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The Combination of Polyphenol and G-90 Glyco Lipoprotein in *Pheretima Aspergilum* as a Promising Modality in Accelerating Cancer Wound Healing

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ABSTRACT

Cancer-related wounds are still one of the healing challenges that are still faced by various health practitioners, where these wounds are often unsightly and associated with foul odor, drainage, and bleeding. Wounds caused by malignant tumors have a wide range of symptoms and severity, thus there is no treatment that has been demonstrated to be able to relieve them effectively. The use of wound dressings, which have antibacterial advantages and are helpful for treating wound infections as well as preventing wound contamination, is one method of wound care. Natural substances known as polyphenols, which are often created by plants, have potential antibacterial and antioxidant properties. G-90 is a mixed macromolecular substance with glyco-lipoprotein properties that aids in tissue regeneration in vivo, particularly when it comes to wound healing. Plenty of flavonoids are present in the polyphenolic chemicals produced by necklace worms (Pheretima aspergillum). Flavonoids contribute to the formation of cross-links with collagen, which can have the impact of accelerating wound healing and the decline in inflammatory cells like macrophages. In this situation, Pheretima aspergillum, which has G-90 glyco-lipoproteins and polyphenols, may be useful for healing malignant wounds.

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INTRODUCTION

Cancer-related wounds continue to provide difficulties for various healthcare professionals in terms of healing. These malignant wounds, which are frequently brought on by leaks, discomfort, and unpleasant odors, will have a negative effect on the patient and carers. It's been said that experiencing a malignant wound was emotional, upsetting, and unforgettable. Patients and caregivers may experience extreme agony as a result of malignant wounds.[1,2]

In some instances, discharge from a non-healing wound followed by an unpleasant odor, bleeding, nearby inflammation, and excruciating pain creates a condition with few alternatives for therapy and a very poor prognosis. Currently, there are a wide variety of modalities, approaches, and wound dressings for cancer wound treatment. But despite the numerous papers, there is still no effective method for wound care.[2]

Living things called earthworms are occasionally despised by humans. Recent studies have shown that this discarded animal has a variety of health benefits and is used in traditional Chinese medicine. It is thought that earthworms can treat a variety of ailments by acting as anticoagulants, anticancer agents, and antimicrobials.[3]

This article will go over how using earthworms as a potentially effective method of treatment for cancerous wounds

MALIGNANT WOUND

Malignant tumors that involve the skin and subcutaneous tissues are frequently unappealing and come with a foul odor, discharge, and bleeding. It is expected that a skin-penetrating tumor will result as a malignant fungal wound, which is frequently mistaken for an infection or an abscess. Malignant tumors are hence frequently confused when making medical decisions, such as premature closure, representativeness constraint, Sutton's slip, and anchoring. This typically happens in aggressive, locally progressed malignancies. These tumors may appear fungal or

ulcerative, and they frequently include excoriation of the skin around them. As a result, there may be an unpleasant odor, fibrinous exudate, profuse purulent exudate, bleeding, or pain. These clinical findings may be misleading to first-line providers, who are used to treating common infections such as abscesses or cellulitis, which can have a similar appearance to certain tumors.[2,3]

Wounds from this malignant tumor occur when cancer cells that attack the epithelium, infiltrate the blood vessels and lymph nodes to penetrate the epidermis. This causes loss of skin vascularization and nutrition, causing tissue death and necrosis. The lesions may be the result of primary cancer or metastases to the skin.[3]

In this case, wound care due to malignant tumors is very important and needs attention. The main goal of wound care due to malignant tumors is wound healing that can be switched to a palliative approach, focusing on three principles.[3] The first rule is symptom control, followed by wound care and, if possible, therapy of the underlying tumor.[3,4]

When it comes to treating malignant wounds, there is a need for education to set realistic expectations, for the tumors to be treated and removed, and for the stigma associated with non-healing wounds to be eradicated. In addition to concentrating on controlling the discomfort brought on by these wounds, the management of wounds brought on by malignant tumors, foul odors, and exudate must be addressed. Prioritizing patient comfort and quality of life in the care of this wound is necessary.[5]

Since malignant tumor-related wounds can have a wide range of symptoms and severity, there is currently no established treatment that can effectively relieve symptoms. The therapy for these wounds must be chosen based on the patient's situation and clinical condition because of their varied nature. In order to maximize mobility, wound dressings often consist of a thin, absorbent material that can handle significant amounts of discharge, evaporate fluids, and solve odor and microbial development issues. During the dressing change procedure, the patient frequently experiences pain and discomfort.[4] Wound debridement is another treatment modality but must be used with caution as debridement can cause unnecessary pain to patients whose life expectancy is limited. Several studies investigated the efficacy of using topical antimicrobials such as metronidazole in the management of odor in wounds due to their efficacy in killing anaerobes.[6,7]

CANCER WOUND HEALING

Wound healing is a dynamic process which consists of several phases, the first phase is the inflammatory phase which is then followed by the epithelial cell proliferation phase and ends by the tissue remodeling phase.[5] In normal tissues, the inflammatory phase is limited, lasting only 3-14 days. The injury triggers the tissue to rapidly destroy neutrophils, which are then coated by macrophages and lymphocytes. Leukocyte infiltration plays a major role in the secretion of inflammatory cytokines, growth factors, and chemokines, which stimulate progenitor cell proliferation and eliminate keratinocytes and endothelial cells. At this proliferative stage, granulation tissue is formed, angiogenesis is induced, and the new extracellular matrix (ECM) is formed. Epithelial cells undergo epithelial-mesenchymal transition (EMT) and migrate to the wound edges to provide damaged tissue re-epithelialization. In the final phase of wound healing, the maturation phase, wound contraction, and differentiation of fibroblasts into myofibroblasts which will then produce scar tissue. Failure to resolve the inflammatory phase will result in inappropriate tissue remodeling and is usually associated with impaired wound healing such as diabetes mellitus, pressure necrosis, and vasculitis. [6-8]

Chronic inflammation is also frequently associated with tumorigenesis, tumor progression, and metastasis in many different cancers. The tumor microenvironment forms many features of chronic wounds. Leukocytes that infiltrate the tumor and stroma will stimulate tumor growth, invasion, and angiogenesis. Tumor-associated macrophages (TAM), tumor-associated dendritic cells (TADC), and tumor-infiltrating lymphocytes are sources of pro-inflammatory mediators in the tumor microenvironment. In addition, external stimuli, such as hypoxia and DNA-damaging agents, give rise to tumor cells secreting chemokines that recruit pro-tumor inflammatory cells and help mount a pro-tumor immune response.[6]

Currently, new strategies in wound care are being developed to reduce hospitalization costs and provide an effective healing process and long-term relief.[6] The goal of any chronic wound care is to control infection if present, through antimicrobial agents, but the biomaterial must also have the right mechanical properties, be biocompatible and non-toxic, remove excess exudate, be easily removed without causing trauma, create the right moisture balance to promote healing. , provides a matrix for cell migration, as well as stimulates extracellular matrix deposition.[7]

Wound dressings with antimicrobial benefits are a must in wound care, this is useful for preventing wound contamination and treating wound infections by protecting wounds from microbial penetration and killing microorganisms that appear. On the other hand, antimicrobial dressings must also be able to enhance the healing process by inducing fibroblast migration.[8] Currently, in an effort to enhance antimicrobial properties along with reducing antibiotic resistance, different natural compounds (inorganic compounds, honey, plant compounds, and natural polymers) and micro to nanoparticles are being studied as potential antimicrobial agents for inclusion in wound dressings. Although the search for natural antimicrobial compounds was in response to the need to find effective

alternatives to traditional antibiotics and enhance the antimicrobial potency of wound dressings, there is also a growing interest by researchers to better understand the benefits of the antioxidant activity of certain natural formulations on wounds. In fact, these agents are also valuable in reducing oxidative stress in chronic wounds.[9-10]

POLYPHENOLS

Polyphenols are natural compounds that are normally synthesized by plants, which are useful as phenolic substances with reported bioactivity to trigger oxidative and inflammatory stress, which can alter the digestion of macronutrients and exert probiotic-like effects on the gut microbiota.[11] Polyphenol compounds can be found in almost all parts of the plant involved in attracting pollinators, performing structural functions, defending against ultraviolet radiation and protecting plants against microbial and herbivore invasions.[11,12]

Recently, polyphenolic compounds have attracted great attention from researchers for their use in the treatment of wounds because of their antimicrobial, regenerative and antioxidant properties. These compounds are usually extracted from plants and marine organisms.[12] There are more than 8000 different polyphenols described in the literature, which are divided into two main subgroups namely flavonoids (for example, flavonols and anthocyanidins) and non-flavonoid compounds (for example, phenolic acids, tannins and lignans). In general, polyphenols are known to have high antioxidant activity, providing protection against ROS through neutralization of free radicals by donating electrons or hydrogen atoms. Some polyphenols also have antimicrobial activity against certain bacteria present in chronically infected wounds. Although the mechanism of antimicrobial activity of polyphenols has not been fully elucidated, it is believed that it may be related to their destructive properties of the bacterial cell wall via the hydrophobic components of phenolic compounds, alteration of intracellular function by hydrogen bonding of bioactive compounds, or to modification of the cell wall rigidly by loss of integrity due to interactions. different from the cell membrane.[12] For that reason, polyphenols with lipophilic characters can increase the effect on antimicrobial activity. In addition, the antimicrobial potency of polyphenols has been reported to be highly significant against antibiotic-resistant strains, such as methicillin-resistant S. aureus.[13]

Polyphenolic compounds that have antimicrobial and antioxidant potential, it is believed that these compounds can be great bioactive agents to be included in wound dressings for chronic wound care. There have been several studies that validated the use of polyphenols with antioxidant or/and antimicrobial properties to accelerate wound healing.[11] Thymol, a polyphenol, incorporated into different wound dressings, such as films and hydrogels, reveals great results as a promoter of wound healing. Besides that, polyphenolic compounds in the form of kaempferol, chlorogenic acid, resveratrol, and ferulic acid are some examples of phenolic compounds with great antioxidant properties to promote wound healing in chronic wounds. Tannic acid is a tannin with interesting properties, such as antioxidant, antiviral, hemostatic, anti-inflammatory, anticarcinogenic and antimicrobial activities.14

G-90 GLYCO LIPOPROTEIN

G-90 is a mixed macromolecule compound with glyco-lipoprotein characteristics. G-90 exhibits many important biological functions in cell proliferation and adhesion. This compound also has fibrinolytic and anticoagulant activity. As a fibrinolytic and anticoagulant, G-90 can participate in the active maintenance of homeostasis, where this compound can stimulate the cellular immune system with molecules (adhesin-integrins) from the immunoglobulin superfamily. G-90 also contains molecules that in vivo help in the process of tissue regeneration, namely in terms of wound healing. Several studies have shown that G-90 can stimulate the growth of fibroblasts and epithelial cells and provide antioxidant activity, both of which can play a role in tissue repair.[15]

G-90 plays a role in several component compounds such as insulin-like growth factor, immunoglobulin-like growth factor (Ig-like), two serine peptidases of tyrosine and the EGF code. Studies have shown that G-90 contains insulin-like growth factor (IGF) with a molecular mass between 14 and 95 kDa. Analysis from SDS-PAGE separated this compound into six fractions antigenically similar to insulin to induce cell proliferation in vitro. G-90 also contains immunoglobulin-like molecules. By affinity chromatography of the 45-kDa fraction named G-90/4. This fraction stimulates cell proliferation in nanogram amounts, but in higher amounts (micrograms) it causes cell lysis. Using immunohistochemical analysis, it was shown that G-90/4 acts as an adhesion molecule. It is involved in signal transduction pathways for the synthesis of biologically active molecules. G-90 exhibits strong fibrinolytic and anticoagulant activity. Of the G-90 mixture, two serine (PI) and tyrosine-like (PII) peptidases, which have molecular masses of 34 and 23 kDa, respectively. The fibrinolytic and mitogenic activity of PIs is much stronger than that of PII.[16]

G-90 is also believed to be able to stimulate and increase EGF in less than 24 hours after injury. This growth factor increase will lead to increased proliferation of fibroblasts and epithelial cells resulting in an increase in the wound healing process. Results in other studies regarding the antioxidant and antibacterial properties of G-90 in certain concentrations show that G-90 can inhibit inflammation so that it will repair scar tissue. G-90's healing potential together with the use of other biochemical,

microbiological, and biomedical properties could be candidates for targeted treatment of human wound healing.[17]

PHERETIMA ASPERGILUM

Earthworms are animals that live in the soil and can also be found in piles of garbage, these animals spend a lot of time in the soil. Earthworms are low-level animals because they have no backbones (invertebrates) and soft bodies. This animal is classified as annelid because it has ring-shaped segments all over its body. Each segment of the body has short, hard hairs called chaeta. Annelids are grouped into the Polychaeta, Hirudinea, and Oligochaeta classes, the difference between the 3 classes is the number of segments and setae.[18]

The use of earthworms as a medicinal ingredient has been reported with the advantage of being more natural, so it is safe for consumption. Earthworms are also widely used in traditional Chinese medicine. Based on their pharmacological effects, earthworms are known to have various activities, such as anticoagulant, anticancer, antimicrobial, and if further developed, it is possible to be used as a therapeutic agent for various diseases. Empirically, earthworms have been reported to be efficacious in curing various diseases. In Chinese medicine, earthworms are also known to have anti-inflammatory, analgesic and antipyretic activities.[19]

As the worm regenerates its amputated body, the worm's segmented body cavity fills with coelomic fluid. This coelomic fluid is then used by many researchers in several studies. Coelomocytes, the leukocytes present in the coelomic fluid, are thought to be responsible for this effect because they contain proteins and glycoproteins that act as opsonins, agglutinins, lysines and certain factors, which mimic factors that inhibit macrophage cell migration.[18,20]

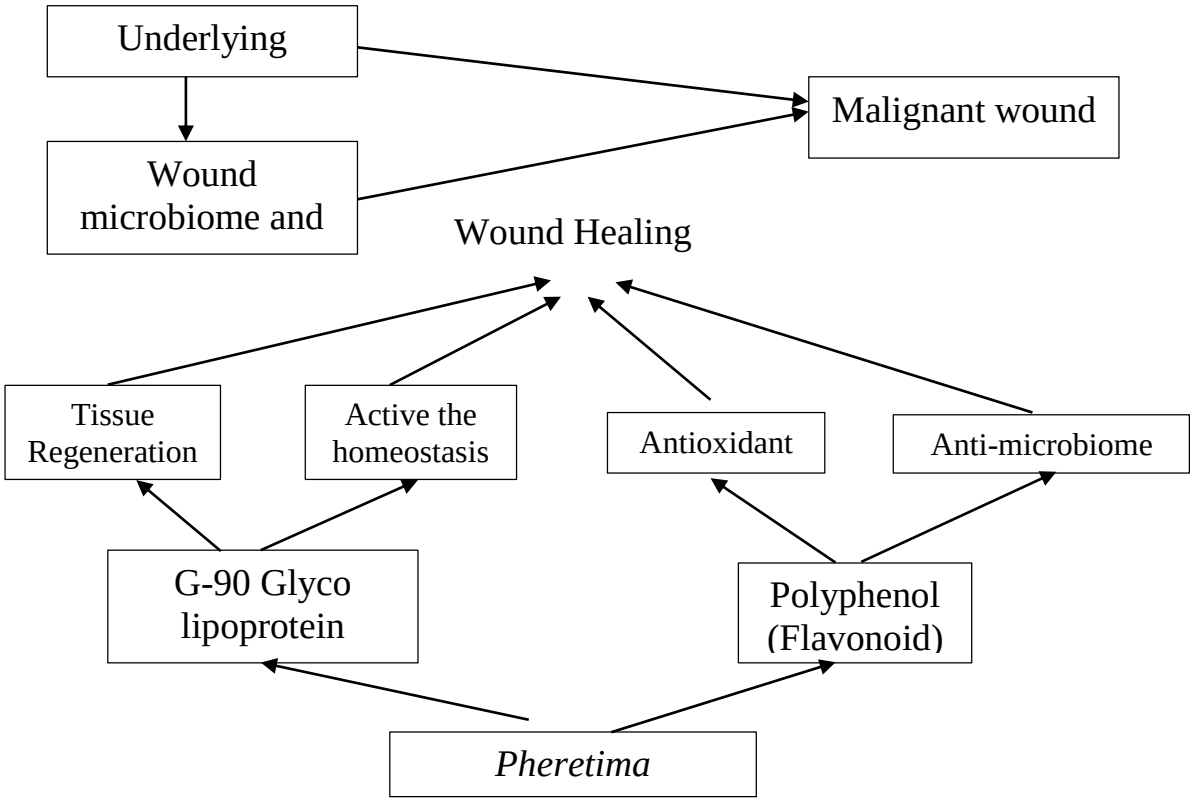

Figure 1. Diagram of the role of *Pheretima aspergilum* in cancer wound healing

Many studies document the benefits of coelomic fluid which has many biological activities such as hemolytic and agglutinative, as well as bacteriolytic and bacteriostatic. This fluid can act in in vitro growth of mammalian cells, regardless of cell type, as either a cytotoxic or a mitogenic agent. In addition, coelomic fluid acts as a mitogen for murine and human lymphocytes in vitro. In addition to their mitogenic and cytotoxic effects, bacteriostatic and bacteriolytic activities which are important for their life in the soil have also been observed.[20]

THE ROLE OF *PHERETIMA ASPERGILUM* ON CANCER WOUND HEALING

The polyphenolic compounds contained in the necklace worm (Pheretima aspergillum) contain lots of flavonoids, where these compounds can be effectively used as antioxidants, besides that they also contain antibiotics, anti-carcinogenic, antiviral, hypo-allergenic and anti-inflammatory. Flavonoids work by forming cross-linking with collagen, so they can have an effect on speeding up the wound healing process, speeding up the decrease in the number of inflammatory cells including macrophages.[21]

In recent research, in vitro and in vivo studies have been carried out regarding earthworm extracts, especially with the use of Pheretima aspergillum, which are known to have fibrinolytic enzymes (as antithrombotic and anticoagulant), polyphenols (as anti-inflammatory and antioxidant) and are secondary metabolites that are most widely used to treat diabetes. inflammation, G-90 glycolipoprotein (as a proliferation stimulant and antimicrobial) which contains immunoglobulin like growth factor (IgGF-I), epidermal growth factor, and serine protease (as fibrinolysis). Research conducted by Mardiati et al regarding the use of earthworm extract (Pheretima aspergillum) in treatment for diabetic ulcer healing based on axon density induction obtained the result that the content in earthworm extract can accelerate the wound healing process. In this study, the experimental animals were divided into 5 groups, namely the negative control group, positive control, topical, oral, and topical and oral treatment groups. It was concluded that the treatment group was given earthworm extract (Pheretima aspergillum) in the form of a topical paste with a concentration of 100 mg/ml can increase wound contraction and peripheral axon density in diabetic ulcers.[21,22]

Several studies have revealed that earthworm extract also has an antibacterial effect because it contains very high protein and symbiotic Streptomtomyces sp. which can produce the antibiotic streptomycin. Lysosomal enzymes in earthworms are effective in destroying bacterial cell walls and are also able to improve the body's physiological processes, in this case related to the role of peroxidase, catalase, and cellulase enzymes as previously done. Another benefit that has been proven is as a febrifuge or antipyretic due to the alkaloid class of compounds contained in earthworms of the types P. aspergillum and L. rubellus.[22,23]

CONCLUSION

Earthworms (*Pheretima aspergilum*) can be used as one of the modalities in wound care. Polyphenols and G-90 glyco-lipoprotein, which are found in earthworms, have the ability to limit bacterial development, reduce inflammation, and promote wound healing by quickening the epithelialization of wound closures. Further investigation is still required about the usage of Pheretima aspergilum in experimental animals and humans, even if it may be a potential treatment option for cancer wounds.

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