

## A REVIEW ON THE THERAPEUTIC APPLICATIONS OF LEECH

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### ABSTRACT

Leeches have been used since the beginning of civilization starting from the Ancient Egyptian, Indian, Greek and Arab physicians to modern era for various therapeutic purposes. They consist of biologically active compounds in their secretions, especially in their saliva and are hematophagous animals. As a result of recent researches which had revealed the presence of variety of bioactive peptides and proteins in leech saliva, it has become a new remedy for many chronic and life-threatening abnormalities, such as cardiovascular problems, cancer, metastasis, and infectious diseases. In the 20<sup>th</sup> century, leech therapy has established itself in plastic and microsurgery as a protective tool against venous congestion and served to salvage the replanted digits and flaps. Despite the efficacious properties of leech therapy, complications of leeching are still controversial.

**Keywords:** Hematophagous, Therapeutic purposes, Bioactive peptides, Microsurgery.

### INTRODUCTION

Hematophagous animals that feed on blood have been known to overcome blood clotting by secreting in their salivary gland secretion a multitude of biologically active compounds, especially the anticoagulants [1]. Amongst the blood-sucking organisms, leech is a distinct example of an invertebrate, which possesses a highly-developed mechanism by which they prevents blood clotting [2]. For various therapeutic purposes, the European medicinal leech species, *Hirudo medicinalis*, also known as the healing leech was preferred by the majority of physicians compared to the American species, *Hirudo decora*, which can suck less blood due to a smaller and superficial inci-

sion on its prey skin [3,4,5].

#### Leech locality and ecology:

Leeches can live in a variety of environments, including aquatic and moist terrestrial regions. Some species live in freshwater, estuaries, rivers, ponds, lakes, and sea. Because moisture is a very essential factor affecting the terrestrial leech's distribution and behavior, they can be found in a large number in the forests and highlands of North America, Europe, and South-East Asia.

#### Leech taxonomy and morphology:

Leeches (*Euhirudinea*) were first named by Linnaeus in 1758 AD [3]. The medicinal leech (*Hiruda medicinalis*) is a segmented annelid belonging to Phylum: *Annelida*,

Class: *Clitellata* and Subclass: *Hirudinea*. In general, early studies classified leeches into 4 subclasses, 3 orders, 10 families, 16 sub-families, 131 genera and more than 696 species [7]. Recently, taxonomists identified more than 1000 leech species [8]. Leech size varies among families and can reach up to 20 cm in length, in addition to some giant species, such as the Amazonian leech, *Hementaria ghilianii*, which is about 50 cm in length [9]. A classic leech body consists of many segments divided as two preoral, nonmetameric segments, and 32 postoral metameres (somites). Somites are subdivided into 2-16 external annuli, and the annulation pattern can be considered as a diagnostic feature for leech genus and species. Sensory structures, such as eyes, oculiform spots, papillae and sensilla are also used by taxonomists to identify genus, and species.

#### **The biology of leech feeding:**

Based on feeding habits, leeches are divided into two major groups. They are predacious and sanguivorous leeches and both digest their food in their intestine. With the help of suckers and the biting jaws, leeches are able to absorb prey blood [10]. It is interesting to note that leeches generally suck 2-20 ml of blood within 10-30 min, then drop-off spontaneously after being completely engorged with no immediate desire of more feeding and store the ingested blood for up to 18 months [11,12].

Symbiotic bacteria named *Aeromonas* species, located in the leech's gut, secrete enzymes that help not only in breaking down the components of the ingested blood, but also in producing antibiotics to prevent blood putrefaction after a long storage period in leech crop. Furthermore, another presumed role of these enzymes is to prevent B

complex deficiency, which often occurs in blood nutrition-depending animals [6,7].

#### **HISTORICAL REVIEW OF LEECHING**

Before the Christian era (BC), medicinal leeching was mentioned in the 18<sup>th</sup> dynasty Pharaohs paintings (1500 BC). Talmud, Bible, and other Jewish manuscripts outlined the medical indications of leeching [13]. Later, in the middle ages, medics depended more on leech therapy, which was prescribed for a wide range of disorders including nervous system diseases, urinary, and reproductive organs diseases, inflammatory diseases and eye illnesses [3,14].

By the end of 19<sup>th</sup> century, leeching gradually fell into disrepute, and almost stopped by the early twentieth because hirudo therapy did not match the new requirements of the modern medical regulations and the great advancement in all medical fields [3]. In 1981, a foundation for leech breeding development and medicinal leech research was established by an American biologist, Roy T. Sawyer [3]. After the recession period of leech therapy, it has resurged after the mid-20th century with new applications in many medical fields including surgical and reconstitution procedures, vascular diseases, arthritis, migraine [14,15]. In 2004, the Food and Drug Organization (FDA) approved leeches for medicinal purposes [14].

#### **MODERN APPLICATIONS OF LEECHING**

##### **Cardiovascular diseases:**

Leech therapy has established itself as an alternative remedy for the treatment of vascular disorders, since leech saliva can temporarily improve blood flow and ameliorate connective tissue hyperalgesia[12]. Clinical studies revealed that it can reduce blood hypercoagulability with an antiinflammatory

effect in patients with thrombophlebitis [20]. The effectiveness of leech saliva in CVDs is the results of specific thrombin inhibitors, hirudin, which was first isolated from *H. medicinalis* [16,17,18] and was shown to possess a potent inhibitory effect on both free and clot-bound thrombin [21,22]. Noteworthy, hirudin is the only hemato-phagous animal-derived anticoagulant which has been approved by FDA for clinical purposes [19]. Many studies revealed that hirudin is more effective than heparin in preventing deep venous thrombosis (DVT) and ischemic events in patients with unstable angina[19]. Hirudin can be used safely in patients with platelet abnormalities or heparin-induced thrombocytopenia because it has no immune effects on erythrocytes [22]. For example, two analogs, lepirudin, and desirudin have been approved by FDA and are currently in use under the trade names, Refludan<sup>®</sup> and Iprivask<sup>®</sup>, respectively [19].

#### **Reconstructive and microsurgery:**

Microsurgery is a type of surgical operations carried out using the microinstruments under the microscope aiming to anastomose small blood vessels, veins and arteries during the replantation of tissues or amputated digits[13]. Venous occlusion is a serious threat in newly transplanted tissues and may lead to thrombus formation, stasis, and eventually tissue necrosis. 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 [24]. On the other hand, surgeons who practice plastic operations considered leeching as a promising remedy, since the Y-shaped wounds caused by leech bites usually heal without scars or complications [12].

Leeches were also used to decongest completely amputated ears [28], to improve blood flow after microsurgery of a severely avulsed scalp [26], to prevent flap collapse [27] and replantation of amputated facial tissues[29], finger tips[30] and penile replantation[31].

#### **Cancer and metastasis:**

A review was carried out based on some studies, which were oriented towards using leech salivary extract as antimetastatic agents rather than using it for treating the tumor itself. It was reported that the metastatic inhibitory activity of leech was due to some anticoagulants such as warfarin and heparin [32]. Later, an antimetastatic and anticoagulant protein named ghilanten was purified from the salivary gland secretion of *H. ghilianii* [33]. It was reported that ghilanten could suppress metastasis of melanoma, breast cancer, lung cancer, and prostate cancer [34]. Another research described a synthetic hirudin preparation as an efficacious metastasis inhibitor of a wide range of malignant tumor cells, such as pulmonary carcinoma, breast carcinoma, bladder carcinoma, colorectal carcinoma, soft-tissue sarcoma, leukemia, and lymphoma [32].

The Mexican leech *Haementeria officinalis* was observed to have antimetastatic activity because its salivary gland secretion contains a 17-kDa protein, called antistasin, having the capability to prevent lung cancer colonization. In 2010, scientists delineated that a 2 month treatment by topical application of *H. medicinalis* can completely cure the local lumbar pain in patients with advanced stages of renal cancer and leiomyosarcoma [35].

#### **Diabetes mellitus and its complications:**

There are no documented scientific reports on leech therapy as an antihyperglycemic medication up to now. On the other hand,

leech application has been used traditionally for the treatment of DM complications [37]. One of the most severe complications of DM is the cardiovascular ones. The peripheral vascular complications in diabetic patients can lead to less blood flow to the distal parts of the body resulting in ischemic diseases like gangrene. The wild leech species *Whitmania pigra* (Family: *Hirudinidae*) has been used by the traditional Chinese therapists to augment blood flow to the distal parts of the body and to alleviate coagulation disorders.

Diabetic patients are at a high-risk of myocardial infarction, which is the main death-causing reason in type 2 DM [36]. First of all, hirudin plays an essential role in preventing clotting process because of its ability to bind thrombin and consequently suppress thrombin-mediated conversion of fibrinogen into fibrin enabling it to be efficacious for the relieving of ischemic events [19]. Calin, isolated from *H. medicinalis*, has been proven to obstruct the formation of thrombi as described above [23]. By the year 2002, an official center for leech therapy was opened, which has been during a short period of time an international center for DM treatment by leeches [37].

#### **Infectious diseases:**

The continuously increasing rates of infectious diseases led to a higher usage of the commercially available antibiotics, which resulted in a new challenging phenomenon known as resistance to antimicrobial agents. For instance, some reported that leech therapy was used by traditional dentists as a remedy for dental infections such as periodontitis and alveolar abscesses [15]. A protein named destabilize with a lysozyme-like activity had been isolated from the medicinal leech extract. It was reported that this pro-

tein had an antibacterial activity against some bacterial strains because it can destroy their cellular components [38,39].

Moreover, it was reported that the nervous system of the European leech, *H. medicinalis*, could initiate an antimicrobial response after injury by signaling the synthesis of Antimicrobial proteins (AMPs) [40]. Three different peptides with antibacterial activities were identified. Hm-lumbricin and neuro-macin were isolated from neurons and microglial cells while peptide B was found in leech body fluids [41]. Recently, it was reported that leech species of the family *Hirudinidae* had a high antibacterial activity against *Shewanella* and *Aerococcus viridans* while a lower activity was observed against *Escherichia coli*, *Salmonella typhi* and *Staphylococcus aureus*.

#### **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 effects [42]. Likewise, some studies proved that hirudin can reduce synovial inflammation in arthritis patients by inhibiting DING protein, a derivative of synovial stimulatory protein acting as autoantigen in rheumatoid arthritis patients [43].

Another clinical trial on patients with advanced osteoarthritis at the knee proved that leech therapy could effectively reduce the need for analgesic intake. It has been outlined that a double treatment regimen at a 4-week interval exhibited a longer term relieving and a better physical activity than a single treatment course [44]. Other reports indicated leech therapy as an analgesic for iliosacral joints pain and cervicobrachialgia syndrome [12].

## OTHER APPLICATIONS OF LEECHING

### Dentistry:

Although, the benefits of leeching in dentistry have not been established yet, many reports mentioned leech application in dental abnormalities [15]. 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 [45]. Other case reports described the use of the medicinal leech in the treatment of sublingual hematoma and massive lingual hematoma [46,47].

### Audiology and ear abnormalities:

It was reported that leeches and their salivary secretion were successfully used for the treatment of tinnitus, acute and chronic otitis [48]. Leeching has been applied in sudden hearing loss. Despite the unexplained reasons of tinnitus, leeches were proven to be of great benefits in the treatment of this disorder [12].

### 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 [12].

### Complications of leeching

Infection is the most common complication of leeching and occurs in 2-36% of the patients [25]. Many reports outlined local hypersensitivity conditions including itching, blister forming, ulcerative necrosis and even local tissue damage (flap death), which might result from the existence of some toxins in leech saliva [15]. Blood loss because of the prolonged hemorrhage and skin marks (scars) left by impaired healing of leech bi-

tes are also reported as post leeching complications [25].

## CONCLUSION

To conclude, leeching was a popular therapeutic practice throughout the ages for a wide range of diseases and it was applied as an unscientific home remedy by traditional therapists. Nowadays, leech came back to the contemporary medicine with fewer applications, which were proven and supported by a huge number of scientific studies and case reports. Leech therapy in the field of plastic and reconstructive surgery is expected to be of paramount importance due to the ease of leech application and reduced side-effects. Hence, more efforts should be undertaken to optimize this utilization. More investigations are required to assess leech efficacy and safety in the treatment of DM and cancer.

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