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Review Article

Use of fly larva (Maggots) in Cancer Treatment: A systematic review

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Abstract

Introduction: Superficial cancers are one of the most common cancers in humans and animals. The use of maggot therapy as an alternative treatment is expanding and has achieved great success in treating superficial. Maggot extracts and secretions have been also demonstrated to have beneficial biological effects. The present study aimed to perform the first systematic review of the use of maggot, as well as its secretions and extracts, in neoplasms.

Methods: In the current review study, online databases, such as Pub Med, Web of Science, Scopus, and Embase, were searched to retrieve the published studies from 1985-2021. The used keywords were Maggot therapy, Larval therapy, Larval extract, Larval secretions, Cancer, Neoplasm, and Tumor. Only research on the larvae of the order Diptera was included in the present study.

Results: Out of 387 screened papers, 9 articles met the proposed inclusion criteria. There were three articles on the use of maggot debridement therapy in tumor lesions and six articles on the effect of maggot secretions and extract on neoplastic cells. Maggot debridement therapy has been able to control the complications of skin tumors and breast cancer. Several studies have also reported anti-tumor effects on larval extracts and secretions.

Conclusions: Maggots were able to improve the appearance of lesions and prevent further tumor growth that was progressing before larval therapy. It seems that maggot therapy can be used to treat necrotic tumors; moreover, its extract and secretions can be used to treat a wider range of cancers in humans and animals. Nonetheless, more studies are needed in non-progressive cancers to determine the true effects of this method.

Keywords: Complementary Therapies, Larva, Necrosis, Neoplasms

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Introduction

Cancer is a major public health problem and a leading cause of death in developed countries (1). Skin cancer is one of the most common neoplasms of whites, with a rising incidence across the globe (2). The prevalence of melanoma is significantly related to skin color and is higher in whites than in other ethnic groups. The risk of developing melanoma increases with age. Men are more likely to get the tumor than women (3). Non-melanoma skin cancers (NMSCs) are the most commonly diagnosed tumors. Most NMSCs are basal cell carcinoma and squamous cell carcinoma (SCC), accounting for 70% and 25% of cases, respectively (2).

The decision to perform surgical excision as a preferred treatment of skin tumors can be affected by various considerations, including co-morbidities, the anatomical site of the lesion, and potential intolerance for repeated excisions. Topical treatments have less toxicity than systemic treatments. The 5-Fluorouracil, Imiquimod, Photodynamic therapies, Ingenol mebutate (PEP005), and retinoids (Vitamin A analogs) are known as surface treatments used in skin cancers (4). Moreover, malodorous and fungal lesions in advanced skin cancers are a challenge for medical staff. Surgical debridement, systemic antibiotics, and dressings are commonly used to treat this condition. However, the results are often unsatisfactory and, in some cases, contraindicated due to the possibility of bleeding and further tumor invasion (5). Maggots (larvae) therapy can help manage these complications.

The larvae of flies (maggots) have long been used by the Mayan Indians, as well as some Spanish and Greek tribes, for the treatment of human wounds. The larvae were even used to heal soldiers' wounds during the Napoleonic Wars; nonetheless, with the development of modern medical equipment, this method received less attention. Maggot therapy is a method in which sterile fly larvae are used to treat superficial lesions in humans and animals. Scientific studies on the use of maggots were started by Dr. W. Bayer (6). Larval therapy was approved by the US Food and Drug Administration in 2003 (7). The most commonly used larvae in larval therapy are Lucilia (Phoenicia) sericata which belong to the Calliphoridae family. (8). Other species of flies, such as Lucilia cuprina, have been used in some studies to treat ulcers (9).

Larval therapy is widely applied in human and animal medicine and nowadays is mostly used in the treatment of human diabetic wounds and infectious wounds of animals. Larval therapy has been also effective in the treatment of pressure, vascular, and surgical ulcers (10-12). The results of using larvae are faster and sometimes more effective than conventional treatments. One of the advantages of larval therapy is no need for equipment, specialist, hospitalization, and intensive care, as well as lower costs. The larvae only need oxygen during the period and due to their photophobic nature, they penetrate deep into the wound, where it is not accessible to the surgeon without invasive surgical intervention. No significant side effects have been reported for larval therapy (8,13). The larval therapy method has been performed by Dr. Mirabzadeh and his colleagues in special centers in Iran for several years (14).

The maggots have received the title of small nature surgeons by the debridement and removal of necrotic material (13). Maggots secrete substances that have antibiotic properties against Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus (15-16). In one experiment, the extract of L. sericata laurel was demonstrated to reduce inflammatory mediators, such as IL-1β, IL-6, TNF-α, and NFκB. In this study, the antioxidant properties of larval extracts were proven by HO-1, SOD, GSH-Px, MPO, and MDA methods (17). Antiviral properties have also been exhibited for the secretion and extract of Lucilia cuprina larvae (18). In summary, maggots have the following therapeutic properties: antibiotic, anti-biofilm, synergy with other antibacterials, antifungal, anti-inflammatory, immune system modulator, a regulator of fibroblast growth, coagulation enhancers, nerve repair, anti-atherosclerotic, and anti-tumor (19). Some papers have suggested that larval therapy is useful in the treatment of tumor lesions; however, a comprehensive study is not available in this context. The present study was performed to find evidence

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to prove or disprove the possible effect of the order Diptera larvae on the treatment of neoplastic lesions. Accordingly, a systematic review study was performed on the use of maggot therapy in cancerous lesions or maggots secretions and extracts in neoplastic cells.

Material and Methods

The present systematic review was conducted based on the Cochrane protocol according to the PRISMA guidelines (Figure 1). A query was conducted on international databases, such as PubMed, Scopus, Web of Science, Embase, and Google Scholar (as gray literature) for a 35-year period from 1 January 1986 to 10 November 2021. This period was selected due to the long history of larval therapy and the initial search. Search terms used were ("Maggot therapy" Or "Larval therapy" OR "Larval extract" Or "Larval secretions") And (Cancer OR Neoplasm OR Tumor). The terms were searched in the topic, title, abstract, and keywords of published articles. Duplicate articles were removed using EndNote X8 (Thomson Reuters, Toronto, Canada).

In the first stage, some unrelated articles were deleted based on the title evaluation. In the second stage, the abstract of the articles was evaluated, and irrelevant papers were deleted. Original articles and case reports on the use of maggot therapy or larval secretions and extracts in lesions or neoplastic cells published online were included in the study. The articles containing at least English abstracts were included in the study since there are limited studies and reports in some scattered areas and their minimal information should not be lost. Only research on the larvae of the order Diptera was included in the present study. The bias may be due to the lack of access to articles published in non-English languages and selective reporting within studies.

Results

A total of 387 articles were retried from the papers published from 1991-2021. The highest number of articles was from Scopus (n=273), Web of Science (n=93), Embase (n=9), and Pambod (n=4), respectively. Eight articles were identified from the results of Google Scholar searches related to our topic. 68 duplicate papers were detected and deleted using EndNote X8 software. Out of 319 articles left after the removal of duplicates, 74 articles remained after reviewing the titles and abstracts, and finally, after a careful review of the criteria, 9 articles were included in the present study (Figure 1).

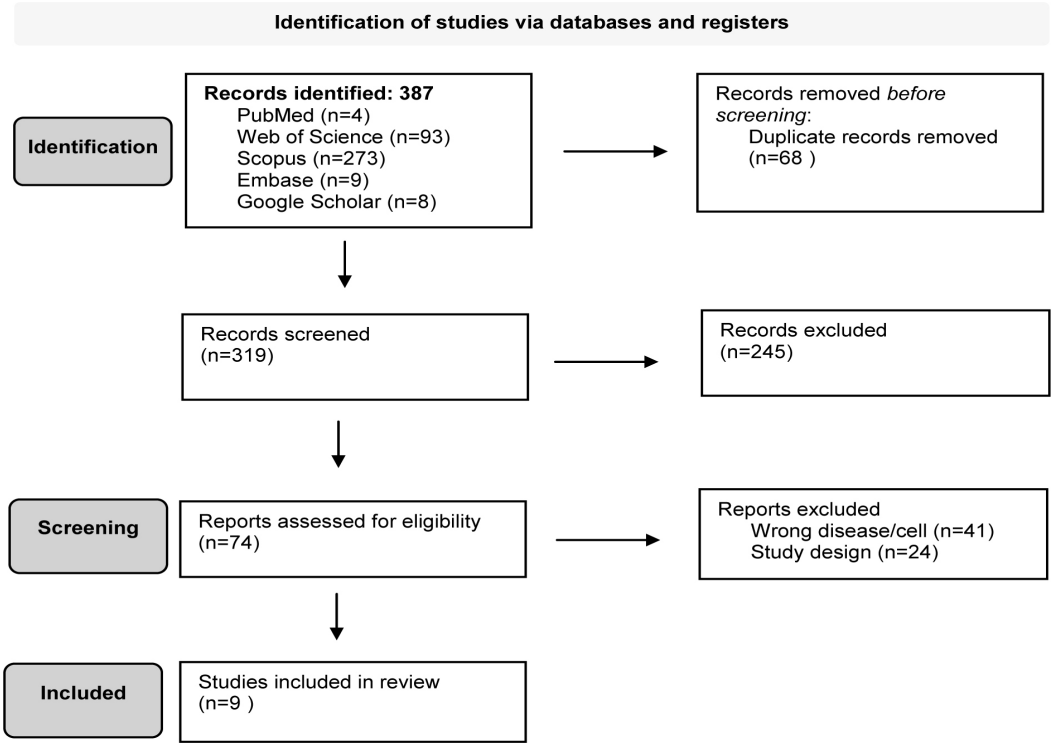


Figure 1. Systematic review PRISMA flow diagram

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The revision of nine eligible articles (Table 1) indicated that 11 cases of maggot debridement therapy have been performed in human proliferative lesions (SCC, Kaposi's Sarcoma, and Endometrial adenocarcinoma metastasis) and horses (Melanoma, SCC, and Sarcoid).

These tumor lesions were located in the legs, chest, head, and neck. One case of myiasis with breast cancer yielded good results. Larvae extract has been also used in the treatment of mice hepatoma, and the effect of larvae extract on human leukemia cells and human lung cancer cells have been investigated.

Lucilia sericata larvae have been used in most cases; nonetheless, Chrysomya megacephala and Phormia Regina larvae have been also used in some cases.

Although we have high hopes that fly larvae can be effectively used in the treatment of neoplasms, limited studies are available on the effect of maggot therapy on these lesions (13,20).

Maggot therapy has been performed for a malodorous lesion caused by SCC in a human chest. In this case, the smell and appearance of the wound improved after two rounds of larval therapy. Pain in the area prevents the next larval therapy (21). Larval therapy with L. Sericata for Kaposi Sarcoma reduces odor and infection, improves blood flow, and prevents amputation. The author considers the use of larval therapy useful for the final stage of malignant wounds and recommends that more studies be conducted in this regard (5). Maggot therapy was performed for a metastatic necrotic wound in the leg following malignant adenocarcinoma of the endometrium.

Conventional treatments before maggot therapy failed to heal the wound. Larvae treatment removed the necrotic tissue on the wound and the granulation process appeared to have begun (22).

Larval therapy has been also used to treat skin tumors in the head and neck (23).

There have been cases, in whom skin cancers have been associated with spontaneous myiasis. In one case, a person with fibroepithelial cell neoplasia of the breast (phyllodes) who had been associated with myiasis lived for 15 years (24). There have been other reports of involuntary myiasis associated with skin neoplasms in humans.

In all of these reports, tumors grew very slowly (25-27). According to some scientists, studies on horse skin can be considered a model for human skin lesions (28). In one article, three uses of maggot therapy on proliferative lesions in the motor organs of horses were presented.

A proliferative lesion in a horse with larval therapy was completely healed. In the case of horse melanoma, debridement and granulation tissue production were observed following maggot therapy.

Nonetheless, maggot therapy in a chronic SCC did not have a positive effect on lesion healing (29). In one study, maggot therapy with L. Sericata larvae was performed on four cases of equine sarcoid lesions (fibroblastic tumor).

In two of the horses, the results were satisfactory and caused the appearance of healthy skin; however, no positive results were observed in the other two cases (30).

Larval secretions and extracts can also have anti-tumor effects. In one study, the effect of two fatty acids extracted from Chrysomya megacephala larval extract was investigated using a colorimetric assay (MTT) and Sulforhodamine B (SRB) methods on human leukemia cells HL-60 and human lung cancer cells A-549.

Both of these substances had an inhibitory effect on cancer cell growth, and HIV-1 integrase. ω-6 PUFA was the main active ingredient in these fatty acids (31). The feeding of C. megacephala larval extract for 10 days to hepatoma-bearing mice models reduced tumor complications.

The protein expressions of p38 mitogen-activated protein kinase (p38MAPK) and phosphorylated-p38MAPK (p-p38MAPK) in tumor tissues, as well as the levels of interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF), were detected in tumors. The antitumor mechanism of the C. megacephala extract may be related to cytokines and activation of the p38 MAPK signal pathway (32).

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Table 1. Reports and research on the use of maggots in the treatment of cancer

No	Patient	Maggot	Application	Neoplasm	Place	Result	Source
1	Human	Unknown	MDT	SCC	Chest	Improve smell and appearance	Jones 1998
2	Human	*L. Sericata*	MDT	Kaposi's Sarcoma	Leg and chest	Reduces odor and infection, Improves blood flow Prevents amputation	Lin 2015
3	Human	*L. Sericata*	MDT	Endometrial adenocarcinoma metastasis	Leg	Removed the necrotic tissue Granulation appeared	Sealby 2004
4	Human	*P. Regina*	MDT	SCC	Head and neck	Improved necrotic wound	Reames 1988
5	Human	Unknown	Associated Myiasis	Phyllodes	Breast	Lived for 15 years	Kudchadkar
6	Human cells	*C. megacephala*	Extracted fatty acids	Human leukemia cells (HL-60) Human lung cancer cells (A-549)	Cell culture	Inhibition of cancer cell growth	Jun-Qing 2008
7	Mice	*C. megacephala*	Larval extract	Hepatoma	Mice model	Reduced tumor complications	Zhang 2020
8	Horse	*L. sericata*	MDT	Melanoma SCC	---	Improved healing	Lepage 2012
9	Horse	*L. sericata*	MDT	Sarcoid	Leg	Removed the necrotic tissue Granulation appeared Improve appearance	Ahmadnejad 2021

DMT: Maggot debridement therapy

Discussion

The results of a systematic study demonstrated that maggot debridement therapy was sporadically used in humans and animals. Due to the successful use of maggot therapy in the treatment of skin and superficial cancers, such as breast cancer (5,21–23), as well as the anti-tumor properties of extracts and secretions of larvae in the laboratory (31-33), it seems that this natural treasure can be effective and practical in the treatment of neoplasms, especially skin cancers, in humans and animals.

The beneficial effects of larval therapy in the treatment of cancers can be exerted via different pathways. The amino acid 3-Guanidinopropionic acid (GPA) isolated from the secretions and extracts of L. sericata larvae, like its other analogs, can be expected to have antitumor properties (33). The substances secreted by maggots have proteolytic properties and similar activity to trypsin, leucine aminopeptidase, and carboxypeptidase. The

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larvae and their extracts can modulate the growth, proliferation, and migration of cells, including fibroblasts, by modifying the extracellular matrix (19,34). These properties may help reduce overgrowth in skin cancers. Since larvae are photophobic, they penetrate deep into the wound without causing destructive effects. However, the application of conventional techniques to access this area is accompanied by an invasion of normal tissues. Studies have suggested that maggot therapy does not adversely affect chemotherapy with antibiotics (13,35).

Most findings confirm the anti-tumor effects of larvae; nonetheless, a recent study indicated that larval therapy expresses some of the genes involved in tumor formation. The activation of such genes can help repair ischemic wounds, such as diabetic wounds, by activating angiogenesis (36); however, it can also be harmful in cancerous lesions. In the past, tetanus transmission was one of the problems of larval therapy, which has now been solved by sterile methods of larvae preparation(37). Another concern over larval therapy is the achievement of human and environmental standards in the production and use of these larvae (38). One of the challenges in animals was the placement of larvae and toleration of dressing in restless horses, which is likely to be much less common in humans (30). Participants in the present study (five humans and seven horses) received maggot therapy. The H22 hepatoma-bearing mice models, Human leukemia cells (HL-60), and Human lung cancer cells (A-549) also participated in the study of the effects of the larval extract. Maggot therapy partially improved the appearance of neoplastic lesions; moreover, the larval extract inhibited tumor growth in mice and neoplastic cells in the laboratory, compared to the control group.

Among the notable limitation of the present study, we can refer to the fact that most information was related to case reports and this may lead to biased conclusions. Another limitation was the mere inclusion of English literature, which may be due to the lack of access to articles published in non-English languages and selective reporting within studies.

Conclusion

Maggot therapy seems to be an effective way to cure malodorous and infectious cancer wounds. Even some secretions from larvae can help control cancer by modifying cell proliferation processes. Nevertheless, to obtain more accurate and reliable information, more clinical trial studies should be performed on the use of larval therapy, as well as larval extracts or secretions, to treat cancers.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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