



REVIEW: A Review on Maggot Therapy by *Lucilia Sericata* Larvae on Infectious Wounds

Yahya Ehteshaminia
Hamid Mohammadi
Seif Ali Mahdavi
Mohammadtaghi Rahimi

Student Research Committee, Mazandaran University of Medical Science, Sari, Iran.
Student Research Committee, Mazandaran University of Medical Science, Sari, Iran.
Assistant Professor of Medical Parasitology, Mazandaran University of Medical Science, Sari, Iran.
Assistant Professor, Center for Health Related Social and Behavioral Sciences Research, Shahroud University of Medical Sciences, Shahroud, Iran.

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Correspondence:


Seif Ali Mahdavi, Mazandaran University of Medical Science, Sari, Iran.

Email: Seifalimahdavi@gmail.com

ORCID: 0000-0003-1522-7796

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ABSTRACT

Introduction: The use of fly larvae has been utilized to heal wounds for centuries. With the advent of antibiotics and new surgical procedures, the application of this method has diminished. With the increase in the prevalence of chronic wounds and emergence of antibiotic-resistant bacteria, it is important to provide a solution that can overcome these problems and treat infectious wounds. This review illustrates the effect of *L. sericata* on the infectious wound healing and the side effects as well as how to employ the method with these larvae.

Material and Methods: In this study a narrative review was carried out. The corpus was collected by searching the keywords of *Lucilia sericata*, *Phanicia sericata*, maggot therapy in the databases of PubMed, Scopus, SID, Google Scholar search engine. The studied articles were those which has been published on the interaction between the maggot therapy and *Lucilia sericata* until 2019.

Results: *L. sericata* larvae only deal with dead, necrotic tissue and do not harm healthy tissue and prevent the bacterial growth by secreting ammonia and also reduce the number of bacteria on the wound by eating them. Furthermore, by moving the larvae and producing cytokines, it increases the blood circulation in the affected area and the diapedesis of phagocytes increases and wound healing facilitates.

Conclusion: Due to wound healing and disinfection of *L. sericata* larvae, with considering the conditions of wound, we could use maggot therapy instead of the other treatment methods because of high efficiency and safety and low complications and costs.

Introduction

The wound is a clinical problem that can be either acute or chronic. Due to the importance of the wound, its management and treatment is a medical priority. Any product and process that can minimize healing time can be of great help to patients (1). The increasing prevalence of unhealable wounds is due to medical advances that have resulted in increased life

expectancy and in turn, acute and deadly diseases are now considered as chronic. Nowadays, most people live in conditions that increase wound sensitivity and disrupt wound healing. In addition, antibiotics are no longer effective in controlling skin and soft tissue infections because the prevalence of antibiotic-resistant bacteria is increasing (2). Impairment of wound healing is common in

diabetic patients. Treatment of diabetic foot ulcers accounts for 25-50% of the cost of admitting to the hospital. Approximately 15% of diabetic patients will have one or more leg ulcers, of which 15 to 25% will eventually have to have an amputation (3). The prevalence of Bedsores in acute patient hospitals is reported to be 38%. Bedsores increase the time and cost of hospitalization and can increase the risk of death by 4 to 6 times. Despite advances in wound dressing over the past two decades, no significant reduction in the prevalence of Bedsores has been observed (4). Bedsores are also a major problem among patients with spinal cord injuries. 20-90% of admitted patients with spinal cord injuries resulted in bedsores, which leads to 1 to 6 months of additional hospitalization (5).

Maggot therapy (using the larvae of *Lucilia sericata* flies to heal wounds) is a form of artificial myiasis under controlled conditions (6). The use of larvae for wound healing has been reported over the centuries and in various cultures. The positive effects of larvae on wound healing were first mentioned by Ambrose Pare in 1557. Baron Larrey also observed that maggots increase the formation of granular tissue while healing the injured soldiers of Napoleon's army. Also, after observing the benefits of maggot-infested wounds in World War I, orthopedic surgeon William Baer proposed a technique for using sterile maggots in order to get rid of infections caused by non-sterile maggots. Then he successfully placed maggots on the infected bones of children. Baer presented his preliminary results in 1929 but his entire work on Maggot Therapy for 100 Children with Bone Infections and soft tissue wounds was published after his death in 1931 (2, 7). This treatment became increasingly popular and was widely used in the treatment of infectious and chronic wounds throughout North America and Europe in the 1930s, and most hospitals set up their own insect breeding grounds to breed and disinfect larvae (2). With the widespread introduction and use of antibiotics, as well as the emergence of new surgical techniques in the

1940s, maggot therapy was forgotten in the medical community and used only as a life-saving therapy (a treatment used when other treatments fail) for a small number of people and for treatment of serious wounds. However, with the emergence of antibiotic-resistant bacteria in the 1980s and 1990s, such as methicillin-resistant *Staphylococcus*, and the realization that modern wound treatments do not always respond to serious infectious wounds such as Bedsores and diabetic foot ulcers, maggots therapy regained its popularity (8, 9). In January 2004, the Food and Drug Administration (FDA) authorized the use of maggot therapy and the manufacture and marketing of maggot as a medical tool (7, 10).

Methods

In the present study, which was conducted by the nonsystematic review method, data were collected using keywords (*Lucilia sericata*, *Phanicia sericata*, maggot therapy) from PubMed, Scopus, SID databases and Google Scholar search engine. In this paper, all studies published up to 2019 that were related to the title of the article were reviewed. It is worth mentioning that in the process of reviewing and selecting articles, unrelated sources and articles were removed and the results of the reviewed articles were summarized.

Findings

To evaluate the performance and safety of the larvae, Sherman et al. compared several types of larvae in terms of wound healing capabilities in comparison with conventional methods except for surgery. The surface area and quality of the wound tissue were weekly inspected and photographed, and the edges of the wound were mapped with clear acetate sheets (4, 8). In a study of 103 patients with Bedsores over 5 weeks, 80% of patients who underwent larval therapy had their dead tissues completely removed, while for patients who received normal treatment this was 48% (4, 10). They also studied the effect

of larvae on diabetic foot ulcers. 14 patients underwent larval therapy and 14 patients underwent other normal treatments. After 14 days, no significant removal of dead tissue was seen in the wounds of the treated group with normal treatment, while larval therapy reduced the dead tissue from the wounds by an average of 4.1 cm and after 4 weeks there was no dead tissue (5, 10). They also examined the effect of larvae on infectious wounds. All 6 patients undergoing larval therapy under 3 days and with a period of maggot use, the dead tissue of the wounds was completely removed while only two patients out of 6, under normal treatment, their dead tissues were completely removed (10, 19). Larval therapy prevents 40-50% of amputations (9). Sherman et al. Applied larval therapy to 8 patients who were recommended for amputation, and finally, only three patients were forced to amputate after larval therapy (11). They also refer to a case in which a woman's intestine was perforated and a diffuse infection in the abdomen has damaged the intestinal wall. Because using surgery to remove the dead intestinal tissue was so dangerous, they decided to try maggot therapy. The patient's abdomen was opened and a dressing of larvae was applied after placing two thousand larvae on the dead tissue. Two days later, the maggots were removed. There was no dead tissue left and she recovered without the need for any other surgery (2, 25).

Mechanism of action of larvae

Three groups of biomolecules (growth factors, cytokines, and chemokines) are involved in regulating wound healing. These proteins are made and released locally. Following injury, the wound healing process begins with the release of a number of soluble intermediates from platelets (including growth factors) during the process of blood clotting. Growth factors are the most important mitogens that stimulate cell division and chemotaxis of wound cells (epithelial cells, fibroblasts, and endothelial blood vessels). The presence of growth factors, cytokines, and chemokines, dilates

and increases the permeability of the arteries at the wound site, and in turn, increases the diapedesis of white blood cells and monocytes. These cells play an important role in removing dead wound tissue. In chronic wounds, one or more normal wound healing processes are not performed (6).

Scientists initially hypothesized that the process of removing dead tissue was due to the mechanical movement of maggot vermiform. Maggots have two hooks or jaws for movement and connection, which facilitate the process of removing dead tissue from the wound. Moreover, on the larvae head, there are many sharp hairs that can cause destruction to microbes by physical contact (11, 8).

Prete investigated the stimulatory effect of hemolymph and *L. sericata* gastrointestinal tract on the growth of human fibroblast tissue and found that both types of secretions stimulate the cell division of fibroblasts (12). When maggots are placed on dead tissue, they effectively stimulate the wound healing process by secretory proteases that participate in the reconstruction of extracellular matrix components because the degradation of extracellular matrix fibrin releases stimulatory components of cell division such as fibronectin fragments (6).

Recently, three classes of proteolytic enzymes have been identified in maggot secretions. These enzymes are involved in the degradation of extracellular matrix components (including laminin and fibronectin). The secretions help digest the wound matrix and cause the dead wound tissue to liquefy and be removed. Maggot secretions alter fibroblast adhesion to collagen and fibronectin, which causes fibroblasts to migrate (not proliferate). This is mainly attributed to serine proteases (proteases whose active site contains the amino acid serine) and metalloproteases (proteases with metal in their structure) (8). Regulation of tyrosine phosphorylation may also increase fibroblast displacement. Maggots secrete fibroblasts and chondrocytes by secreting cytokines (such as interferon-gamma, interleukin 10, and interleukin 6) and epidermal growth factor, and cause wound

healing. Maggots also synthesize type 2 collagen and allantoin, which have a soothing effect on inflammation and irritation of the skin (13, 14).

wounds disinfection by larvae

The presence of bacteria and infection is a factor in delaying wound healing. Antibacterial agents have been identified in maggot secretions that inhibit biofilm formation and have an inhibitory effect on gram-positive and gram-negative bacteria, such as methicillin-resistant *Staphylococcus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Clinical observations showed that maggots are more successful in the treatment of gram-positive infectious wounds compared to gram-negative infectious wounds (7, 9,10). The pH of maggot secretions is between 8 and 8.5. The ammonia in maggot exudates creates an unfavorable environment for bacterial growth by raising the pH of the wound. 90% of nitrogenous wastes of *L. sericata* are ammonia and 10% allantoin (Allantoin: 2,5-dioxo-4-imadazolidinyl urea) (6, 8, 10). One possible explanation for how maggots fight against wound infection is that the larvae eat the wound bacteria and are killed when the bacteria pass through the maggot's digestive tract. In a study in which the bacteria were labeled with fluorescent material, it was shown that the larval gastrointestinal tract is full of bacteria at first, and as we get closer to the end of the larval digestive tract, the density and number of bacteria decreases and the end of the larval intestine, it was sterilized and free of bacteria. The larvae of Blowflies kill bacteria in their stomachs and intestines. In addition, in the intestines of *L. sericata* larvae, there is a companion bacterium called *Proteus mirabilis* which secretes agents such as phenylacetic acid and phenyl acetaldehyde, that have antibacterial properties (6, 8, 15-18).

Treatments to remove necrotic tissues

Necrotic and dead tissues slow down wound healing and prevents the proliferation of healthy skin cells, the formation of granulation

tissue and angiogenesis, as well as the proliferation and spread of infectious agents and odor of the wound. There are several methods for removing dead tissue including acute or surgical debridement, enzymatic debridement, autolytic debridement, biological debridement, and mechanical debridement. The best type of debridement for each person depends on the type of wound, age, general health, and risk of complications and usually, a combination of the following methods is recommended by the doctor (19).

Sharp debridement or surgery: It is the fastest and most effective method known so far. The surgeon quickly removes the dead tissue, which may or may not be associated with anesthesia, depending on the patient's physical condition and the size of the tissue that needs to be removed. One of the disadvantages of this method is that only people who have sufficient knowledge and skills of surgery should use this method and if the area of tissue to be removed is large, it needs anesthesia (19).

Enzymatic debridement: Dead tissue is removed using enzymatic agents. Varidase, a combination of streptokinase and streptodornase, digests dead tissue against healthy tissue. Varidase breaks down fibrin and denatures collagen and elastin. Varidase solution can be applied directly to the wound or injected into dead tissue. Collagenase and papain are other enzyme products used in this method. One of the disadvantages of this method is that it is expensive (19).

Autolytic debridement: This method enhances the effect of the body's own enzymes to lubricate dead tissue without damaging healthy tissue with a moisturizing dressing. Hydrogel and hydrocolloid dressings are used in this method. This method is easy to use and non-invasive and causes minimal pain and discomfort. The disadvantages of this method is being slow, the possibility of peeling skin, bad smell of dressing, and being ineffective in some cases. However, this method is the most selected of the types of dead tissue removal methods (19, 20).

Mechanical debridement: In this method,

dead tissue is removed from the wound with a driving force, which includes 1- Hydrotherapy: In this method, running water is used to wash the wound and requires special equipment. 2- Wet to dry dressing: Wet gauze is placed on the wound and when the dry gauze sticks to the wound and by removing it, dead and healthy tissues are removed, which is a cheap and easy method to use but the disadvantages are including the time it takes from the nurse, being non-selective and painful. 3- High-pressure hydrotherapy: which uses high-pressure water to wash the wound and removes infectious agents that are usually not removed with running water, and its disadvantages are special equipment requirement and the possibility of spreading bacteria to other tissues. (19, 21, 22).

Bio debridement: Also known as maggot therapy, larval therapy, and biosurgery, *L. sericata* larvae are used to remove dead tissue and wound bacteria. The activity of the larvae shrinks the wound little by little, while in the surgical method a part of the healthy tissue is removed by the surgeon along with the removal of the infected and necrotic part, thus the wound becomes larger (19, 22).

Larvae

The larvae of most fly species (such as *Musca domestica*) are invasive, attacking healthy tissue and causing myiasis. Common larvae used for larval therapy are the larvae of the green bottle fly *L. sericata* or *Phaenicia sericata*, which have been selected for their high impact and ability to feed on dead tissue without damaging living tissue and belong to the flesh fly family (Calliphoridae or blowflies) and the order Diptera (20, 23).

Flesh flies lay their eggs on open wounds and dead parts of birds and mammals that are not covered with feathers or hair, and sometimes even on feces. Maggots can be obtained by placing raw beef in the open air on which flies lay eggs. The required time for the *L. sericata* cycle (from the time of spawning to the time of turning into flies) is approximately 10 to 23 days. Thus, the eggs hatch after 8 to 24 hours, and the larvae with the size of 1-2 mm

emerge. The larvae feed on dead tissue in a humid environment. Larvae secrete proteolytic enzymes that are capable of exodigestion. After that, the food becomes liquid and is consumed. The larvae grow very fast and after 4 to 5 days they become 10 mm and it takes about a week or two for the larvae to become pupae then after a few days, they become adult flies (5, 24).

Sterilization and breeding of fly larvae *L. sericata*

The larvae used for maggot therapy is breed in a humid environment. Moreover, it is needed to be sterile in order not to cause contamination by itself. Young larvae should be used within 8 hours or stored in a refrigerator between 8 to 10 °C to slows the metabolism. To maximize the activity of maggots, it is necessary that the optimal body temperature of the larvae and required oxygen and moisture are sufficiently provided. It should be noted that occlusive dressing should not be used because larvae need oxygen to survive. High humidity also kills larvae. In addition, propylene glycol and hydrogel dressings limit the growth and survival of larvae, while systemic antibiotics (antibiotics that spread throughout the body through the circulatory system, which can be absorbed through the gastrointestinal tract or injected into the blood is used) has no effect on larval growth (8).

According to the history of maggot therapy, non-sterile larvae resulted in one case of erysipelas and two cases of tetanus. Baer observed that the treatments he performed with maggots were sometimes infected with anaerobic bacteria such as *Clostridium perfringens* and *Clostridium tetani* (15). Attempts to sterilize maggots with hydrogen peroxide were unsuccessful because although the bacteria on the larval surface were killed, the bacteria inside the larvae's gut survived and soon formed colonies outside the larval body. Baer found that the surface of unopened fly eggs could be sterilized by soaking them in a bichloride solution at room temperature for one hour. This method produces sterile larvae that can then grow in

a sterile environment to be placed on the wound. Adult flies are kept in a room with a temperature of 25 °C and a humidity of 33%. After spawning, the fly eggs are sterilized in 0.05% sodium hypochlorite solution for 8 minutes, then washed with sterile water, afterward placed in 4% formaldehyde, and then rinsed again with water for breeding on sterile sheep blood agar to allow the larvae to hatch. The larvae are ready to lay on the wound 24 to 48 hours after hatching. Young 1–3 mm maggots remain in cage-like dressings in cycles of 48 to 72 hours (5, 13).

Dressing

Maggot therapy had three common drawbacks in the 1930s: 1) Maggots contained germs. 2) It was difficult to make a dressing that was durable and suitable for growth. 3) Making dressing was expensive. Advances in the manufacture of synthetic adhesives and fabrics, and the design of cage-like dressings and biological bags that hold maggots close to the wound bed, and advances in disinfection and breeding methods, have overcome these problems (2). A suitable dressing should prevent the maggots from escaping and be well-aerated so as not to impede oxygen supply to the maggots, and with their absorption power, facilitate the discharge of wound secretion, and have the least dependency for maintenance and cleaning, and most importantly be inexpensive (25). Sometimes the maggot dressing may loosen, especially if it is left in place for 48 hours. The escaped larvae that have not been collected become pupae and emerge from their hiding place as adult flies 1-2 weeks later. Although these flies are not mature enough to lay eggs, they are annoying. In addition, previously used maggots and flies are considered to be the main factors that cause infections. Therefore, the dressing of maggots should be limited and all maggots should be collected at the end of the treatment cycle and discarded like other infectious components of the dressing (2). There are two types of dressings for maggot therapy. 1-Maggot confinement dressing or cage-like dressing that restricts maggots to

the wound. This product provides free and full access to wounds for maggots while preventing them from escaping (2). In this dressing, the skin around the wound is covered with a hydrocolloid pad that is cut to the size and shape of the wound. This hydrocolloid ring prevents maggots from crawling on the healthy surrounding skin and from exposing the fluid secreted by wounds and proteolytic enzymes of larvae to healthy skin (11). It also provides a base to which the dressing adheres. The 5 to 8 larvae per square centimeter are placed on the wound. A perforated mesh of dacron cluffon or nylon stocking or nylon mesh is glued to the top of the hydrocolloid ring, covering the entire wound (3, 4). On top of this perforated mesh, a gauze pad is placed that absorbs the fluid secreted from the wound and the dissolved necrotic tissue (25). The top layer of the gauze pad is replaced every 4 to 8 hours because it is impregnated with the fluid secreted from the wound and also provides oxygen to the larvae, while dressing after a cycle of 24 to 72 hours when the larvae are reached to the size of about 1 cm, are discarded (20, 26). Usually, two cycles of 48 hours per week are used. Between these cycles and after the end of maggot therapy, a 0.125% sodium hypochlorite moistened gauze dressing is used as a disinfectant, and lasts for 1 to 4 days (3, 4).

The most common reason for maggot therapy failure is the drying of the larvae. To prevent this, a gauze pad above the dressing can be moistened with saline solution. The larvae also dry out when the eschar (dry black dead tissue) covers the entire surface of the wound because they cannot reach below the eschar. In these cases, the edges of the eschar can be softened with a hydrogel dressing a few days before using the larvae (20).

2- Maggot containment dressing prevents maggots from escaping like dressing, but on the contrary, this bag-like dressing completely surrounds the larvae and even restricts their free access to the wound bed. This reduces the likelihood of discomfort, complain, and pain of patients. This is because of the fact that maggots cannot crawl

near exposed nerves, thus reduces the patient's discomfort. The work of the therapists is also easier because the therapists can use this type of dressing and/or throw it away without observation or making contact of larvae directly (2).

Complications

Most patients do not have any symptoms during treatment, but some may experience itching (such as when something crawls on the skin), flu-like symptoms (fever and weakness and respiratory symptoms), bleeding and maceration (skin deformity to swelling of the face with softening and discharge due to prolonged skin exposure to moisture), which is usually rare (27). The most common complication is pain at the wound site and it begins when the larvae reach 30 hours of age (28). At this time when maggots grow, pain may be felt due to nerve stimulation which can be relieved by removing the larvae or using painkillers. On the second or third day, the wound becomes slightly smelly and watery (2, 11).

Applications of larval therapy

Larval therapy is of great help to diabetic foot ulcers, bedsores, burn wounds, chronic venous leg ulcers (or varicose veins due to a disorder in the structure of the venous valves that impedes the return of blood to the heart and usually begins to clot in the legs), acute surgical wounds, trauma wounds (severe and fatal wounds) (6), inflammation of the temporal lobe (29), necrotic tumors of the face and gangrene of the genital tract (5, 13). Non-surgical removal of dead tissue from the wound is slower than the surgical counterparts, but when we do not want to perform surgery, larval therapy will be a more effective and better alternative method (27, 30).

Yuck factor

The biggest obstacle on the way of using this type of treatment is the yuk factor and the non-acceptance of this type of treatment by the patients and doctors. In fact, the resistance and instinctive disgust of society to new and

unknown technologies are called the so-called yuck factor. Research has shown that patients' fears and rejection of treatment are unfounded (2, 7) and that patients who are given sufficient information about treatment are more likely to start and continue treatment. Thus, experience has shown that maggot therapy is less frightening than it is thought and more beneficial than it is imagined (8).

Factors affecting the larval therapy result

Steenvoorde et al. examined the conditions that affect maggot therapy outcomes. They treated 101 patients with 117 wounds. Out of 116 wounds, 78 (67%) wounds were healed successfully, and for 38 (33%) of wounds, the treatment was not successful. They analyzed their data through multivariate analysis and concluded that the result of treatment was influenced by gender, body mass index (BMI), diabetes, smoking, ASA-classification (patient physical status classification system which has 6 categories: 1-Healthy, 2-Mild systemic, 3-Severe systemic, 4-Severe systemic that threatens the patient's life, 5-Patient who experiences definite death if not undergo surgery, 6-Patient with brain death), wound location and the size of the wound do not fit and therefore there is no reason not to use the larvae. The results also showed that all the wounds created after the injury were completely healed, but the wounds of the joint infection failed to heal and half of them led to amputation. Most maggot feeding occurs when spiracles (holes in the exoskeleton of some arthropods) are exposed to the air, so increasing wound depth is a major predictor of failure. Wounds older than 5 months, chronic ischemic wounds, joint infection wounds, and deep wounds aged 60 years and older have a negative effect on the success of larval therapy. Careful selection of patients can improve the outcome of maggot therapy and reduce the overall cost of treatment (9).

The application of maggot extract

Sometimes the patient complains about the

pain at the wound site during treatment and sometimes, for psychological reasons, the presence of live larvae on the wound is not pleasant for the patient, so replacing healthy larvae with larval extract can be a good alternative in these cases. Sanjari et al. Investigated the effect of *L. sericata* maggot extract on wound healing and found that the best period of treatment with the extract is 24 hours which leads to induction of cell proliferation, but after 72 hours it has an inhibitory effect. The best therapeutic concentration is 12.5 micrograms per milliliter and higher concentrations cause toxicity and cause cell death (1).

Conclusion

Maggots dissolve dead (but not healthy) tissue with their enzymes (3, 5). Maggots swallow bacteria and kill them in their digestive tract. They also disinfect wounds by secreting antibacterial and alkalizing agents. Maggots increase granular tissue production and wound healing by secreting growth factors and cytokines, as well as increasing oxygen delivery to tissues (24, 28). Oral antibiotics and phagocytes require sufficient blood supply to reach the wound, while open-wound maggots need only oxygen and moisture to destroy necrotic tissue and kill bacteria (11). Evidence shows that as an alternative to surgery, maggot therapy removes the dead tissue at a faster rate than other comparing methods and thus accelerates the wound healing process (8). The prevalence of antibiotic-resistant bacteria and chronic ulcers, such as Bedsores and diabetic foot ulcers, which cannot be stopped by normal treatments, make doctors more willing to use maggots. Considering the condition of the wound and the fact that these conditions do not adversely affect the outcome of larval therapy, this treatment can be used instead of other treatments due to its high efficiency and safety, low side effects, and cost.

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IR.MAZUMS.REC.1398.6136 has been approved by the Ethics Committee of the Vice-Chancellor for Research and Technology of Mazandaran University of Medical Sciences. The authors of the article express their gratitude to the Vice-Chancellor for Research and Technology of Mazandaran University of Medical Sciences for supporting this project.

Conflicts of interest

Authors declare that there is no conflict of Interests.

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