving blood flow, and restoring vascular permeability.

Destabilase: Destabilase produced by the medicinal leech Hirudo medicinalis. Destabilase displays antimicrobial activity by disrupting bacterial cellular components. the enzyme's various isoforms with distinct capabilities and degradation actions on stabilized fibrin render it a potential candidate for evaluation as an anticoagulant agent

Apyrase: Apyrase, an enzyme first isolated from the saliva of the leech Hirudo medicinal is. . Its primary function lies in strongly inhibiting ADP induced platelet aggregation by acting as an ectonucleotidase. This enzymatic action involves the hydrolysis of nucleotide triphosphates (such as ATP and ADP) into their respective diphosphates (ADP and AMP), and further into monophosphates (AMP), thereby regulating platelet aggregation, blood clotting, and vascular tone. By reducing the concentration of ATP and ADP, Apyrase was used to enhancing tissue permeability, preventing platelet aggregation and excessive clotting during surgical procedures.

Eglin: Eglin C, the principal isoform within the natural protein family, comprises 70 amino acids. it was purified from the saliva of the leech Hirudo medicinalis. It classified within the potato type I proteinase inhibitor family, Eglin C vigorously inhibits various enzymes, eglin demonstrates a pivotal role in mitigating the levels of free oxygen radicals in neutrophils, thereby curbing tissue inflammation and damage, Leech therapy treats diabetic neuropathy by applying an anti-inflammatory effect on nerves through the saliva of Bdellins and Eglins.

Bdellinsa: Their amino acid sequence varies across leech species, influencing their functional properties and interactions with other molecules. Bdellins interfere with blood clotting by inhibiting enzymes involved in the coagulation cascade and exhibit potent inhibitory activity against the trypsin-like proteinase. Leech-derived bdellins possess anti-inflammatory effects, aiding in reducing inflammation in conditions like joint pain or arthritis

Decorsin: Decorsin, a protein identified from the American medicinal leech Macrobdella decora. The mechanism of action is a strong inhibitor of platelet aggregation and an antagonist of platelet glycoprotein II bIII receptor. It has anticoagulant properties, effectively preventing the formation of blood clots and promoting improved blood circulation by regulating clotting processes.

Hirustasin: Hirustasin, derived from the saliva of the leech species Hirudo medicinalis, Hirustasin exhibits robust inhibitory activity against trypsin, chymotrypsin, and neutrophil cathepsin G, in addition to its tight binding inhibition of tissue kallikrein. The tissue kallikrein/kinin system, pivotal in regulating normal blood pressure

Piguamerin: Piguamerin, a peptide initially identified in the blood-feeding Korean leech Hirudo nipponia, comprises 48 amino acids. They elucidated its role as a serine protease inhibitor, demonstrating its inhibitory effects on plasma and tissue kallikrein, as well as trypsin. Notably, it shares similarities with antistasin-type inhibitors in the spacing of ten cysteine residues but diverges from hirustasin and antistasin at residues surrounding Arg27, a common P1 reactive residue for these inhibitors. Piguamerin is a pivotal enzyme in the blood clotting cascade, rendering it valuable in preventing clot formation. It has anticoagulant properties and can enhance blood flow by impeding thrombosis and fostering vasodilation.

Histamine-like Substances: Histamine-like substances exert vasodilatory effects, augmenting blood flow to tissues. This property proves advantageous in conditions necessitating enhanced blood circulation, such as ischemic diseases and wound-healing processes. A inhibitor, and histamine-like substances, which improve blood flow and reduce congestion to treat diabetic microangiopathy.

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Carboxypeptidase A Inhibitors: Carboxypeptidase A inhibitors, discovered from the saliva of the leech Hirudo medicinalis. . Although inhibition of carboxypeptidases by leech secretions does not affect bradykinin action via B2 receptors, it may be impeded by B1 receptors, which are associated with chronic inflammation, in contrast to B2 receptors linked to acute inflammation. Carboxypeptidase-A inhibitors exhibit antiinflammatory effects, particularly relevant in conditions like multiple sclerosis, asthma, and rheumatoid arthritis, associated with B1 receptor activity. This bioactive substance has a vasodilator effect which increase inflow of blood to wound site, that mean it reduce local swelling.

Guamerin: Guamerin is a bioactive substance isolated from the saliva of the Korean medicinal leech Hirudo nipponia. Guamerin selectively inhibits human leukocyte elastase and porcine pancreatic elastase. Guamerin's elastase inhibition presents a promising avenue for managing inflammatory conditions and potentially reducing tissue damage. It has analgesic and ant inflammatory effects by modulating inflammatory responses, it may also contribute to pain relief, offering potential applications in managing certain vascular disorders.

Ghilantens: Ghilanten is one of the most important bioactive substances of leech saliva which is used to suppress metastasis of melanoma, breast cancer, lung cancer, and prostate cancer in the experimental animal model .it plays a pivotal role in the therapeutic mechanisms of leech therapy for inflammatory conditions because this bioactive molecule has both analgesic and anti-inflammatory importance as reviewed.

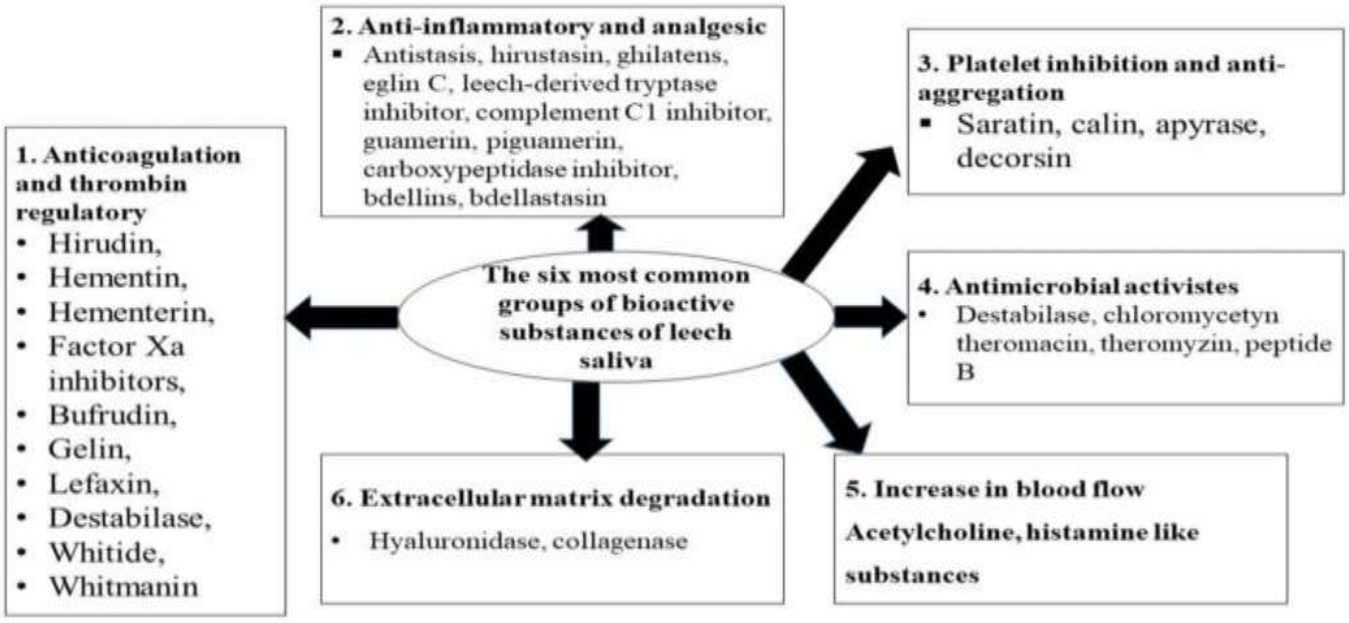
Hementerin: Hementerin exerts its anticoagulant effect by cleaving peptide bonds in fibrinogen and inhibiting thrombin activity, a pivotal enzyme in the coagulation cascade. This property facilitates prolonged blood-feeding by the leech from its host Hementerin helps to prevent blood clots by inhibiting platelet aggregation and the coagulation cascade.Similarly, it is an effective inhibitor of human platelet aggregation, presumably through activation of the platelet's nitridergic pathway.

Complement C1 Inhibitor: A protein C1 component inhibitor was isolated and characterized from the saliva of the medicinal leech, Hirudo medicinalis. This protein was identified as a potent inhibitor of the complement system, particularly targeting the C1 component factor. The complement C1 inhibitor can reduce inflammation by inhibiting the activation of the complement system, which plays a critical role in the body's inflammatory response..

Poeciguamerin*:* Poeciguamerin was a bioactive peptide, purified from the saliva of leech Poecilobdella manillensis. Poeciguamerin serves as an anticoagulant by inhibiting thrombin, thus impeding clot formation and facilitating blood flow during leech feeding. Featuring an antistatic-like domain, it acts as a serine protease inhibitor, particularly targeting elastase while also moderately inhibiting FXIIa and kallikrein.

Mechanisms Action of Leech Therapy:

Figure: 3 Mechanisms of Action Leech Saliva in Pharmacology Is Based on Its Ability to Modulate Various Biological Processes. The Saliva Contains a Variety of Bioactive Compounds.



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Anticoagulant effect:

The leech saliva components stop platelet aggregation and inhibit coagulation factors at different levels through different mechanisms, which mainly include the following compounds:

Hirudi : a peptide consisting of 65 or 66 amino acids with 3 disulfide bonds, its main feature is 63-position sulfated tyrosine, which increases hirudin and thrombin binding affinity by 10 times. It is a highly specialized thrombin inhibitor that blocks thrombin between platelets and inhibits platelet aggregation which is stimulated by thrombin, a property that leads to the disintegration of platelets.

Antistasi : derived from Mexican leeches, a peptide containing 55 amino acids that can precisely act on factor Xa, thereby preventing the conversion of prothrombin to thrombin and exerting anticoagulant effects.

Saratin: a 12 kDa molecule that binds to exposed type I and II collagen, competitively inhibits collagen binding to vWF, and also prevents platelet aggregation.

Calin : a 65 kDa protein that closely resembles Sartain's mechanism of action and binds primarily to type I collagen, thereby preventing vWF from binding to exposed collagen and platelet aggregation.

Apyrase : a small number of studies have reported it as a 45 kDa enzyme. The increase in ADP concentration can lead to increased platelet affinity for vWF, which mainly degrades ADP into AMP, thereby inhibiting the ability of platelets to adhere to the site of vascular injury

Thrombolytic effect:

Destabilizing enzyme: a protein with a molecular weight of approximately 12.3 kDa Destabilizing enzymes have a unique D-dimer monomerization ability, which presupposes the splitting of Lys-isopeptide bonds between the γ chains of ε-(γ-Glu)D-dimers. The effect can change the balance between fibrinogen and fibrin products during fibrin degradation, which is conducive to the formation of fibrin degradation products and inhibits the activation of fibrinolysis.

Anti-inflammatory effect:

Proteolytic enzyme inhibitors are present in the saliva components of leeches, a special class of proteins that have different structures and protease inhibition mechanisms that can jointly block different kinds of proteolytic enzymes. Verm protease inhibitors are a group of peptides and they are inhibitors of trypsin, Hirustasin is a serine protease inhibitor that, unlike Antistasin, doesn't block the activity of Xa coagulation factor but inhibits trypsin, chymotrypsin, cathepsin G, and kallikrein. Trypsin is the main component of mast cell secretory cytoplasmic granules and trypsin has also been found that it has a very important pathogenic role in allergic and inflammatory diseases, which is related to mast cell dysfunction (asthma, rheumatoid arthritis, psoriasis, etc.).. Although trypsin inhibitors extracted from leech saliva have shown great efficacy, they have shown inconsistent effects in different studies of recombinant trypsin inhibitors, making it difficult to evaluate the actual clinical efficacy of recombinant trypsin inhibitors. Leech inhibitors are proteins with a molecular weight of about 8 Da, which are mainly found in leech saliva and have been reported to inhibit the effects of chymotin, chylase, mast cell chymotrypsin, subtilis protease and human blood neutrocyte protease, elastase and cathepsin.

Immunosuppressive effect:

Compounds in leech saliva enter the body's internal environment, and as foreign bodies, they are supposed to undergo an appropriate response from the immune system. However, no expression of immune response was seen in the body after multiple applications of leechsaliva. In addition, through the use of leeches some scholars have successfully treated patients with autoimmune diseases such as bronchial asthma, rheumatoid arthritis, systemic scleroderma and so on, which may be the credit of unknown components of saliva.

Lymphatic circulation stimulating effect:

This action of leeches may be related to the presence of hyaluronidase, which reduces the viscosity of hyaluronic acid by breaking the C1-acetylglucosamine and C4-glucuronic acid bonds, increases the permeability 3094 of tissues, improves their nutrition, increases the elasticity of scar-modified areas, relieves the diffusion of fluid.

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Cardiovascular diseases:

- Cardiovascular diseases (CVDs) encompass a broad range of chronic conditions that affect the heart, veins, and arteries, leading to impaired blood circulation and increased risk of serious health events such as heart attacks and strokes

- Leech therapy, an ancient medical practice, is gaining renewed interest as a complementary treatment for vascular disorders. The saliva of medicinal leeches contains a complex mixture of bioactive substances, including anticoagulants, vasodilators, and anti-inflammatory agents, enhance blood flow and reduce pain associated with connective tissue hyperalgesia.

- Clinical studies have demonstrated that leech therapy can effectively reduce blood hypercoagulability—a condition where the blood has an increased tendency to clot—thereby lowering the risk of thrombosis.

- **Destabilase:** This unique enzyme is found exclusively in leeches and plays a crucial role in the process of fibrinolysis, which is the breakdown of fibrin in blood clots. Before the discovery of Destabilase, the scientific community had limited understanding of this specific mechanism. In medical practice, Destabilase is significant because it enables leeches to dissolve old, stabilized thrombi (blood clots) effectively. This property is particularly valuable in treating conditions where blood clots pose a risk, such as in certain cardiovascular diseases, by promoting natural clot breakdown and improving blood flow.

- **Inhibitors of Platelet Aggregation:** Leeches also produce substances that prevent platelets from clumping together, which is a key step in clot formation. One important compound is Apyrase**,** an enzyme that hydrolyzes ATP and ADP into AMP. By breaking down ADP, Apyrase strongly inhibits ADP-induced platelet aggregation, thereby reducing the likelihood of new clot formation. This anti-platelet effect complements the fibrinolytic action of Destabilase, making leech therapy a multifaceted approach to managing cardiovascular conditions by both dissolving existing clots and preventing new ones from forming.

Use of Leech Therapy in Cardiovascular Diseases:

The combined action of these enzymes highlights why leech therapy has been explored as a treatment option in cardiovascular diseases. By leveraging the natural biochemical tools of leeches, medical practitioners can address complex clot-related issues with a biological approach that supports the body's own mechanisms for maintaining healthy blood flow and preventing complications such as thrombosis and embolism.

Leech Therapy in Vascular Disease

Leech therapy enhances mobility, alleviates discomfort, diminishes swelling, and restores normal skin tone in patients suffering from phlebitis. Treatment involves placing 4 to 6 leeches directly on the affected region. The therapy is also effective for managing conditions such as high blood pressure, varicose veins, haemorrhoids, and skin disorders linked to poor blood flow.The therapeutic benefits stem from compounds in leech saliva, notably thrombin inhibitors like hirudin, which help improve cardiovascular health. Noteworthy, hirudin is the only anticoagulant derived from hematophagous (blood-feeding) animals that has received FDA approval for clinical use. This highlights its unique origin and the rigorous evaluation it has undergone to ensure safety and efficacy in medical treatments. making it a safer alternative in these cases. Use of Leech Therapy in Vascular Diseases: The therapeutic use of leeches, which secrete hirudin in their saliva, has a long history in medicine. Leech therapy is employed to improve blood flow and prevent clotting in various vascular conditions, leveraging the anticoagulant properties of hirudin to promote healing and reduce complications.

Maintenance of Local Blood Circulation:

Increased Local Blood Perfusion This refers to the enhanced flow of blood through the small vessels in a specific area of the body. Improved perfusion ensures that tissues receive adequate oxygen and nutrients, which is essential for healing and normal function.

Vasodilatation of Local Blood Vessels (Histamine-like Substances) Vasodilatation is the widening of blood vessels, which reduces vascular resistance and allows more blood to flow through. Substances similar to histamine play a key role in this process by relaxing the smooth muscles in the vessel walls, thereby increasing blood supply to the affected area.

Dissolution of Vascular Thrombi (Such as Carboxypeptidase-A, Histamine) Vascular thrombi are blood clots that can obstruct blood flow. Enzymes like Carboxypeptidase-A help break down these clots, restoring circulation. Histamine also contributes by promoting vasodilatation and increasing permeability, which facilitates the removal of clots and supports tissue repair.

Overall Maintenance of Local Blood Circulation Together, these mechanisms ensure that blood flow is sustained and optimized in localized regions, which is crucial for tissue health, immune response, and recovery from injury.

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. 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. Leeching has been reported as a successful remedy to improve blood flow after microsurgery of a severely avulsed scalp (ripped away by an injury). The scalp was partially salvaged with normal hair growth in the whole injured areas. By the year 1984, some physicians used leech therapy to treat seven patients with engorged (swollen) skin flaps. They applied leeches 2-4 times a day for 2-4 days. They reported that leeching prevented flap collapseMore recently, some medics outlined a successful application of leech to salvage an ischemic finger. At the 7th day of the treatment, the patient described sensation improvement and sensitivity to pinprick at the top of the finger. Penile replantation by no microsurgical operations achieved a great success when accompanied with Hirudotherapy. Leeching-treated patients revealed no edema and normal functions, such as emptying, sensation, and erection. Leech therapy was successfully applied to avoid venous insufficiency in patients who received free perforator flaps for the medial sural artery which supplies the medial gastrocnemius muscle and the overlying skin. Recently, it was reported that leeching was used to treat six patients with venous congested microvascular free flaps in

Cancer and metastasis:

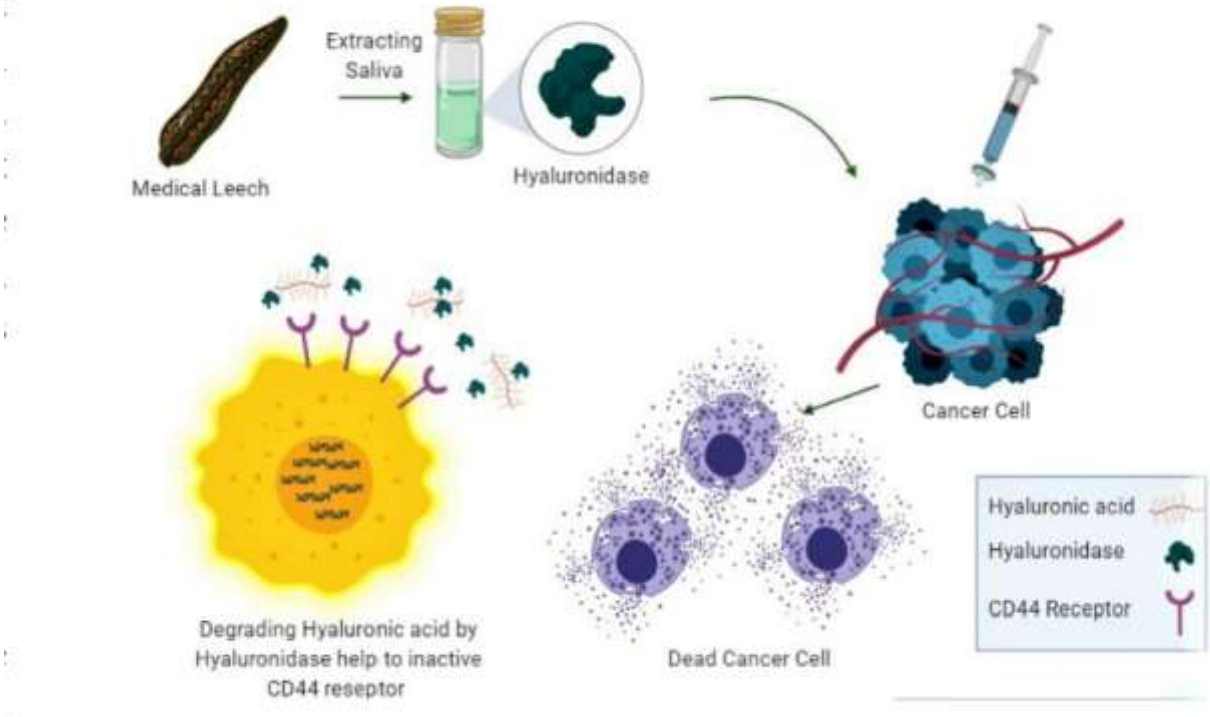

Figure 4: Activity of Hyaluronidase in Cancer. Degrading hyaluronic acid by hyaluronidase, inhibiting CD44 activation and after a while mRNA of VEGF reduced and it helps to reducing angiogenesis of cancer cells.

In 2008, cancer was responsible for about 13% of all global deaths. Leech application as antimetastatic agent was inspired from a previously reported metastatic inhibitory activity of some anticoagulant such as warfarin and heparin. DM has been considered as a global pandemic due to the progressive increasing rates of people suffering from diabetes, expecting to be a worldwide burden by 2030 with 366 million diabetic patients. The peripheral vascular complications in diabetic patients can lead to less blood flow to the distal anticoagulants, protease inhibitors, and other components in leech saliva could be more powerful as an antimetastatic drug. such as pulmonary carcinoma, breast carcinoma, bladder carcinoma, colorectal carcinoma, soft-tissue sarcoma, leukemia, and lymphoma. Many reviewers who investigated the therapeutic importance of the medicinal leech cited that leeching could be effective for the treatment of infection without mentioning more details or information about leech application protocols and the nature of the active component. Three different peptides with antibacterial activities were identified from this leech species. They outlined that leech extract could be used in the treatment of bacteria-induced illnesses including arthritis, foodborne disorders, and nosocomial infections.

Arthritis and analgesic

The painkiller effects of leech application were ascertained in many trials on patients with osteoarthritis who claimed that leeching was more relieving than topical diclofenac with no adverse

Skin disorders:

Leeching has been practiced by traditional therapists for the treatment of skin disorders with no scientific studies supporting this utilization like in the viral skin infection named shingle disease

Dentistry:

Although, the benefits of leeching in dentistry have not been established yet, many reports mentioned leech application in dental abnormalities The bloodletting by leeches was reported to be considerably successful in the management of severe post operation macroglossia cases when the common treatment method was not satisfactory. Others outlined the usage of leeches in gum diseases. For example, the direct application of 3-4 leeches can be a successful remedy for abscess and inflammat Audiology and ear abnormalities one behind the ear and the other one over the jaw in front of the ear, and the treatment was repeated 2-3 times at intervals of 3-4 days

Preclinical Studies In Leech Therapy:

Leech therapy, has garnered attention across various systems of medicine, for its therapeutic potential. Clinical studies have shown its efficacy in treating a range of conditions, such as pain management, wound healing, and blood circulation disorders. In Unani medicine, leeches are used for their detoxifying properties, promoting balance within the body and addressing issues related to blood disorders and inflammation Similarly, traditional Ayurvedic practices utilize leech therapy for detoxification and to balance bodily humors. In Western medicine, leeches are frequently employed in reconstructive surgery to enhance venous drainage and minimize blood clots. Research highlights promising outcomes in areas such as osteoarthritis, where leech therapy has been associated with reduced inflammation and improved joint function.

Studies On Joint Disorders methodology:

This study was a prospective, randomized controlled trial involving 40 participants divided into two groups of 20 through block randomization. The test group received both leech therapy, 5 gm. twice daily, which is comprised of Suranjan, Boozidan , and Asgand in equal proportions, along with Suranjan oil 10 ml BD for local application, while the control group received only the herbal treatment. The study lasted 6 weeks with follow-ups at the 14th, 28th, and 42nd days. Results showed a significant reduction in pain (29.02%), stiffness (58.87%), and an increase in functional ability (40.56%), all with p-values < 0.001. However, there was no notable difference in the secondary outcomes between the two groups.

Studies On Pain Managements:

proof-of-concept study, conducted as a two-center, open, nonblinded, randomized controlled clinical trial with Test Group – Leech therapy at L1 to S3; Control Group – Exercise for 60 min each week for 4 weeks. Primary Outcomes were Change in average back pain intensity, as measured using a 100-mm visual analog scale (VAS), after 28 days & secondary outcomes were functional impairment, quality of life & pain perception,

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depression and analgesic consumption (questionnaire/ diary). Study lasted for 56 ± 5 days with follow up after 28 ± 3 and 56 ± 5 days.

Studies In Dermatology and Cosmetology:

Two patients participated in this study. A 56 years old man who had a wound on his left hand & a 43-year-old lady who had a facial cut, both were identified as Cutaneous Leishmaniasis. They took Leech therapy sessions. 5 leeches were applied during the intervention over the course of 4-5 sessions, spaced 2–4 weeks apart. Before & after treatment photographs were taken.

Diabetic Neuropathy:

A 61 years old man who had diabetic neuropathy in left foot was studied for 58 days. Two Leeches were applied around the lesion once a week for nine weeks. With, Irsal-e-Alaq the sensation was restored completely within 58 days, the symptoms of the patient improved a lot and the size of the lesion reduced with subsequent sittings.

Diabetic foot:

A 60-year-old woman suffering with diabetic foot on the left leg was having severe pain in the gangrenous foot and foul-smell. After 3 months of Leech therapy, the wound was completely healed and free from any deformity and pain after 3.5months.

Gangrene:

A 45 years old male patient was admitted in the male ward of National institute of Unani Medicine, Bengaluru, having complaints of severe pain and wound in right greater toe from 1 month. Leeches were applied on the dry gangrenous wound twice a week for 30 days[27]. The wound was completely healed at the end of 1 month.

Figures show before & after treatment results.

Leeches may not bite if:

- The skin is cold
- Older humans
- Smokers
- Perfumed skin

5. SAFETY AND COMPLICATION OF LEECHING

- Anemia
- In extreme ages i.e., in children and old age.
- Weak patients
- Allergic patients
- In extreme hot or cold climate
- Diseases like hemophilia
- Pregnancy

Table 2 Leech extract-based pharmaceuticals.

Leech extract-based product	Route of administration	Claimed usage	Year of marketing	Used for
Hirudin Sachsse and Co., Leipzig, Germany	Injection	Anticoagulant	1904–1925	Blood transfusion,Eclampsia, hemodialysis
Hirudin Passek and Wolf Hamburg	Injection	Anticoagulant	1920–1925	hemodialysis

Piyavit	Oral	Anticoagulant	1993–1995	acquired heart valvular disease
Shuizhi and other oral Chinese formulation	Oral	Anticoagulant antiplatelet aggregation	1960s- today	Acute and chronic cerebrovascular diseases, atherosclerosis], ischemic stroke, acute coronary syndrome
Shuxuetong Recombinant hirudin derivatives	Injection	Anticoagulant	1990s-today	heparin-induced thrombocytopenia
Lepirudin	Injection	Anticoagulant	1997	Ischemic stroke
Desirudin	Injection	Thrombin inhibitor	2003	Antithrombin in elective hip replacement surgery
Bivalirudin	Injection	Anticoagulant	2000	unstable angina

CONCLUSION

Leech therapy is a biologically sophisticated therapeutic approach with substantial pharmacological relevance. Its bioactive salivary compounds offer promising avenues for anticoagulant and anti-inflammatory drug development. However, rigorous clinical validation and molecular characterization are essential for its acceptance in modern pharmacotherapy. MLT is a valuable traditional technique with strong biochemical actions. Although modes of action and bioactive substances still await further exploration, their utility in certain medical conditions is obvious. Indications and potential complications should be evaluated, including antibiotic prophylaxis and application frequency, and dosage and delivery timing depend on the patient and physician's opinion. It must be noted that MLT is not a treatment method by itself, but it can be an important part of a multidisciplinary approach.

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