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An Overview on Medicinal Leech Therapy

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Abstract: In the traditional treatment of pain and inflammatory illnesses, *Hirudo medicinalis* (Medicinal leeches) are used therapeutically. Leeches are connected to the afflicted areas and start sucking blood after a first, painless bite. Instead of the blood extracted during biting, the majority of these therapeutic benefits originate from the numerous bioactive substances found in saliva, such as hyaluronidase, hirudin, calin, destabilase, apyrase, eglin, and many others. Treatments focus on reducing regional pain syndromes, primarily for osteoarthritis of the knee or other joint conditions. The use of this technology extends to plastic surgery, where it is used to maintain blood flow in clogged skin flaps, reconstructive procedures, cardiovascular complications, varicose veins, haemorrhoids, gastrointestinal disorders, dermatology, gynaecological abnormalities, and traumatic conditions like the reattachment of severed extremities, finger, toe, and ear. Recently, new applications in the treatment of diabetes, asthma and cancer have been found. Due to the increasing therapeutic potential of HT, researchers are striving to find and synthesize several new salivary compounds.

Key words: Hirudotherapy, Leech, Blood-thinning, Skin flap, Arthritis.

1. Introduction

Blood-sucking leeches are used in a complementary and integrative therapy called medicinal leech therapy (MLT), often referred to as hirudo therapy. Once the leeches have begun feeding, the goal is to attach one or more leeches to the skin of the troublesome location in order to store potential benefits from the saliva produced by the leeches [1].

MLT has been around for a while, and the word “leech” comes from the word “laece” (physician). In the year 1984, the first applications were recorded. Since the early 1900s, there has been a lot of focus on the number of medical professionals has increased over the previous 30 years, notwithstanding a recent decline. In recent years, MLT has grown to be an important component of many scientific studies 2. In freshwater, leeches are segmented, hermaphrodite, predatory worms. They are divided into many divisions, including “Brain parts”, each of which has a unique organ, such as the testicles and ganglions needed for crawling, and two sucker portions. The three jaws on the anterior one, one of which is packed with teeth, are used to bite the warmest parts of the host. by performing frequent contractions, sucking in blood. Feeding occurs typically. A leech takes about 40 minutes to digest 10 to 15 mL of blood. Many enzymes are involved in digesting during each feeding. Aeromonas hydrophila and other creatures that they both share Pseudomonas hirudinean is one of the species. Numerous investigations have shown that a variety of biochemicals are secreted by leeches. Additionally, while some of their tactics have been discovered, others have not. It is true that these substances have analgesic effects, anticoagulant, anti-inflammatory, platelet inhibitory, and thrombin regulating functions, as well as extracellular antibacterial and matrix degrading effects [2].

1.1 Mechanism of Leech Therapy

Numerous scientific investigations have examined leech impact processes up to this date. Among the more than 100 distinct proteins with various molecular weights detected in leech secretions, only a small portion have been determined to have therapeutic

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promise. To make them simpler to comprehend, the effect mechanisms are divided into six groups, but they are interrelated and should be treated as such. Following a leech bite, an extracellular matrix-based sucking mechanism must form. Adhesion, aggregation, and coagulation are all inhibited. There is a rise in blood flow, antimicrobial activity, analgesic and anti-inflammatory effects, platelet function inhibition, and anticoagulant activity. Many scientific studies have been conducted to date to clarify the impact [3].

1.2 Extracellular Matrix Degradation

Leeches release hyaluronidase (27.5 kDa) and collagenase (100 kDa) enzymes soon after biting to aid tissue penetration and dissemination of their bioactive compounds. Antimicrobial action is also supported by these enzymes.

1.3 Application of Leech Therapy

Traditional therapists used leeching as an unproven home treatment and as a common therapeutic technique throughout history for a variety of diseases as follow.

Analgesic and anti-inflammatory effects.

In order to avoid being discovered by the host while feeding, leeches are said to possess analgesic and anti-inflammatory effects. Despite this, no such analgesic molecule has up till now been identified from leech secretions. Research has therefore focused on indirect impacts. a group of methods for reaching this goal According to certain research, kininases and antistasins may play a part in the development of cancer. Block the major kinin-kallikrein channel of nociceptive signals, the kinin-kallikrein mechanism [4].

Eglin C inhibits both cathepsin G and human neutrophil elastase. These two enzymes are immunological serine proteases of the chymotrypsin family and are present in the azurophil granules of polymorphonuclear neutrophils. It is created and secreted as a result of the inflammatory response [5, 6]. The body produces fewer free radicals when Eglin C is suppressed. Oxygen radicals are lessened in neutrophils, which lessens tissue inflammation and damage. In test models, Eglin C was proven to be productive. Emphysema therapy has shown to be effective in treating shock and anxiety [7].

Similar anti-inflammatory activities can be found in other isolated eglins [8]. Another leukocyte elastase inhibitor comes from the Philippines and is called Guameri. It is a cysteine-rich protein (Korean medicinal leech). Component that complements C1 is a crucial part of the conventional route of the complement system, and it comes from the same poisonous leech as pegamine. The mechanism of action of the 60–70 kDa protein, known as complement C1 inhibitor, is present in leech secretions. The protein pool may have only one element that stops the enzyme from functioning. Additionally, factor Xia, factor Xian, and plasma factor Xia are all inhibited by the original C1 Inhibitor in humans. This substance inhibits the coagulation cascade and the kinin-kallikrein system. There is currently no proof that a leech C1 inhibitor has comparable effects, but it is feasible and deserves more research. Forbidding Leech secretion carboxypeptidases should have no effect. B1 (inducible) receptors should be avoided since bradykinin acts through B2 (constitutive) receptors. Despite the fact that these two receptors share a lot of the same activities, the study found that B1 receptors are associated with chronic inflammation whereas B2 receptors are associated with acute inflammation. It has been found that B1 and B2 are strongly related. Inflammatory illnesses include rheumatoid arthritis, asthma, and multiple sclerosis. Investigations, however, have revealed that bradykinin’s effects are not limited to these. As a result, inhibiting carboxypeptidase might have anti-inflammatory properties [9].

1.4 Blood Flow Regulation

Boosted blood flow is necessary for both the therapeutic effects and leech feeding. Chemicals that resemble histamine, which promote vasodilation and come from local vascular permeability, are the main causes for this. Acetylcholine is also present in a variety of foods [10].

1.5 Inhibition of Platelet Functions

The leech dies as a result of the platelet activation and coagulation cascade that occurs when the blood vessel wall is disrupted for blood sucking. Leech secretions include a variety of bioactive compounds as a result, preventing harmful effects locally. When platelets act as a bridge, this molecule has a very high affinity for glycoprotein (GP). As platelets bind to one another via Glib-IIIa and fibrinogen, this interaction causes the activation of up-regulating mechanisms, especially when Adenosine diphosphate (ADP) is involved. Insert a plug to stop any bleeding [11].

Sartain, a 12-kDa protein, competes with collagen to prevent the collagen-vWF interaction but only impacts the initial stage of platelet attachment. The recombinant Sartain molecule has showed promise as a therapy option in several animal studies. A local therapeutic agent is necessary for antithrombotic treatments, and atherosclerosis. Calin and other proteins produced by leeches anti-platelet proteins produced by leeches have a similar effect on platelet adhesion. Decorsin, on the other hand, is isolated from the rest of the body. *Macrobdella decora*, an American therapeutic leech, has a distinctive structural design [12].

Since it stimulates GPIIb-IIIa receptors and raises platelet affinity for vWF, ADP is essential for platelet aggregation. ADP is converted into adenosine monophosphate, which is then blocked, by indirectly blocking certain receptor pathways. Arachidonic acid and ADP have a close relationship. Apyrase indirectly fights against both epinephrine and platelet-activating factor by inhibiting their functions. By lowering thromboxane, it reduces platelet-activating factor and thrombin-induced platelet aggregation. The production of platelets, an enzyme called collagenase can decompose. In addition to accelerating the actions of the inhibitory enzyme, collagenase is an enzyme that breaks down the collagen molecules responsible for all of these adhesion and aggregation processes [13].

1.6 Anticoagulant Effect

Leeches coagulate to death as they eat, hence anticoagulant properties are required. Bioactive chemicals found in leech secretions cause a series of events known as the coagulation cascade that result in diverse outcomes at various places. Hirudin and gelatin are the major components [14]. A 7.1-kDa protein called hirudin binds to thrombin in an irreversible manner, which results in the consumption of active thrombin and the production of antithrombin activity. The most fascinating substance, this has been the subject of many investigations. There is general consensus that it is a good treatment choice. Heparin has a higher anticoagulant effect than heparin, making it superior [15]. A factor Xa inhibitor functions as a direct anticoagulant and stops the coagulation cascade. It performs a crucial role in rheumatoid arthritis and osteoarthritis MLT. In addition, as previously mentioned, Antistasin directly inhibits factor Xa. Giantess, LDTI, C1 inhibitor, and eglins may all have anticoagulant effects; these effects may be caused by direct or indirect inhibition. A collection of proteins called coagulation factors aids in blood clotting. Destabilase is an enzyme that activates glycosidase. It possesses fibrinolytic and antibacterial effects. This enzyme comes in a number of isoforms, each with its own unique set of properties, and is derived from numerous leech species [16].

1.7 Process of Hirudrotherapy

The first bite of a leech is painless, and then the leech attaches for 20 to 45 minutes, drawing between 5 and 15 ml of blood. The blood that is drawn when it

is bitten does not supply the majority of its medical properties. Leech saliva contains vasodilators and anticoagulants that initially offer a lot of relief. Due to these qualities, the incision can leak up to 50 mL of blood for up to 48 hours. Bites from leeches often bleed for six hours on average [17]. Before administering sterile distilled water to the targeted area, clean the area to be exposed to leeches. The skin can occasionally be pierced with a sterile needle to prompt the leeches to feed by spitting blood, but they typically begin eating immediately away. The leech is injected into a specified region of the skin using a 5 ml syringe. The barrel of the syringe is used to implant the leech. The area to be treated is placed on the open proximal end of the syringe. The syringe is introduced when the leech starts to eat. A typical feeding session lasts 45 to 120 minutes, and the leech is observed throughout. Throughout the course of treatment, it is important to routinely check for different clinical signs, infections, and allergic reactions. Long after the leech has been removed, blood still seeps from its attachment point. The bite region is cleaned every 3 to 4 hours using a gauze sponge soaked in physiological saline and a heparin-soaked gauze (5,000 U/ml) to promote blood flow and remove any locally generated clots. Time for some oozing blood. Used leeches are never reapplied, not even to the same patient. The disconnected leech gets killed in this instance [18].

1.8 Venous Congestion

By reducing the pain and swelling that varicose veins cause as well as eliminating blood clots, it has been shown to benefit persons with venous disorders. Beneficial enzymes found in leech saliva protect the body from disease and stop blood clotting. These two characteristics work together to thin the blood, facilitating easier vein flow. Another enzyme is also involved in this process, acting as a vasodilator to improve blood flow. Moreover, the antimicrobial qualities of leech saliva can aid those who have open sores brought on by venous illness [19, 20].

1.9 Skin Flap

They are applied during the skin flap transplantation process. As soon as the leeches are attached to the skin flap site, they start sucking blood. They release hirudin, which is necessary for inhibiting platelet aggregation and the coagulation cascade. If these two problems persist, there will be considerable venous congestion beneath the skin flap, which will impede the healing of the skin graft. The skin flaps turn cyanotic and congested when the venous outflow is insufficient. A Xa inhibitor discovered in the leech's saliva blocks these pathways since hirudin and the Factor are present [21].

1.10 Arthritis

Leech saliva is beneficial in the treatment of arthritis because it includes a variety of substances and chemicals that lessen joint inflammation. The anti-inflammatory compounds bedellins and eglins are among them. Moreover, it has an analgesic chemical in its saliva that reduces joint pain. Furthermore, a histamine-like vasodilator molecule is present. Another component of the brain is acetylcholine [22]. As a vasodilator, leech saliva also functions. Because artery dilation also causes joint dilation, this is crucial for the treatment of arthritis, improves blood flow, which removes toxins from the area and lessens swelling, pain, and discomfort [23].

1.11 Leeches in Cancer

A patient with basal cell carcinoma underwent leech therapy for nine months after surgery, with good results in achieving blood flow across the flap. Masaki I et al. reported utilizing medical leeches in a patient with intraoral malignancy to ease venous blockage of a free forearm flap during reconstruction [24]. Saliva from the Mexican leech *Haementeria officinalis*

possesses antimetastatic qualities. Lung cancer is prevented from colonizing by the protein antistasin, which is present in its saliva. The secretions contain antiproteolytic enzymes, anticoagulants, and platelet aggregation inhibitors. *H. manillensis*, a distinct tropical leech, has demonstrated an antiproliferative impact in vitro when used to treat small cell lung cancer [25, 26].

1.12 Safety and Complication of Leeching

Infection is the most frequent adverse consequence of leeching, affecting 2 to 36% of patients [27]. The causative agent is the Gram-positive rod *Aeromonas hydrophila*, which can result in septicemia, pneumonia, flap failure, mascular necrosis, and pneumonia. *Aeromonas* spp., *Pseudomonas* spp., and *Vibrio* spp. are all involved in these illnesses. As *A. hydrophila* is resistant to penicillins and the first generation of cephalosporins, aminoglycosides and fluoroquinolones should be used in the treatment of such infections [28-30]. Several studies have described local hypersensitivity issues, such as itching, blister development, ulcerative necrosis, and even local tissue loss, which may be caused by the presence of specific toxins in leech saliva [31]. Blood loss from prolonged hemorrhaging and skin scarring brought on by insufficient leech bite healing are two post-leeching effects [32, 33].

1.13 Remarks

A fascinating illustration of how medical study has tried to cure the clinical symptoms over time is the history of leeching. The Food and Drug Administration authorized the therapeutic leech as a medical device in 2004. It has been used for more than 3500 years, and it is currently the subject of fascinating biological and pharmacological research. More than 100 proteins and peptides have been found in leech saliva, although only 15% of them have been identified. All of these proteins and peptides are linked to therapeutic effects [34, 35]. The varied therapeutic effects of these compounds are due to their anti-inflammatory, anaesthetic, antiplatelet, and thrombin regulating actions, as well as their bacteriostatic and extracellular matrix degradative actions [36, 37].

2. Conclusions

Herbal medicines have been utilized to treat people since the dawn of time. Non-operative tissue salvaging with medicinal leeches — an FDA-approved treatment for the control of venous congestion in graft tissue — should be taken into account in patients having plastic surgery. Leech “bloodletting” has been a long-standing tradition, and more recently, it has found a unique application in the treatment of thrombosis, several venous diseases, arthritis, glaucoma, and myasthenia gravis. Further research is necessary in order to precisely and lately assess the dangers and advantages of employing therapeutic leeches in cases of venous congestion.

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