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Perspective

## Exploiting leech saliva to treat osteoarthritis: A provocative perspective



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### ABSTRACT

Plant and animal-derived products are crucial components in complementary and alternative medicine. Although modern medicine has provided numerous innovations and advancements, these often fail to reveal new and dependable, inexpensive treatments nor real cures that are relatively free of adverse side effects. We present evidence that hirudotherapy, which utilizes leeches, improves certain diseases, including osteoarthritis. Osteoarthritis, a disease in joints, could benefit from use of medicinal peptides found in leech saliva, components of its immune system.

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### 1. Functional anatomy of the leech

Complementary and alternative medicine (CAM) is an increasingly popular field of medicine characterized by its beneficial holistic approach. CAM is internationally implemented in Traditional Chinese Medicine in China, Ayurveda in India, Kampo in Japan, and elsewhere. Often the effective treatments are derivatives of the immune systems of many plants and animals.<sup>1,2</sup> Leeches are hematophagous annelids previously used for various medicinal purposes prior to developing advanced medical technologies.<sup>1</sup> Leech therapy was discovered as early as 1500 BCE, in an Egyptian painting.<sup>2</sup> There are various species of leeches including those from Taiwan: Taiwanese *Haemadipsa rjukjuana*, *Haemadipsa picta*, and *Tritetrabdella taiwana*<sup>3</sup>; however, the most common leech species is the European, *Hirudo medicinalis*.<sup>2</sup> Preferred by professionals, it has a deep bite and capacity for extended extravasation.<sup>2</sup> This freshwater leech is characterized by its 102 annuli (segments) and its ability to grow to 12 cm, which is three times its normal length.<sup>2</sup> *H. medicinalis* has a large posterior sucker used for movement and a smaller anterior sucker that assists feeding.<sup>2</sup>

Contributing to its medicinal functions, the leech's three jaws allow it to cling to humans and inflict a bite.<sup>2</sup> Leeches were well known only for bloodletting in the past. For treating numerous other ailments, however, modern usage of leeches has expanded targeting cardiovascular diseases, reconstructive surgery, diabetes, infectious diseases, arthritis, skin disorders, osteoarthritis, ear abnormalities, and even dentistry.<sup>1</sup> In these instances of intervention, leech therapy involves multiple approaches. First, leeches assist in removing excess host fluids, which ultimately benefits host homeostasis.<sup>4</sup> Second, and perhaps more importantly, leech bites allow its immunological medicinal enzymes from its own saliva to penetrate the host.<sup>4</sup> These enzymes are often anti-inflammatory and anticoagulant, crucial in producing various therapeutic effects in humans.<sup>4</sup>

The immune system of leeches and other invertebrates is crucial when its products are used in medicine. Leeches are annelids grouped with earthworms, known as lophotrochozoans, that possess an innate immune system.<sup>5–7</sup> The innate humoral immune system equips leeches with pattern recognition receptors and proteolytic cascades, as well as with multiple cells and peptides that protect from infectious microbes.<sup>7</sup> Antimicrobial peptides are crucial components of humoral responses that mediate inflammation and initiate other immune cascades and processes.<sup>8</sup> Leeches also possess innate cellular immunity, which strengthens their immune system against pathogens.<sup>7</sup> From an evolutionary perspective, leeches developed many bioactive substances that facilitate penetration into host surfaces without detection.<sup>9</sup> To

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increase efficiency of feeding, leeches have also evolved bioactive saliva that decreases the host's normal humoral and cellular immune responses, including inflammation, pain and swelling.<sup>9</sup>

## 2. Knee osteoarthritis

In 2012, a National Health Interview Survey reported that over 51 million people consider themselves as victims of arthritis, a debilitating condition that occurs when any joint in the body becomes inflamed or irritated.<sup>5</sup> The knee is a frequent anatomical site for arthritis that causes loss of many functions. Osteoarthritis, a common form of arthritis, is classified as a, “wear-and-tear” disease. In most cases, osteoarthritic knees develop over time, affecting individuals past 50 years of age. Pain caused by knee osteoarthritis results from a loss of cartilage in the knee joint. In a healthy knee, articular cartilage protects the three major knee bones: femur, tibia, and patella. This cartilage, or meniscus, is wedged between the bones and acts as a cushion and shock-absorber facilitating knee movement. The gradual loss of this so-called meniscus causes the space between the two bones to decrease and often results in bone rubbing and an anomaly, called bone spurs. The knee joint then becomes swollen and inflamed resulting in decreased motion. Many individuals with knee osteoarthritis experience difficulty moving their knees or experience knee locking, cracking, or buckling.<sup>5</sup>

There are currently no cures for knee osteoarthritis; however, there are many treatments available to manage pain, including both nonsurgical and surgical procedures. A common nonsurgical treatment involves medications such as those that are non-prescribed; e.g. acetaminophen, ibuprofen, and naproxen.<sup>5</sup> Others often require a prescription or an injection, such as corticosteroids, disease-modifying anti-rheumatic drugs, viscosupplementation, and glucosamine and chondroitin dietary supplements. After unsuccessful nonsurgical treatments, patients frequently undergo surgical remedies, including arthroscopy, cartilage grafting, synovectomy, osteotomy, or even a knee replacement.<sup>5</sup> Although these treatments may provide temporary benefits for relieving pain and progression of arthritis, several are not successful or can cause adverse side effects. Many over-the-counter pain relievers exert adverse side effects, e.g. nausea, dizziness, mood changes, or negative drug interactions. This treatment can also be unsuccessful since patients may eventually develop drug resistance.<sup>10</sup> Cortisone injections are unsuccessful due to transient improvement.<sup>5</sup>

## 3. Hirudotherapy for knee osteoarthritis

The numerous components of leech saliva that enter the host after a bite may improve osteoarthritic conditions in the knee. Incorporating leech therapy into the treatment of arthritis could provide successful relief from pain, while also minimizing any negative side effects of many, carefully selected, western treatments. Various clinical studies suggest that leech therapy is beneficial to osteoarthritic conditions (Table 1). Whether these clinical findings result from secreted leech peptides or from a placebo effect, at least the positive effect that leech therapy exerts on knee osteoarthritis has been interpreted as statistically significant. This argues in support of leech therapy as a possible successful alternative for treating knee osteoarthritis, yet repetitive treatments must be employed to confirm the significance.

The major effects of leech therapy on knee osteoarthritis result not from amounts of ingested blood, but from abundant medicinal peptides and enzymes in leech saliva that may penetrate hosts.<sup>4</sup> There are over 100 bioactive substances found in leech salivary glands.<sup>15</sup> Some can function as analgesics, vasodilators, bacteriostatics, anti-inflammatories, anti-edematous, and anti-coagulants.<sup>15</sup> These bioactive substances are injected into the affected site through salivary ductule openings in the leech jaw that can break blood vessels (Fig. 1).<sup>9</sup> These bioactive enzymes may improve



Fig. 1. Application of a leech to the area to be treated using a syringe.<sup>11</sup>

Table 1

Various experiments suggest leech therapy is beneficial to osteoarthritic conditions.

Experiment	Population size	Groups	Results
Effectiveness of leech therapy in osteoarthritis of the knee: a randomized, controlled trial. <sup>12</sup>	51 Patients with knee osteoarthritis	1. 28-day diclofenac treatment 2. Single leech treatment; 4–6 leeches	Leech therapy: Mean pain at day 7 decreased 53.5 to 19.3. Diclofenac: Mean pain at day 7 decreased 51.5 to 42.4.
Assessment of leech therapy for knee osteoarthritis: a randomized study. <sup>13</sup>	113 Patients with advanced knee osteoarthritis	1. Single treatment 2. Double treatment 3. Artificial treatment (control)	Three groups' pain scores decreased; double treatment group experienced most significant improvement in function and decrease in joint stiffness. Use of pain medications also decreased.
A systematic review and meta-analysis of medical leech therapy for osteoarthritis of the knee. <sup>6</sup>	237 Patients total	Database screening found and analyzed: 3 randomized clinical trials; 1 nonrandomized controlled clinical trial; analyzed effects of hirudotherapy	Short-term pain reduction, immediate improvement in physical function, long-term reduction in joint stiffness; few adverse effects of leech therapy.
Safety and efficacy of leeching therapy for symptomatic knee osteoarthritis using Indian medicinal leech. <sup>14</sup>	40 Patients with joint pain	1. Combination of leech therapy and Unani herbal formula 2. Traditional Unani herbal formula alone	Combination group pain decreased 29.02%; stiffness decreased 58.87%; functionality increased 40.56%. Unani group pain level decreased 14.39%; stiffness decreased 8.04%; functionality increased 18.39%. <sup>14</sup>

blood circulation, increase thrombolysis, and enhance anti-inflammatory responses.<sup>4</sup>

The anti-coagulant properties of leech saliva are crucial to healing potential and include substances such as hirudin, calin, inhibitors of kallikrein, histamine-like substances, hyaluronidase, and collagenase.<sup>4</sup> Anticoagulants are therapeutic; they cause blood to circulate from the affected area, even after leech detachment.<sup>4</sup> Hirudin, one of the important bioactive components of leech saliva, inhibits thrombin.<sup>16</sup> It is crucial in surgeries, for phlebitis, and prevents postoperative pulmonary inflammation.<sup>4</sup> To clarify specificity, Hirudin has been cloned for cardiovascular and hematological usage.<sup>16</sup> Calin, an anti-coagulant, can clean wounds via secondary bleeding.<sup>4</sup> Histamine may dilate blood vessels causing blood to rush to the leech's bite.<sup>4</sup> Related to coagulation, hyaluronidase, allows medicinal enzymes to enter.<sup>4</sup> Apyrase, or adenosine 5'-triphosphate diphosphohydrolase, inhibits platelet aggregation through adenosine 5'-diphosphate.<sup>16</sup> Whereas, another component in leech saliva inhibits coagulate factor Xa.<sup>16</sup> Finally, antimicrobial peptides include theromacin, theromyzin, peptide B, and lumbricin, which share many properties with lumbricinase from earthworms, revealing annelid linkages (Table 2).<sup>7</sup>

**Table 2**

The healing peptides in leeches and how they function to improve arthritic conditions.

Medicinal peptide	Function
Hirudin	Inhibits thrombin <sup>16</sup>
Calin	Anti-coagulant & cleans wounds <sup>4</sup>
Hyaluronidase	Facilitates the entering of enzymes <sup>4</sup>
Apyrase	Inhibits platelet aggregation <sup>16</sup>
Histamine	Dilates blood vessels <sup>4</sup>

#### 4. Conclusion and perspectives: leeches

Although there are various treatments that may improve conditions of arthritic patients, efficient approaches to an actual cure are nonexistent. Thus, osteoarthritis may continue to progress in over 51 million individuals.<sup>5</sup> On a more positive note, hirudotherapy, or leech therapy, is statistically significantly linked to improving arthritic conditions.<sup>6,12–14</sup> The various medicinal peptides in leech saliva allow healing; it contains over 100 bioactive substances: analgesics, vasodilators, bacteriostatics, anti-inflammatories, anti-edematous, and anti-coagulants.<sup>15</sup> These functional properties may allow arthritic individuals to experience limited, but improved conditions. Aside from osteoarthritis, leeches also may be significantly used in

veterinary and clinical medicine. For example, application to soft tissue hematomas, tissue flap reconstructions, setting of severe soft tissue injury, surgical replantation, and penile replantation.<sup>2,17</sup> Although research on medicinal leeches is limited, the future of hirudotherapy is promising.

#### Conflict of interest

Dr. Edwin L. Cooper and Natalie Mologne have no conflicts of interest.

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