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Leech; a Threat, an Intervention or a Pharmacy, a Review.

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ABSTRACT

Leeches have a complex relationship with the human race. They act as vampire attackers that can induce various complications and might be life-threatening in some cases (especially in orificial hirudiniasis). On the other hand, there is a long history of seeking medicinal uses for leech bites (leech-therapy) since 1500 BC in ancient Egypt. This therapy is resurging in the last few decades aided this time by ongoing scientific investigations and case reports. What surpass expectations are the potentials of the unique chemical substrates found in leech saliva, like hirudin, which has propelled modern research and inspired the development of new therapeutic generations. Still, the understanding of leech biology and the extracted chemical substrates is in its beginnings and future research can reveal various therapeutic candidates. Thus, this review represents a trial to explore this multifaceted leech-man relationship by discussing three main aspects; therapeutics discovery, parasitism and leech therapy.

INTRODUCTION

Leech (Hirudinea) is a segmented worm of the phylum Annelida (Yadav and Zhan, 2020). The word "leech" comes from the Anglo-Saxon “loece”, which means "to heal". The usage of leeches has been documented in Egyptian paintings dating back to 1500 BC. It has been used in medicine since ancient Greece, Rome, and Arabia for "local depletion" (bloodletting) (Hyson, 2005; Pourrahimi *et al*., 2020).

Leeches are classified into two groups based on their feeding patterns. Predacious leeches, for example, are predators of various invertebrates. The sanguivorous leeches, a second group, are ectoparasites that feed on the blood of vertebrates, including humans. Leeches absorb prey blood with the help of their suckers and biting jaws, then drop off spontaneously after becoming completely engorged, with no urgent desire for continued feeding (Abdualkader *et al*., 2013). They live in both water (ponds, streams, lakes, and the sea) and wet terrestrial settings (Shakouri and Wollina, 2021). Bloodsucking leeches can be found all around the world, but they are most common in North America, Europe and Southeast Asia (Ghosh, 2019).

Leech saliva components are a complex mixture of various biologically active substrates that are not only crucial for leech survival and feeding processes but have shown various applicable pharmacological potentials (Ahirrao *et al*., 2017). Thus, this review represents a trial to explore this multifaceted leech-man relationship by discussing three main aspects; therapeutics discovery, parasitism and leech therapy.

Leech Morphological Characteristics:

Leeches are invertebrates of different colours; brown, dark green, or black. They might have brown, orange, or red striped lines on their bodies. A leech has anterior and posterior suckers. The anterior sucker is used for blood-sucking, whereas the posterior sucker is used for motility and attachment. It has three jaws, each with around 100 teeth and makes a characteristic Y incision on biting the skin. It swims in a vertical undulating pattern in water and crawls outside the water using its posterior sucker. It lacks lungs and breathes through its skin and has two-segmented tubular pumping hearts (Abdisa, 2018). Leech has a thin flexible cuticle and no outer exoskeleton. It dries fast, that is why it is so closely associated with water (Tilahun *et al*., 2020).

Its mouth is in the center of the anterior sucker (Hyson, 2005) and is equipped with three jaws grouped in a triradiate arrangement. The body of a leech has 102 annuli (Porshinsky *et al*., 2011), but its internal structures are separated into 32 segments. The first four front segments are categorized as head segments, the next 21 are midbody segments, and the final seven segments form the tail sucker (Ahirrao *et al*., 2017). Taxonomists use the annulation pattern and sensory organs to distinguish the genus and species of these worms (Abdualkader *et al*., 2013).

The General Life Cycle of Leeches:

Leeches have three life stages: egg, young leech and adult. Most leeches take 1-2 years to mature. In a proper environment, an adult leech can live for 18-27 years and may not require feeding for up to a year after its last meal. Between 1 and 9 months after copulation, eggs are laid where a specialized organ "clitellum" begins to secrete four cocoons. Each cocoon contains approximately 15 eggs, resulting in a total of 60 progeny per year (Abdisa, 2018).

Leeches are hermaphrodites; however, they need another leech to reproduce (Porshinsky *et al*., 2011). If no suitable partners are available, leeches have demonstrated the ability to self-fertilize (Phillips *et al*., 2020). Eggs are subsequently put in damp soil and enclosed in a cocoon consisting of secretions that polymerize when exposed to air and water. For the first few days of their lives, young leeches hatch from eggs and feed on liquid protein material within the cocoon. Leeches feed mostly on amphibian-body fluids after emerging from the cocoon since their skin is delicate and thin, easily penetrable by the juvenile leeches' jaws (Elliott, 2008).

Leech Physiological Functions:

Leeches have a variety of sensory structures that they utilise to locate suitable habitats and approaching prey or hosts. Photoreceptors (eyes), chemoreceptors (for chemicals in the air and water), and mechanoreceptors (for vibrations or sounds) are the most characteristic. Leeches employ all three senses to detect probable prey. Photoreceptors can detect light and dark, as well as some movement, but they are unable to produce high-resolution images (Phillips *et al*., 2020). Leech is sensitive to water waves, light, touch, sound, heat and a variety of chemicals. They can bite and suck the blood through frequent contractions (Shakouri and Wollina, 2021).

A leech digests 10-15 ml of blood per feeding, which takes around 40 minutes on average (Shakouri and Wollina, 2021). Because a leech only eats blood from a suitable host on rare occasions, a single blood meal can cause a leech to consume more than ten times its own body weight (Lent *et al.*, 1988). The blood is collected in a crop with 10 pairs of diverticula to preserve it. The excess salt and water in the host's plasma are expelled (Zerbst-Boroffka and Wenning, 1986; Wenning, 1996), and the concentrated substance is retained in the crop for several months. Leeches have symbiotic bacteria (*Aeromonas* spp.) in the crop, which may help to prevent untimely spontaneous or microbial food deterioration (Graf *et al.*, 2006). Small amounts of crop material are transported to the gut and get digested at regular intervals (Roters and Zebe, 1992). The anus releases indigestible

elements (mostly heme derivatives). The leech starts secreting saliva in tandem with its jaw movements. The leech may empty the gland reservoirs over the course of the entire feeding period (Hildebrandt and Lemke, 2011).

A- Leech Salivary Active Components:

Leeches release a complex mixture of physiologically and pharmacologically active chemicals into the wound during feeding (Iqbal *et al*., 2018). According to many studies, leech saliva contains a large number of peptides and proteins, possibly over 200, as well as a variety of small organic chemical compounds. Only a limited number of these bioactive components, particularly from the genus *Hirudo*, have been described at a molecular and biochemical level. Other leech species have been shown to have similar chemicals (Hildebrandt and Lemke, 2011).

Following a bite, a leech uses its salivary secretions to open a "sucking" pathway (involving extracellular matrix destruction using hyaluronidase and collagenase); inhibit platelet adhesion, aggregation, and coagulation (anticoagulant effect) (Salzet, 2001); increase blood flow with histamine-like and acetylcholine secretions; protect itself (antimicrobial activity) and try not to be noticed (analgesic and anti-inflammatory effects) (Sig *et al*., 2017). Some of these active compounds and their actions will be discussed below.

The most famous leech salivary component, Hirudin, has shown a direct inhibitory impact on thrombin, a key component in blood clotting. Thrombin activates other clotting factors, enhances platelet activation and converts soluble fibrinogen into insoluble fibrin. In recent years, research has revealed hirudin's anticancer properties, impact on diabetic complications, potential use in pulmonary fibrosis, wound healing and a variety of other illnesses (Montinari and Minelli, 2022). Hirustasin suppresses the blood coagulation factor Xa and inactivates kinins that activate nociceptive nerve cells to cause pain sensation in tissues. Ghilantens slows the activity of factor Xa in blood coagulation and prolongs the prothrombin time of normal human plasma. Guamerin is an inhibitor of leukocyte elastase. Bdellin is an anti-inflammatory and plasmin inhibitor (Singh and Rajoria, 2020).

On the other hand, the prevention of platelet aggregation is linked to calin, saratin, apyrase, decorsin and collagenase present in leech saliva (Singh and Rajoria, 2020). Calin prevents platelets from adhering to collagen by blocking the binding of the von Willebrand factor to collagen (Munro *et al*., 1991). Saratin disrupts platelet aggregation mechanisms (Seymour *et al*., 1990). Collagenase breaks down the collagen chain that aids platelet aggregation (Salzet, 2001). Destabilase has fibrin destabilization (dissolving blood clots) and antibacterial properties. It has a glycosidase activity (Zavalova *et al*., 2000; Zavalova *et al*., 2006) and can digest glycosidic linkages in bacterial cell walls and causes bacterial cell lysis (lysozyme-like activity) (Baskova and Zavalova, 2008). Also, protease inhibitors prevent the microbial breakdown of stored blood in the crop from occurring too soon (Hildebrandt and Lemke, 2011).

Moreover, leech saliva can suppress both host immune cells and antibody-mediated immunity. Eglin C protects host tissues by acting as an anti-inflammatory agent (Hildebrandt and Lemke, 2011). It binds to human neutrophil-surface proteins (Braun and Schnebli, 1987) and inhibit the activities of neutrophil elastase and cathepsin G (Braun *et al*., 1987; Junger *et al*., 1992), which cause significant tissue damage (Snider *et al*., 1985).

At the feeding site, leech-derived tryptase inhibitors (Sommerhoff *et al*., 1994; Stubbs *et al*., 1997) help the leech decrease mast cell-mediated inflammatory reactions in the host tissues which is marked by released tryptase levels. Mast cell activity is linked to inflammatory diseases and anaphylactic reactions. C1 complement

inhibitor is also isolated from leech saliva (Hildebrandt and Lemke, 2011). C1 complement detects antigen-antibody binding and initiates complement activation in the classical pathway (Sarma and Ward, 2011).

Histamine-like substances (vasodilator) and carboxypeptidase-A inhibitors increase blood flow to the bite location and minimize local edema (Jha *et al*., 2015). Hyaluronidase, also known as the spreading factor, degrades tissue hyaluronic acid, while simultaneously acting as an antibiotic, allowing the other contents in leech saliva to infiltrate and diffuse into deep tissues. Acetylcholine improves circulation by inducing endothelium muscle relaxation and vasodilation (Abdisa, 2018). The source of these active compounds is still debatable. They may be generated in the salivary gland or may be found also in regurgitated crop material and thus might be related to symbiotic bacteria secretions or activity by-products (Hildebrandt and Lemke, 2011).

Leech Related-Research and Pharmacotherapeutics:

Piyavit, a thrombolytic and antiplatelet preparation first introduced in Russia in 1997, was made up of medicinal leech saliva extract and used to treat phlebitis (Baskova *et al*., 1997). Hirudin was the first animal-derived anticoagulant to be licensed by the Food and Drug Administration (FDA) for clinical use (Corral-Rodriguez *et al*., 2010) and it was quickly followed by the development of many promising new anticoagulants employing recombinant technology (Abdualkader *et al*., 2013).

Cloning hirudin gene made recombinant hirudin available for widespread use. Hirudin and its analogs are promising therapeutic agents that, unlike heparins, block thrombin that is already linked to blood clots and do not require the binding of cofactors like antithrombin

III. Direct thrombin inhibitors (DTIs) are revolutionary 'hirudin-derivatives' that are utilized in the prevention and treatment of deep vein thrombosis, acute coronary thrombosis, coronary events and cardioembolic stroke caused by nonvalvular atrial fibrillation. They include first-generation DTIs (indicated for parenteral use) and second-generation DTIs (indicated for oral usage). Lepirudin, desirudin, argatroban, and bivalirudin are among the first-generation DTIs. In the United States and Europe, neither lepirudin nor desirudin is now available. Argatroban, on the other hand, has recently been used successfully and safely in patients with coronavirus-induced coagulopathy and hyper-inflammation; as an anticoagulant in patients who showed heparin resistance related to SARS Cov-2 infection. Bivalirudin has also been used as an anticoagulant in patients on extracorporeal membrane oxygenation (ECMO), due to severe respiratory failure caused by SARS-Cov-2 infection, instead of heparin. Furthermore, bivalirudin therapy has produced positive results in patients with suspected-vaccine-induced thrombotic thrombocytopenia and cerebral venous sinus thrombosis that was observed with viral-vector vaccines administration; Ad26. COV2 vaccine (Johnson & Johnson) and ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca) (Hildebrandt and Lemke, 2011; Montinari and Minelli, 2022).

On the other hand, oral direct thrombin inhibitors (DOACs) are second-generation DTIs. After the successful completion of several large randomized controlled trials, they have now overtaken vitamin K antagonists for many indications.

They are all easily administered, at a fixed-dose, without the need for anticoagulation monitoring, with less intracranial bleeding risk and have become the preferred long-term treatment for atrial fibrillation and deep vein thrombosis patients. DOACs may be used for cancer-related venous thromboembolic illness. Rivaroxaban, apixaban, and edoxaban are other related factor Xa inhibitors (Montinari and Minelli, 2022).

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Also, other saliva recombinant products have demonstrated encouraging benefits in animal trials. Allergic and inflammatory illnesses like anaphylaxis, arthritis and asthma were treated with recombinant tryptase inhibitors. Destabilase was beneficial in thrombophlebitis because of its antibacterial properties and capacity to dissolve blood clots. In keloids and hypertrophic scars, fibrinases and collagenase diminished scar tissue, adhesions and fibroblast activity (Singh and Rajoria, 2020). Recombinant antistasin was used to prevent vascular graft thrombosis, lower the risk of atherosclerotic artery re-stenosis after balloon angioplasty and speed up arterial thrombosis reperfusion (Nutt *et al*., 1991). Recombinant saratin has also been utilized to prevent thrombosis and arteriosclerosis (Cruz *et al*., 2001; Vilahur *et al.*, 2004). Also, leech saliva extracts showed the potential to help protect against brain ischemia-reperfusion injury (Sig *et al*., 2017).

Cancer and Metastasis:

Interestingly, antimetastatic efficacy was observed in studies utilizing leech saliva and leech extract, reducing metastatic colonization of lung carcinoma cells in experimental mice. Also, recombinant antistasin and ghilantens have shown remarkable antimetastatic properties. Ghilanten has shown the ability to inhibit melanoma, breast, lung and prostate cancer metastasis. Another study found that synthetic hirudin was effective in preventing the spread of cancer cells from lung, breast, bladder and colon carcinomas, soft-tissue sarcoma, leukemia and lymphoma (Abdualkader *et al*., 2013; Singh and Rajoria, 2020).

B- Leeches and Parasitism:

Many outdoor recreationists and travellers today come in contact with leeches and develop leech attachments. The results of these encounters range from mild inconvenience to serious consequences (Joslin *et al*., 2017). Human leech infestation is also a disease that affects the impoverished in rural places who drink contaminated water (Tilahun, 2015). When visiting tropical nations, where leeches are highly endemic, travelers should be aware of the potential risks (Karunaratne *et al*., 2015).

Land leeches live on tropical rainforest vegetations in Australia, Southeast Asia, India, Latin America and the Pacific Islands. When a host comes into contact with contaminated plants, they attach to its skin. On the other hand, aquatic leeches can enter the human body through body orifices and are found all around the world. Human attacks by land leeches are more frequent than by aquatic leeches, but the latter is more likely to produce serious infestations (Heukelbach and Hengge, 2009). With their robust muscular jaws, land leeches can penetrate the thick skin of the extremities, whereas the aquatic leeches can only feed on delicate mucous membranes due to their weaker jaws (Karunaratne *et al*., 2015). The incision in the skin is followed by anticoagulant and anaesthetic secretions released, which dull the pain and keep the host unaware of the attack (Ghosh, 2019).

Underlying diseases including coagulation disorders or subsequent bacterial infections can swiftly worsen a patient's health from a minor to a life-threatening situation (Phillips *et al*., 2010). For instance, in Kenya, pharyngeal leech infestation led to severe anaemia and death (Asrat, 2009) and historically, thirsty soldiers of Napoleon's army in 1799 and the British army in World War I drank from leech-infested ponds while crossing Sinai in Egypt, and many died from bleeding or asphyxia when the leeches obstructed their respiratory tracts (Hyson, 2005).

Land Leech:

Land leeches live in humid habitats like rainforests (Asrat, 2009), on the surface of trees, grass and under stones in damp spots (Tilahun *et al*., 2020). They rest on vegetation, waiting for the chance to attach to a host (Joslin *et al*., 2017). Terrestrial settings are among the harshest for leeches and land leeches have evolved to produce

vast amounts of mucus. Because of their mucus layer, even aquatic leeches can endure some time out of water. There are several types of land leeches. The most well-known belong to the Haemadipsidae family, which can be found in tropical and sub-tropical areas. Movement, ground vibrations, warm moist air currents indicating a mammalian breath, shadows and other sensory cues, can all attract terrestrial blood-feeding leeches (Phillips *et al*., 2020).

Even after the leech has fallen off or has been removed, wounds from land leeches continue to bleed. People can become anaemic in situations of hyperinfestation. Leeches drop to the ground after feeding to continue their life cycle. Land leeches should be removed with caution to avoid their jaws remaining attached to the skin, which could lead to subsequent bacterial infection and ulceration (Heukelbach and Hengge, 2009). Avoiding leech-infested areas is the simplest and most efficient strategy of protection. Wearing clothes that cover the lower extremities (tucked, long socks), using body oil (since leeches cannot stick to slippery surfaces) and using insect repellents such as N, N-diethyl-meta-toluamide or N, N-diethyl phenylacetamide are all recommended. The majority of land leech attachments are external, resulting in bruising, itching, burning, swelling, discomfort, irritation, redness, and irritating contact dermatitis. A single leech detected should trigger a search for further associated leeches (Joslin *et al*., 2017).

Aquatic Leech:

The water chemistry in various settings where aquatic leeches are prevalent, such as springs, lakes, ponds, swamps, and marshes, may be prone to temperature and oxygen extremes (Phillips *et al*., 2020). *Limnatis nilotica* (the commonest in Egypt), *Myxobdella africana*, *Dinobdella ferox*, *Phytobdella catenifera* and *Theromyzon tessulatum* are all common aquatic leeches (El-Shimy,1986; Heukelbach and Hengge, 2009).

Aquatic leeches have been observed to invade human orifices, causing a condition known as mucosal, orifical, vesical, or internal hirudiniasis. Human orificial hirudiniasis is most commonly found in rural areas of Africa, Asia, and the Middle East, but cases have been reported on nearly every continent. According to a recent study, the nose is the most common site of infestation (71 %), followed by the hypopharynx (14 %) (Phillips *et al*., 2010). Hungry leeches prefer to rest along the water edge and can swim accurately toward objects that elicit waves or turbulence (Porshinsky *et al*., 2011). The majority of human infestations happen in a lack of awareness while swimming, working in water, or drinking unfiltered water, with leeches invading the mouth, throat, nasal passages, or eyelids. Aquatic leeches can bite and feed many times within the orifice over the course of weeks or months (Phillips *et al*., 2020). When bathing in contaminated waterways, suitable clothing should be worn, and drinking water should be filtered, boiled, or passed through a gauze or a cloth (Heukelbach and Hengge, 2009).

Mucosal (Orificial) Infestation Attacks:

In almost all cases, taking a history is critical to determine the diagnosis (Asrat, 2009). It may be suspected in patients with lower socioeconomic status or those who live in rural regions and have a history of drinking dirty water or bathing in stagnant ponds or puddles (Phillips *et al.*, 2010), or those dealing with infested pools or mud (Demirören and Calişkan, 2003). The main causes of morbidity after a leech bite include mechanical obstruction of a vital organ and/or significant bleeding (Saha *et al*., 2005). After leech separation, the incision can bleed for hours (typically 10 hours, but can be as long as 7 days) (Karunaratne *et al*., 2015).

Clinical presentations vary as follows:

Upper Aero-Digestive Tract and Lower Airways Hirudiniasis:

The most common presentations of a leech in the upper aero-digestive tract are unilateral nasal obstruction, mass sensation and unilateral recurrent epistaxis (Sarathi, 2011). Also, odynophagia and dysphagia are common. On the other hand, dyspnea, hemoptysis and hoarseness are typical presenting problems in case of lower airway involvement; many of these are induced by mechanical blockage as the leech grows larger with feeding (Ali and Mehta, 2017).

In critical sites, such as the laryngeal inlet or vocal cords, leech attachment may not elicit symptoms at first, but as it grows in size (Kaygusuz *et al.*, 2001; Anajar *et al.*, 2017), it can induce lethal acute airway blockage and stridor. Leech infestation of the airways can also mimic other respiratory illnesses including bronchial asthma and can be chronic. Airway reactivity and the possibility of the worm migration into the distal airways, following detachment, necessitate laryngoscopic or bronchoscopic removal of a leech from the airway. It is important to remove it as soon as possible to avoid distal obstruction. Recently, the use of a cryoprobe to recover these engorged worms from the airway appeared to be an effective solution (Oghan *et al*., 2010; Ali and Mehta, 2017, Harun, 2020).

Infestation of the oropharynx and oesophagus can cause haematemesis and blood-colored saliva (Butt *et al*., 2006) or mimic the symptoms of angioedema (Oghan *et al*., 2010). Leech can hide in the maxillary sinus, access through its ostium (Saha and Nagi, 2011), take cover in the posterior nasal cavity and hypopharynx, or keep migrating which makes extraction difficult (Demirören and Calişkan, 2003). If the leech is in the nasal cavity, visualising it is relatively simple. Endoscopic inspection under local anaesthetic is required if the parasite is trapped in the nasopharynx or maxillary antrum. Following leech removal, magnetic resonance imaging is indicated to ensure there are no more leeches, especially in the sinonasal area (Chow *et al*., 2005).

Gynecological Infestation:

The most common presenting symptom is prolonged vaginal haemorrhage. The bleeding is brilliant red and not accompanied by pain, but rather an ill-defined discomfort and a sensation of something moving inside. The amount of bleeding can range from leaking to heavy clotting (Asrat, 2009). Premenarchal and postmenopausal bleeding caused by a leech bite are of great gynaecological and medicolegal significance, as it is frequently misdiagnosed (Karunaratne *et al*., 2015) for sexual abuse (Sebazungu *et al.,* 2021), dysfunctional uterine bleeding (Asrat, 2009), and endometrial carcinoma (Saha *et al*., 2005).

In most cases, a speculum examination can reveal the worm's darkish bulk, allowing for a definitive diagnosis. The most prevalent site of leech bite is the vaginal wall, followed by the vulva, cervix, and in rare cases, the uterus. In parous women, a speculum can be used to get access to the vaginal cavity; in young girls with an intact hymen, a catheter can be introduced through the hymenal opening to irrigate the vagina with normal saline or an endoscopic extraction can be performed under anesthesia. Supportive care should be offered such as fluid or blood transfusions and antibiotics (Asrat, 2009; Karunaratne *et al*., 2015).

***Lower Gastrointestinal Hirudiniasis*:**

Leech can enter the rectum through the anal sphincter. It induces intermittent or severe painless fresh rectal bleeding that is unrelated to feces, anorectal discomfort, tenesmus, and the sensation of a moving foreign object in the rectum, mimicking symptoms of lower gastrointestinal haemorrhage. The suspected differential diagnosis includes hemorrhoids, anorectal polyps, malignant tumours, and angiodysplasia. A high degree of suspicion can guide the diagnosis in endemic areas with sufficient history (Behçet *et al*., 2011).

A precise diagnosis can be made by proctoscopy or colonoscopy to visualize the leech. Its removal using forceps is difficult due to the leech's soft and slippery body, which ruptures readily, while forceful removal can leave the jaws behind and induce more bleeding. Being aquatic, allowing the patient to sit in a water bath can stimulate its appearance at the anal orifice and facilitate its removal (Tilahun *et al*., 2020).

Urinary Hirudiniasis:

Leech entry through the urethra is uncommon. Patients report recent gross hematuria and examination can reveal a blood-tinged urethral meatus. Hypertonic saline irrigation of the bladder with Foley's catheter could be used to remove intravesical and intraurethral leeches. The hypertonic saline squeezes the water out of the leech, causing it to shrink and die, and exit with micturition. Cystoscopic removal and suprapubic cystectomy have been employed as therapeutic options for resistant cases (Mansoor *et al*., 2016).

Occular Hirudiniasis:

Conjunctiva can be infested by leeches. Red-eye, pain and a foreign body sensation in the eye are common symptoms, as are hemorrhagic signs such as bloody eye discharge, bloody tears, and blood clots in the eye corners. A moving worm may also be seen in the eye, especially when approaching water (Ito *et al*., 2022). Conjunctival congestion or a moving black foreign body can be observed with slit-lamp examination. A common consequence is a subconjunctival hemorrhage. Unwanted eye irritation should be avoided when receiving treatment. Leech can be removed with saline irrigation, 3% hypertonic saline drops, or anaesthetic eye drops. Following removal, antibiotics and corticosteroids should be administered (Lee and Chiu, 2015). In a case report, Li *et al*. (2013) mentioned a minute leech larva misdiagnosed for a conjunctival pigmented nevus, while Shirzadeh (2005) and Hosseinirad *et al*. (2017) reported suspicion of globe rupture and iris prolapse in undiagnosed ocular leech infestation cases.

External Auditory Canal Hirudiniasis:

Recent otalgia or otorrhagia (bloody discharge), with no previous ear disease, and a sensation of a motile foreign body in the ear can be indicative. Active hemorrhage, on the other hand, can reduce the field of vision, making it hard to remove the leech and can dilute the effect of applied hypertonic saline or anesthesia. Also, leeches can resist ear washing, but they can be killed by filling the ear with an oily substance (like glycerin) (Askari and Eshaghian, 2012).

Unusual Presentations:

A 2-year-old female infant with vaginal hemorrhage, abdominal distension, and indications of peritonitis and shock was diagnosed with an intraperitoneal leech. Ultrasonography of the abdomen revealed a crawling worm in the peritoneal cavity. The leech punctured the uterus and entered the peritoneal cavity after entering her vagina. A dead 10 cm leech was removed during laparotomy. The patient survived on blood transfusion and broad-spectrum antibiotics (Saha and Nagi, 2011). Another case came with swelling on the mouth floor. A surgical incision was done and a moving leech was discovered in the swelling (Kantekin *et al*., 2015).

Awareness and Management Precautions:

In areas where leech infestations are frequent, health workers should be aware of the risks of leech bites. A high index of suspicion can help early diagnosis and ensure rapid treatment (Butt *et al*., 2006). Furthermore, the importance of drinking clean water and improving access to it should be emphasized (Tilahun, 2015). According to Sebazungu *et al*. (2021), different substances have been used to remove leeches, including anesthetics such as lidocaine and anesthetic spray. If not available, other alternatives include salt, saline, vinegar, alcohol and heat.Patients may present with bleeding from different

orifices. This could indicate that leech secretions in their blood could have altered their coagulation profile (Mansoor *et al*., 2016). Eosinophilia and hypochromic microcytic anemia may also be observed in blood picture (Behçet *et al*., 2011). Complications might range from moderate bleeding to severe hypovolemic shock (Karunaratne *et al*., 2015). Anemia, pallor, tachycardia, low blood pressure and dyspnea (up to heart failure) are common in extended or massive bleeding (Tilahun *et al*., 2020) and complicate children in a shorter time (Demirören and Calişkan, 2003; Krüger *et al*, 2004). Unexplained orifical bleeding in residents of endemic areas (Iynen *et al*., 2010) and bleeding that does not react to vitamin K injection should raise suspicion of leech infestation (Sebazungu *et al*., 2021). The leech may discharge infective material into the human body in response to any type of stress. As a result, precautions must be taken during removal to avoid infection (Ali and Mehta, 2017). Pressure should be applied to the wound rather than suturing due to coagulation changes at the bite site. Also, a blood transfusion might be required (Saha *et al*., 2005).

C- Modern Applications of Leech Therapy:

The European medicinal leech species, *Hirudo medicinalis*, was preferred to other species 200 years ago (Abdualkader *et al*., 2013; Glombová and Schenková, 2015). In Egypt, *Limnatis nilotica* was used in ancient times (El-Shimy, 1986). Modern leech therapy (Hirudotherapy) seeks benefits related to blood decongestion and bioactive saliva released in the bite. *In vitro* coagulation of 50-100 ml of human blood was inhibited by a single leech secretion (Porshinsky *et al*., 2011; Bhat *et al*., 2014).

Vascular Problems and Associated Skin Ulcers:

Leech therapy is currently utilized in cases of thrombophlebitis, post-phlebitis syndrome, deep vein thrombosis, varicose veins, hemorrhoids (Goessl *et al*., 1997), peripheral circulation abnormalities and other vascular illnesses (Singh and Rajoria, 2020). Greater walking ability, reduced pain and edema, and improvement in skin color were noted. Also, chronic skin ulcers; like venous leg ulcers, resistant diabetic foot ulceration (unresponsive to anti-diabetic and anti-infective therapy) and thromboangitis obliterans (a gangrenous inflammatory illness of the arteries and veins of the limbs) were all obviously helped by leech bites. Trials revealed complete epithelization, healing and amputation salvage (Abdualkader *et al*., 2013).

Reconstructive And Microsurgery:

Under the microscope, micro-anastomosis of small blood vessels, veins and arteries can be performed, however, arterial thrombosis and venous blockage are expected and can cause tissue necrosis (Knobloch, 2010; Whitaker *et al*., 2005). In 2004, FDA approved medical leech therapy as an adjuvant to help the healing of transplant tissue and venous congestion cases (Abdualkader *et al*., 2013; Koeppen *et al*., 2020). In published trials, congested skin flaps and replants of avulsed digits, ears and noses, that were at risk of loss due to venous congestion, were salvaged at high rates of 65% to 80% vascularization (Jeng *et al*., 1994; Whitaker *et al*., 2012). Reconstructive procedures after tumor removal also showed better cosmetic effects (Michalsen *et al*., 2007).

Arthritis and Pain Management:

Researchers from the Essen-Mitte Clinic in Germany found that leech therapy helped those with knee osteoarthritis by reducing inflammation and pain (Iqbal *et al*., 2018). Leech therapy was found to reduce pain, enhance walking distance, reduce joint stiffness over time and improve daily activities in elderly people who were not responding to traditional medications (Singh, 2010). It is also reported to help treat pain and inflammation in other conditions such as rheumatoid arthritis, fibromyalgia and myasthenia gravis, as well as gout, tendonitis and abscesses (Singh and Rajoria, 2020). In advanced kidney cancer

cases, a two-month treatment entirely healed lumbar discomfort, according to a published trial (Kalender *et al*., 2010).

Other Applications:

Tinnitus, acute and chronic otitis, periorbital hematomas, glaucoma (Singh and Rajoria, 2020), salivary glands diseases (Singh, 2010), alopecia areata (Bhat *et al*., 2014), ovarian cysts (Mory *et al*., 2000) and polycystic ovary syndrome (Bahman and Tansaz, 2019) are among the medical conditions for which leech therapy studies are being conducted.

Limitations And Complications:

Hemorrhagic tendencies, allergies, chronic liver and kidney diseases, immunosuppressive conditions, chemotherapy, radiotherapy, keloid scarring and pregnancy are all contraindications to leech therapy (Stange *et al*., 2012). The most common complication is infection with symbiotic *Aeromonas hydrophila* (Iqbal *et al*., 2018). Johns Hopkins and Georges Pompidou European hospitals reported that about 11% of patients had post-therapy infections. Researchers recommended using sulfamethoxazole/trimethoprim and ciprofloxacin prophylactically (Pourrahimi, *et al*., 2020). Repeated use of the same leech may result in the regurgitation of germs from prior meals, such as HIV, hepatitis C, Dengue fever, and Methicillin-resistant *Staphylococcus aureus* (MRSA). Leeches must be bred in certified bio farms, kept in a sterile environment, used once and then discarded as biological waste (Wilmer *et al*., 2013). Psychological refusal of susceptible patients is encountered (Singh and Rajoria, 2020).

Leeches and Other Parasites:

There are reports of resistant cutaneous leishmaniasis, with ulcers on the hand and face that improved with leech therapy. It healed entirely in 4 to 6 months with no relapse (Koeppen *et al*., 2020). Nevertheless, leeches have been described as potential vectors for parasitic diseases such as toxoplasmosis, *Trypanosoma* spp., and *Plasmodium* spp., although the risk of transmission to man has yet to be determined. *Plasmodium berghei* was discovered to live and proliferate in stored red blood cells in the gut of leeches (Heukelbach and Hengge, 2009; Joslin *et al*., 2017).

CONCLUSION

Leeches can be considered a wandering threat on land and in waters; they can inflict real harm and endanger human health and lives. However, this lethal enemy can salvage lives, as revealed by the gift of hirudin and its recombinant analogs. In old times, this was believed too and the only available method of delivery at that time was Hirudotherapy. This leech-hidden treasury of substrates may hold answers to treating cancer, diabetes and many other ailments. It is now up to modern technology and scientific research to tailor elimination and protection strategies in inhabited endemic areas and to develop suitable safe delivery formulas of recombinant leech-derived active compounds that can be easily administered to patients.

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