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Maggot Therapy and Cancer

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ABSTRACT

Due to the rising prevalence of non-healing wounds, therapists all over the world have rediscovered the benefits of maggot therapy. Maggot debridement therapy was used historically for necrotic tissue healing but its use diminished with early decades of antibiotic discovery. Today, several persons live with ailments that increase their susceptibility to wounds and/ or worsen their wound healing such as cancers and/ or ulcerating tumors. In spite of obvious correlations of maggot's secretions to many mechanisms that are important in tumor growth and metastasis such as angiogenesis,inflammation and cell migration, till this moment, there are no well-knownstudies of maggot secretions biology and biochemistry, mechanisms of actions and its probable anticancer effect. We therefore think that more efforts should be done towards a better understanding of the role of medicinal maggots in cancer therapy. In this review examines the biology of maggot therapy, its preparation and application for wound care, the molecular mechanisms linking maggot therapy to cancer, and finally discusses all published cases of ulcerating tumors and cancers managed with maggot therapy till date.

INTRODUCTION

The primitive, carrion-breeding habit of blowflies has been known, recorded and used for medical purposes for centuries past. The aboriginal Ngemba tribe of New South Wales, Australia commonly used maggots to clean suppurating or gangrenous wounds, a practice which they traced back to their remote ancestors [1]. The Hill people of Northern Burma were observed during World War II placing maggots on a wound and then covering them with mud and wet grass [2]. The Mayans of Central America ceremoniously exposed dressings of cattle blood to the sun before applying them to certain superficial tumors. After a few days, the dressings were expected to squirm with maggots [3]. Modern maggot therapy was founded by a military surgeon Willian Baer who recalled that during the war, soldiers whose wounds were infected with maggots did far better than their wounded comrades whose wounds were not similarly afflicted [4]. He began to use the technique more widely but unfortunately, several of his patients developed tetanus and he established the importance of sterile maggots for future work [4,5].

After these experiences, the use of larvae in wound management became very common in the United States where over 300 hospitals introduced maggots into their programme of wound healing between 1930 and 1940 [6].

BIOLOGY OF THE BLOW FLY, "*Lucila sericata*"

Flies in Disease and Health

About 120,000 fly species have been described, a small number of which are vectors of diseases such as malaria [7], zika virus disease [8], filariasis [9] and trypanosmiasis [10]. These diseases are transmitted by adult flies, which have become adapted structurally and physiologically to a bloodsucking mode of life. Other species such as the common housefly, *Musca domestica* represent a potential threat to health because the adult may contaminate food with pathogenic organisms [11].

The larvae form of some fly species like the Screw-worm fly, *Cochliomyia hominivorax* can be highly invasive. The adult lays its eggs in the margins of wounds or mucous membranes of body openings such as the nose or vagina.

And the newly hatched larvae burrows downwards into the tissue causing massive tissue damage or even death [12]. Other larval species like the Blowfly are fortunately far less hostile and limit their activity to dead or necrotic tissue.

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Taxonomy and Description of the Blowfly

The Blowfly (*Lucilia sericata*) also known as the "Green Bottle" is the most commonly used fly for larval therapy. The adults are attractive metallic coppery green, hence the common name, "Green Bottles" [13]. They resemble house-flies in appearance and adult flies hibernate in homes. Similar to houseflies, larvae feed on dead animals or garbage. The Blow Fly is classified in Kingdom Animalia as follows [14]:

Phylum: Arthropoda

Class: Insecta

Order: Dipteria

Suborder: Brachycera

Infra order: Muscomorpha

Family: Calliphoridae

Genera: Green bottles: *Lucilia*

The adult female fly lays large number of eggs in clusters (150-200 eggs per batch) on organic matter such as suppurating wounds or carrion [15]. Tiny maggots hatch from eggs in 6 to 48 hours producing powerful mixture of proteolytic enzymes including collagenase, which break down the dead tissue to a semi-liquid form that is then reabsorbed and digested [16].

THE THERAPY OF MAGGOTS

Preparation of Sterile Larvae

Baer was the first individual to initiate the concept of sterilization of larvae. This was because several of his patients developed *Clostridium tetani* and *Clostridium perfringens* and he resolved that it would be essential to use sterile maggot for future work [4].

Over the years, several sterilization techniques were used. Some of which achieved sterility but proved lethal to the eggs. These techniques have since then been optimized and they include pre-treatment in Dakin's solution (dilute sodium hypochlorite or bleach) followed by immersion in mercuric chloride or formaldehyde. Satisfactory sterilization has also been achieved using 5% formalin and 1% sodium hydroxide [17].

Methods of Application

Maggot therapy is typically administered by applying disinfected fly larvae to the wound within a cage-like dressing [18]. The cage-like dressing is usually topped with a light gauze pad to absorb the necrotic drainage. About 5 to 8 larvae are placed per square centimeter with a loose guaze. A ring of hydrocolloid is placed onto the skin surrounding the wound 5 and secured with a covering of porous Dacron chiffon or nylon sticking with glue and tape [19]. This serves as a protection for the skin from irritation by the maggot's proteolytic enzymes and forms the base of the adhesive dressing.

Maggots are removed by peeling back the dressing with one hand while whipping up the larvae with a wet gauze pad held in the other hand. One or two cycles are applied each week [20].

MOLECULAR AND BIOLOGICAL MECHANISMS LINKING MAGGOT THERAPY TO CANCER

Angiogenesis

Angiogenesis involves the formation of new capillaries from pre-existing vascular network [21]. Thus, making it a critical component of wound healing. Aberrant angiogenesis is evident in chronic wounds and cancer. Hence, it is a vital step in the alteration of tumors from a benign to malignant state [22].

Clinically, maggots are renowned for their 3-fold action: debridement [18], disinfection and healing [23]. Studies have shown that maggot secretions can provoke modifications in cell-morphologies that incite fibroblast migration [24]. Three pro-angiogenic factors: L-histidine, 3-guanidinopropionic acid and Lvalinol have been identified within the maggot secretions [25]. Furthermore, a study to investigate the effect of dried extracts of *L. sericata* larvae on wound healing observed after 72 hours of treatment, a significant increase in wound capillary density, VEGFA mRNA expression and VEGFA protein expression in rat wounds treated with *L. sericata* fatty acid extracts when compared to the controls [26]. The study concluded that the observed wound healing properties of *L. sericata* were due to its pro-angiogenic properties via the up-regulation of VEGF expression.

A study by van der Plas and colleagues showed that maggot secretions increased the production of pro-angiogenic growth factors bFGF and VEGF in anti-inflammatory macrophages [27]. This observation therefore suggests that wound healing occur via the promotion of angiogenic growth factors.

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Inflammation

Many tumors develop from sites of infection, chronic irritation and inflammation. Thus, inflammation coordinates the micro-environment around tumors giving rise to proliferation, survival and migration [28]. Chemokines, selectins and their receptors are used for migration, metastasis and invasion by tumor cells [29].

Wound healing is facilitated mainly by monocytes and macrophages [30]. In a study aimed at investigating the effects of maggot secretions on the differentiation of monocytes, it was observed that they differentiated towards macrophages with a decrease in production of the proinflammatory cytokines and pro-inflammatory macrophages tended towards an anti-inflammatory morphology [27].

In another study [31], maggots secretions were observed to dose-dependently inhibit the production of the pro-inflammatory cytokines TNF-α, IL-12p40 and macrophage migration inhibitory factor by lipoteichoic acid-stimulated monocytes. It was also observed to enhance the production of anti-inflammatory cytokine IL-10. The secretions were observed to induce transient rise in intracellular cyclic AMP concentration in monocytes and Rp-cyclic AMPS repressed the effects of secretions. It was concluded that the maggot secretions inhibited the pro-inflammatory responses of human monocytes via cAMP-dependent mechanism.

Cell Migration

A fundamental phase in wound healing is the migration of resident epidermal kerationcytes, fibroblasts, dermal and micro-vascular cells from the wound margins into the wound bed. The PI3K: AKT1 and MEK1/2: ERK1/2 pathways are both involved in the regulation of cell migration and cancer.

In a study to investigate maggot secretions-induced cell migration, human micro-vascular epidermal cells were used for wound healing assay [32]. It was observed that maggot secretions significantly increased micro-vascular epidermal cell migration when compared to control group. Specific inhibitors of the protein kinases AKT1 and ERK1/2 were added to culture medium to assess the effect of maggot secretions on the PI3K: AKT1 and MEK1/2: ERK1/2 pathways. The PI3: AKT1 inhibitor partially blocked maggot secretion enhanced cell migration but there was no change with the MEK1/2: ERK1/2 inhibitor. It was concluded that the activation of AKT1 by maggot secretions plays a role in the wound healing effects.

CANCER TREATMENTS AND CASE STUDIES USING MAGGOT THERAPY

Successful use of Maggot Debridement Therapy (MDT) has been reported in ulcerating tumors. Ulcerating tumors also known as fungating wounds or malignant wounds begin when a tumor growing under the skin breaks through the skin's surface [33]. They are rare in people with cancer but usually develop from breast cancer, head and neck cancer or even melanoma.

Weil et al. of the school of medicine at the University of Pittsburgh, USA observed very weak defense of malignant tissue against the activity of the larvae in two inoperable ulcerating carcinomas of the breast and two sarcomas. The larvae attacked almost any type of abnormal viable structure, notwithstanding devitalized soft or bony tissues. With maggot therapy, malignant tissue was cleared away, clean healthy granulations appeared, the odor disappeared, the pain was relieved and the wound attempted to close [3]. Besides, they never witnessed any detrimental action of the larvae upon normal viable human tissue.

In 1985, Bunkis et al. reported a case of necrotic facial tumor that was infested with maggot larvae when the patient was first presented for treatment [34]. The wound contained several blowfly larvae on examination but no evidence of surrounding cellulitis or palpable adenopathy. The tumor was confirmed to be a squamous cell carcinoma. They decided to continue the wound management with the resident maggots. The wound was found to be clean and void of any necrotic residua by the third day.

In United Kingdom, sterile larvae were used in the management of squamous cell carcinoma of an 80-year-old ex-miner [35]. Despite chemotherapy, radiotherapy and conventional dressings, the wound from the tumor continued to deteriorate until maggot therapy was applied. It was concluded that maggot therapy might have a role to play in the effective management of some types of malignancy.

Gericke et al. in Germany reported the management of a post exenteration orbital infection from a malignant extrapleural solitary fibrous tumor in an 82-year-old man by the use of sterile maggots [36]. Due to an infection of the urinary tract and a transient ischemic attack, the patient's general condition worsened leading to pus-filled wound secretions despite conventional treatments and antibiotics. With the use of maggot therapy together with the systemic antibiotic therapy, the orbit was free of purulent secretion in about a week.

In United States, ulcerating tumor from Kaposi's sarcoma of a 26-year-old Hispanic male also diagnosed with HIV was treated using MDT [37]. It was observed that maggot therapy helped debride, disinfect and heal the Kaposi's sarcoma wound. As a result, amputation and potential death as an outcome of severe infection was evaded and time was allowed for chemotherapy and anti-HIV medications to be effective in the patient. The study postulated that malignant wounds are worthy candidates for MDT since tumors are known for neovascularization leading to areas of high vascularity in and around the tumor and it can aid control infection, moderate odor and circumvent possibly deforming surgeries even if wound closure was not accomplished [37].

In Poland, a recently reported case of what was suspected to be massive basal cell carcinoma of face, forming large ulcer covering most of right side of face in neglected 80 years old female. Maggots covered the ulcer, although it was not advised to use

therapeutic maggot in this case due to the eye socket and facial cavities involvement, but surgeons believed that natural maggot infestation had removed cancer tissues enabling the patient to stay a life [38].

CONCLUSIONS AND FURTHER RESEARCH

Maggots till date are unable to cure cancer, however they can effectively diminish the necrotic mass, decrease wound drainage and control odor resulting from necrotic tumors. Managing these complications with maggot therapy has enhanced the quality of life of many patients with inoperable cancer. Besides, infections have been better managed and deforming surgeries like amputations averted.

Further studies of maggot biology and biochemistry are therefore needed especially in the areas of having a better understanding of its mechanism, characterization of the active substances from maggot secretions and possibly, its use in the regulation of cancer.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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