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Origin of Innate Immune Responses: Revelation of Food and Medicinal Applications

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ABSTRACT

Much is known about the strong ecological impact that earthworms (蚯蚓 Qiū Yǐn; *Pheretima*) have on soil in terms of fertility, nutrient production, and tilling. Even more interesting though is the impact they have had on our understanding of innate immunity, and from this discovery, there has been a simultaneous recognition of their potential through their historical use as food and their use in treatment of certain chronic health problems that often afflict humans. This bifurcating growing knowledge base has stemmed from centuries of honing and practicing traditional and complementary forms of medicine such as Ayurveda (India) Traditional Chinese Medicine (China), Kampo (Japan), and Traditional Korean Medicine (Korea). Earthworms (Dilong) have also been credited as a model for research concerning the nervous and endocrine systems. One of the reasons behind the earthworm's tremendous impact on research into these biomedical endeavors is partly due to its lack of ethical restrictions, like those imposed on vertebrate models. Using invertebrate models as opposed to mice or other mammalian models bypasses ethical concerns. Moreover, financial constraints consistently hover over biological research that requires living subjects, preferably mammals. Earthworms are a rich source of several vital biological macromolecules and other nutrients. They have long been used as food in several cultures such as the Ye'Kuana in Venezuela, the Maori in New Zealand, and the nomadic populations in Papua New Guinea. Earthworms and their nutritious products have been shown to exert significant effects in treating humans for disorders of inflammation and blood coagulation. One area that continues to be examined is the earthworm's ability to regenerate lost appendages, and these effects have been extended to mammals. Evidence reveals that earthworm extracts may actually promote the regeneration of damaged nerves. This presentation will explore how earthworms may reveal significant advances and conclusions that decipher innate immunity. This is intimately associated with them as sources of their various nutritional and medicinal benefits.

Key words: Complementary and alternative medicine, Earthworm, Innate immunity, Integrative medicine, Nutrition, Traditional Medicine

AN ORIGIN IN NUTRITION

We begin our exploration of innate immunity and nutrition by first looking at the use of invertebrates as food. Many cultures around the world such as the native tribes found in Venezuela, New Zealand, and Papua New Guinea have long consumed earthworms (蚯蚓 Qiū Yǐn; *Pheretima*) as a form of cuisine.[1] This initial use of earthworms as a substantial source of biological macronutrients provided the springboard from which analyses of medicinal applications have begun [Figure 1]. Earthworms have been found to

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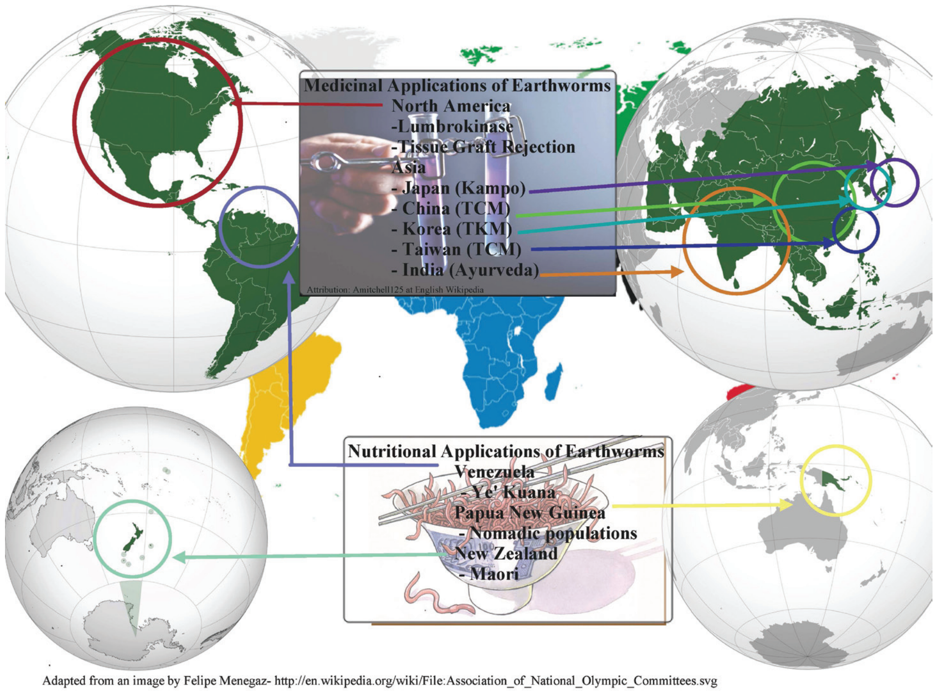


Figure 1. Graphical representation of the geographic distribution of medicinal and nutritional applications of earthworms. Traditional medicinal systems as well as tribal usage of earthworms are displayed

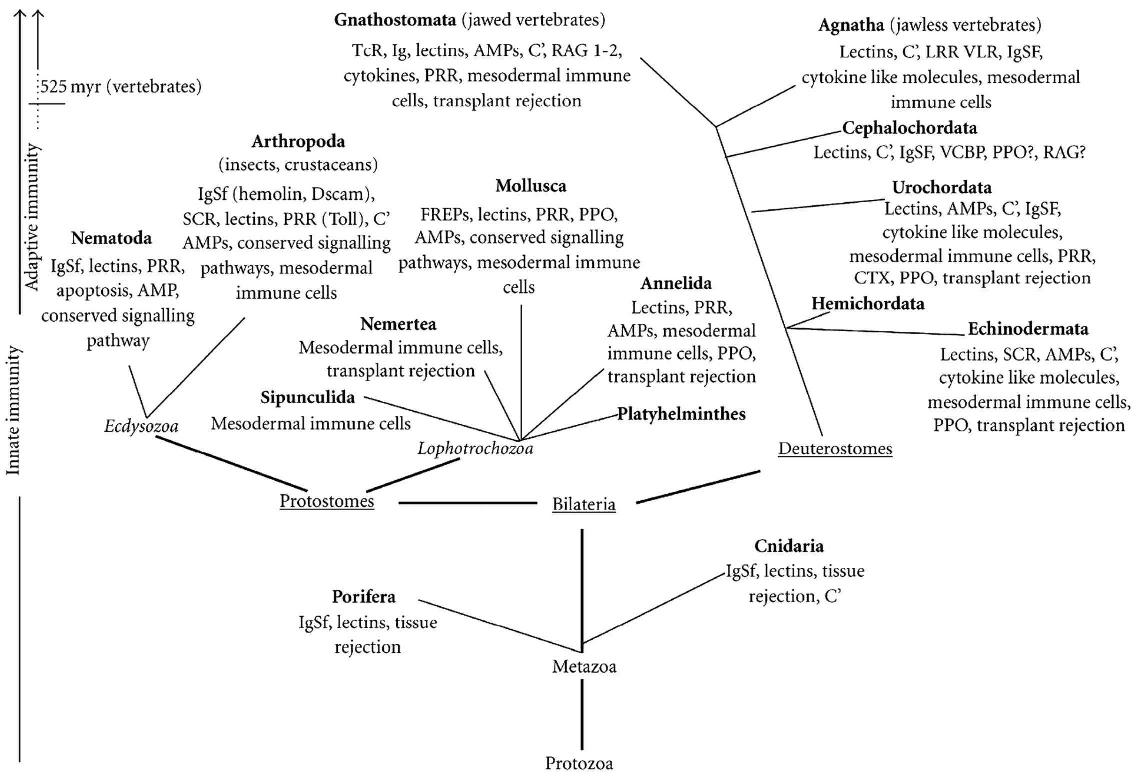
contain high levels of essential nutrients like amino acids, vitamins, and minerals.[2] Investigations into the diet of tribes of Amerindians in Venezuela yielded the conclusion that several invertebrate species are used as fundamental sources of protein, fat, and vitamins.[3,4] Only after depending on these organisms as sources of nutrition did a realization of medicinal and immunological benefit become evident. Initially, these primitive cultures did not view earthworms as potential sources of therapeutic benefit, but only as sustenance. In a recent publication, investigators found that 354 organisms are used in traditional Brazilian medicine and 157 of these are also used as food.[5] This is obviously not an antiquated practice. We will now examine immunity as it relates to these fascinating invertebrates where their contributions to understanding the origins of innate immunity for now far outweigh the credit accorded them as food.

ORIGINS OF THE INNATE IMMUNE RESPONSE

Introduction: Innate and adaptive immunity

At one point, the immune system and its analysis were largely limited to explorations of the humoral immune system. After the discoveries of phagocytosis by Metchnikoff, we now envision that cells are crucial components of the immune system. He found in starfish larvae as well as in the water flea *Daphnia* that phagocytic leukocytes crippled invading pathogens and elicited a powerful and ubiquitous response.[6] This discovery caused a dramatic paradigm shift to the dichotomous school of thought that exists in immunology today: cellular and humoral. Not only did this discovery revolutionize the central dogma of immunology, but also it brought to light the importance of invertebrate animal models in the study of immunology, as they possess this newly discovered, yet more primitive form of immunologic defense. It was only later through contributions from many diverse laboratories that immunity possesses two crucial arms that differ significantly. The innate immune system is natural, non-specific, non-anticipatory, non-clonal, germ line, and does not produce memory from past encounters. The adaptive immune system is acquired, specific, anticipatory, clonal, somatic, and allows for the production of memory from past encounters.[7]

The distinguishing factors between the two forms of immunity lie in their responses to foreign antigens as well as the classifications of organisms that they are associated with. Innate immunity produces non-directed, non-specific, and non-anticipatory responses, while adaptive immunity typically produces a directed, specific, and anticipatory response. As stated above, innate immunity was discovered in invertebrates, while adaptive immunity has always been associated with vertebrates exclusively [Figure 2].[8] It was later found that even vertebrates themselves employed innate immunologic mechanisms as well. While these two systems are different, they are not mutually exclusive in vertebrates; they interact with, depend on, and are undoubtedly intertwined with each other.[9-11] What will appear depends on the antigen but will certainly prime the host by activating and even finishing the future adaptive response. Some have proposed that innate immunity provides the immediate, yet weakened first response to foreign invasions until the more specific and more robust, yet slower adaptive immunity can take over.[12] Also, at least in vertebrates, there is evidence that the substances and even small molecules such as peptides and compounds produced and utilized by an innate immune response may induce changes in the type and constitution of the elicited adaptive response.[13] In many instances, the nature of the vertebrate innate immune response



AMP: antimicrobial peptides
C': complement pathway elements
CTX: cortical thymocytemarker in *Xenopus*
Dscam: drosophila homolog for Down syndrome cell adhesion molecule
FREPs: fibrinogen related peptides
IgSF: immunoglobulin superfamily
LRR VLR: variable lymphocyte receptors with leucine rich repeats
PPO: prophenoloxidase cascade
PRR: pattern recognition receptors
RAG: recombination-activating genes
SCR: scavenger receptors
VCBP: variable chitin binding proteins
TCR: T cell receptor

Figure 2. Evolutionary tree representing the emergence of specific immunological components. Innate immunity is observed among all members of the animal kingdom, while adaptive immune system is typically restricted to vertebrates. Some adaptive immune characteristics do appear in invertebrates, however. (Reproduced with permission from Kvell K, Cooper EL, Engelmann P, Bovari J, Nemeth P. Blurring borders: Innate immunity with adaptive features. Clin Dev Immunol 2007:836-71)

seems to parallel variations and combinations of the invertebrate immune response.[14]

Importance of innate immunity in invertebrates

There are three major reasons we are reviewing innate immunity in invertebrates: a quest for understanding, therapeutic possibility, and ecological importance. First, invertebrate animal models provide phenomenal alternatives for research. They are exempt from the significant ethical and practical considerations including expense imposed upon other animal models, e.g. mice. They offer vast opportunities for research and inquiries about the inner and uncharted workings of the innate immune system that can be applied to closely or even distantly related organisms. Because much of biomedical research today is only validated by medical practicality, and therefore conducted solely using human cells, invertebrate analyses are viewed as less valid.[15] This neglect of invertebrate models presents a significant problem to furthering, in this case, immunological investigations, and also to biology as a whole as we seek to understand more about the living world around us. Second, many of the extracts and products found in these animals exhibit therapeutic effects, observed both in the host organism as well as in others where these extracts have been applied. Any new treatments that can be derived from these animals must be explored to their fullest extent as we are always in search of new and possibly quality-of-life improving medicines. Third, as are all living members of the planet, invertebrates are linked and entwined with all others interconnected in our ecology. Studying one population of organisms sheds light not only on that particular species, but also on all the other species that it interacts with in its natural habitat. In fact, there are many invertebrate species, such as crustaceans, e.g. crabs, shrimp, that we as humans, as well as other predatory animals, use as sources of nutrition. This paper will examine the interdisciplinary importance that invertebrates, as exemplified by earthworms (蚯蚓 Qiū Yǐn; *Pheretima*), play not only in the analysis of immunology, but also in nutrition and medicine. In an attempt to attribute specificity to our exploration of this interesting topic, we will quickly review: 1) the earthworm as an ideal animal model for research in innate immunity and 2) various immunologic responses associated with the earthworm's immune system.

Earthworm immunity

The earthworm's importance in biology at large has been known since Charles Darwin's time. He examined *Lumbricus terrestris* and its role in tilling soil.[16] His publication explaining his experiments with worms actually outsold his more widely known book, *On the Origin of Species.* Stemming from this initial interest, we now know that earthworms have a much wider scope of application that is no longer limited to ecology, but most importantly includes immunology.

One common characteristic of all earthworm species is the presence of a celom or cell-lined body cavity. This celom houses the coelomic fluid, which also contains various types of leukocytes, even some that mirror vertebrate leukocytes.[17] These leukocytes and their products contribute to and guide immunologic responses via various mechanisms including opsonization, inflammation, phagocytosis, agglutination, mitogenesis, lysis, and transplant rejection.[18-25] Typically, leukocytes are associated with immunologic responses involving phagocytosis and intercellular communication.[26] In contrast, leukocyte products are associated with pathways involving lysis, agglutination, and phenoloxidase/peroxidase systems.[27-31]

THERAPEUTIC PROPERTIES OF EARTHWORMS: HOW DO THEY FIT THE CONCEPT, PRACTICES, AND PROPERTIES OF TRADITIONAL CHINESE MEDICINE AND AYURVEDA?

Ayurveda, a traditional medicine that originated in India, has been practiced since mid 2000 BC.[32] This ancient medicine encompasses countless treatments and procedures that have been proven to work over the many years that this system has grown. Earthworms (蚯蚓 Qiū Yǐn; *Pheretima*) especially are used to explore this school of thought, and have shed light on certain biological functions as well as accepting the necessity of integrative medicine.[32] Some significant work in this discipline was supported when Balamurugan experimented on rats treated with earthworm extracts and pastes (no distinctions between the two made).[33] He found therapeutic anti-inflammatory, antioxidative, hematological, and serum effects (changes in enzyme concentration and regulation) in rats exposed to the earthworm paste.

Traditional Chinese Medicine (TCM), which is probably better known and engrained in the common conception of traditional medicine, also has long relied on the earthworm.[34] According to *The Eu Yan Sang Heritage: An Anthology of Chinese Herbs and Medicines*, the earthworm is typically associated with coldness. It is purported to affect the bladder, liver, and spleen "channels," inhibit spasms, decrease heat-toxins, soothe wheezing, and increase urination. Some symptoms that it was commonly used to treat are high fever, seizures, joint inflammation, chronic cough, urinary impairment, and hypertension.[35]

Antioxidative characteristics

Antioxidants protect other chemicals of the body from damaging oxidation reactions by reacting with free radicals and other reactive oxygen compounds that may form, thus hindering the process of oxidation. There is currently a limitation where only one free radical can react with only one antioxidant molecule. Earthworm extracts have been demonstrated to exhibit extremely potent antioxidant activity since they are able to donate electrons to reactive free radicals, stopping them from reacting with and damaging the surrounding tissues.[36] Earthworm tissues have been found to contain large concentrations of antioxidants like glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD).[37] Tissue homogenate extracts from *Eisenia fetida* containing glycolipoprotein (G-90) actually possess antioxidative, tissue-healing properties.[38] In albino rats, the extract of the earthworm, *Lampito mauritii*, actually promoted liver antioxidants such as GSH, GPx, CAT, and SOD, while inhibiting their peroxidation.[33]

Antiulcer activity of earthworms

Somewhat related to the antioxidative properties, earthworm extracts possess antiulcerative properties. Stomach pain is associated with the common clinical syndromes known as organic and functional dyspepsia. Organic dyspepsia can be caused by peptic ulcer disease, or the condition of forming painful sores in the gastrointestinal tract. Research conducted over the last 25 years is providing breakthrough insights in the pathophysiology and treatment of gastric and duodenal ulcers. The antioxidants promoted by earthworm extracts (from the same species, *La. mauritii*) also prevent free radical wear on the gastrointestinal mucus membranes in albino rats. These extracts also help to decrease acidity in the stomach by inhibiting the release of acidic secretions.[39]

Anti-inflammatory activity of earthworm paste or extracts

Inflammation includes vasodilation, extravasation, production of chemokines and cytokines, and recruitment of leukocytes to the damaged tissue. These responses are some of the mechanisms that the immune system uses to destroy foreign pathogens, and have been found to be inhibited by some earthworm extracts. Derivatives of *La. mauritii* containing petroleum decreased edema as well as exudates in albino rats where inflammation had been induced.[33,40] In this experiment, rats were given indomethacin (a standard anti-inflammatory drug), acetaminophen (a standard antipyretic drug), and earthworm extract. The results showed that when these three treatments were combined, the rats returned to ordinary conditions in a dose-dependent manner. In these same rats, anti-carcinogenic activity was also observed. The researchers hypothesized that the antioxidative molecules within the earthworm extracts were also responsible for anti-inflammatory, anti-pyretic, and anti-carcinogenic properties. The true composition and mechanism are unknown and await detailed analyses.

Anti-carcinogenic effects of earthworm extract

In vertebrates including humans, there are numerous benign and malignant cancers that can involve any part of the body. Their pervasiveness and devastation throughout society shows the pressing need for preventing and treating cancerous symptoms. In the same albino rats mentioned earlier in this section,[33,40] induced granulomas were also stunted by exposure to earthworm extracts. Many other investigators have confirmed these results and also found similar properties in various earthworm species [Table 1].[41-44]

Antibacterial activity of the coelomic fluid of earthworms

Antibiotics are substances that kill or inhibit bacteria, e.g. growth, by any of several mechanisms that specifically target the bacterial cell. Earthworm extracts, especially the coelomic fluid are potent against some pathogenic and nonpathogenic bacteria such as *Escherichia coli, Streptococcus pyogenes, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Salmonella enteritidis.*[36] Specifically, *Eisenia andrei* coelomic fluid displayed antibacterial properties against *Bacillus megaterium.*[45,46] G-90, the anti-carcinogenic molecule mentioned earlier, also possesses demonstrable antibacterial activity against *Str. pyogenes, P. aeruginosa, Sta. aureus,* and *Sa. enteritidis.*[47] There are the bacteria that infect patients in hospitals and cause intractable sepsis. Methicillin-resistant *Sta. aureus* (commonly known as MRSA), which is typically acquired in hospitals, is largely a product of overuse of antibiotics.[48] By using novel sources of antimicrobial substances like G-90, it seems that the potent activity of certain earthworm products could be tried in an attempt to stifle or control this microbial menace.

La. mauritii, the earthworm associated with several therapeutic applications as discussed earlier, also possesses antimicrobial properties. Balamurugan tested these qualities against eight common species of human pathogenic bacteria and eight species of fungi by employing the disk diffusion method (a technique for assessing the susceptibility of certain microbes to specific antimicrobial substances).[49] The extract of *La. mauritii* proved successful against four Gram-negative species of bacteria, *Es. coli, P. aeruginosa, K. pneumoniae,* and *Vibrio cholerae* and four Gram-positive species of bacteria, *Sta. aureus, Streptococcus pneumonia, Staphylococcus epidermidis,* and *Bacillus subtilis*. This extract also exerted fungicidal activity against four yeast-like fungi, *Candida albicans*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis*, one dermatophytic fungus, *Trichophyton mentagrophytes*, and three mold-like fungi, *Aspergillus niger*, *Aspergillus flavus*, and *Aspergillus fumigatus*. On in-depth exploration, these extracts were found to contain phenolic and humic (components of organic matter found in dirt and sediment) substances found in earthworms previously and the antibacterial and antifungal activity was supported by further evidence.[50] The finding that earthworm extracts prove effective as antimicrobial substances against a broad range of bacteria and fungi demonstrates just one of their many potential benefits as therapeutic agents.

Anticoagulative properties of earthworm extracts

G-90, the same glycolipoprotein extract that has anti-carcinogenic and antibacterial properties, also exerts anticoagulative and fibrinolytic activities.[51] From this extract, P I and P II (serine proteases) have been isolated and shown to dissolve blood clots in cancer patients.[52] Popoyic *et al.* demonstrated the same effect in dogs with cardiac disease and cancer.[53] Kim *et al*. also showed this anticoagulative property when orally administering extract from *Lumbricus rubellus* to rats.[54]

Hepatoprotective activity of earthworm extracts

In terms of hepatoprotective activity of earthworm extracts, it seems that these substances not only exert antioxidative properties, but also may regulate the expression of specific genes. In an experiment performed by Balamurugan, the efficacy of *La. mauritii* extract was tested against silymarin, a common hepatoprotective drug, in rats where liver injury had been induced by acetaminophen.[49] The particular damage induced in the rats caused a decrease in liver antioxidants and an increase in serum enzymes like alkaline phosphatase, glutamate oxalate transaminase, and glutamate pyruvate transaminase, as well as in bilirubin and liver lipid peroxidation. When treated with either silymarin or earthworm extract, these effects were reversed. This suggests that not only does earthworm extract promote antioxidative molecules that protect liver cells from free radical degradation, but also it regulates the expression of genes controlling the production of specific enzymes that affect the reactivity of molecules within the liver.

Lumbrokinase

Lumbrokinase is a specific molecule that can be extracted and purified from earthworms and has significant benefit. It has been extracted and purified from the earthworm *Lu. rubellus* and found to contain six proteolytic enzymes.[55] In the presence of fibrin, it shows antithrombotic activity which is of particular interest to patients who consume medications that may induce thrombosis. No negative side effects on the kidney and liver or carcinogenic effects have been observed in rats. In addition to these encouraging results, there were no deleterious effects on blood glucose and lipids.[51] More specifically, lumbrokinase is touted to have other beneficial effects as follows: 1) reduces blood clots and guard against ischemic heart disorders and stroke; 2) decreases fibrinogen concentration in cancer patients, which greatly reduces the risk of metastasis, slows the growth of tumors, and promotes overall better outcomes; 3) assists in degrading bacterial biofilms during chronic infections in patients suffering from autism and Lyme disease; and 4) regulates hypercoagulation. One of the most significant effects to be noted here is that it lowers the levels of fibrinogen. Fibrinogen, which induces hypercoagulation, is a common symptom associated with some cancers and is a side effect of chemotherapy. There has been growing evidence that reducing the amount of fibrinogen and, therefore, the severity of

Table 1. Anti-carcinogenic activity of earthworm extracts on mammalian tumors[41-44]

Molecule	Effect	Species	Reference
Lombricine	Restricts proliferation of mammary tumors in SHM mice.	*Lumbricus terrestris*	Nagasawa *et al*. 1991
G-90	Slows tumor growth in mice.	*Eisenia foetida,*	Hrzenjak *et al*. 1992
	Promotes mitogenesis on human fibroblasts, cervical carcinoma, and pancreatic carcinoma	*Lumbricus rubellus*	Hrzenjak *et al.* 1998
Glycoprotein	Cytotoxicity to several tumor cell lines	Eisenia foetida	Xing *et al.* 1997

hypercoagulation in cancer patients or former cancer patients will reduce their chances of recurrence.[56]

Since their discovery, the genes that code for this fibrinolytic enzyme have been identified, cloned, and characterized.[57] After identifying and characterizing a lumbrokinase gene found in *Ei. fetida*, Li *et al*. expressed it within *Es. coli* and were able to reproduce the original fibrinolytic activity. Lumbrokinase offers immense potential for use as a medication if this molecule can be manufactured on a large scale, and is worthy of more extensive research.

ANALYSES OF NERVE REGENERATION

Slightly different than what we have discussed above, there have been several demonstrations of earthworm extract effects that aid in regeneration of nerve cells. In TCM, the earthworm (Dilong) has long been used as a source of treatment for several ailments including spasms, stasis, and seizures. Noting this as well as the earthworm's ability to regenerate severed appendages, it is no wonder that the *Lumbricus* extract displayed the ability to promote regeneration in damaged nerves in rats.[58] Moreover, earthworm extracts have been shown to promote survival and proliferation of Schwann cells via insulin-like growth factor-I signaling pathways [Figure 3].[59] Various other studies have supported these findings and built upon them, notably when the earthworm, *Pheretima aspergillum*, was found to promote PC12 (a common rat cell line that sheds light on the mechanisms of neuron differentiation) cell differentiation and the production of new axons after peripheral nerve damage.[60,61] This proves to be particularly important for patients with neurological diseases where nerves degenerate or in patients with spinal cord injury. If we can isolate a molecule that can reverse this effect, the treatments would be revolutionary.

OTHER MEDICINAL MOLECULES EXTRACTED FROM EARTHWORMS

In this section, we will discuss several other specific molecules found in earthworm extracts that exhibit medicinal qualities, but have not been subjected to initial clinical trials. Fetidins extracted from *Ei. fetida*, which are heat-labile, polymorphic, and multifunctional proteins, cause cytolysis, antimicrobial functions, and increased blood clotting.[62] Another molecule isolated from the celom of *Ei. fetida* is hemolysin (or EFAF), which was hypothesized to bind antigen.[63] This proposal was significant since it revealed that earthworms (蚯蚓 Qiū Yǐn; *Pheretima*)might be able to affect a primitive form of adaptive immunity, as the ability to bind antigen is typically limited to only vertebrates. However, Rejneck *et al.* suggested that this protein was not a homolog of the vertebrate IgE.[64] Eiseniapore and lysenin have been isolated from *Ei. fetida* which show lytic

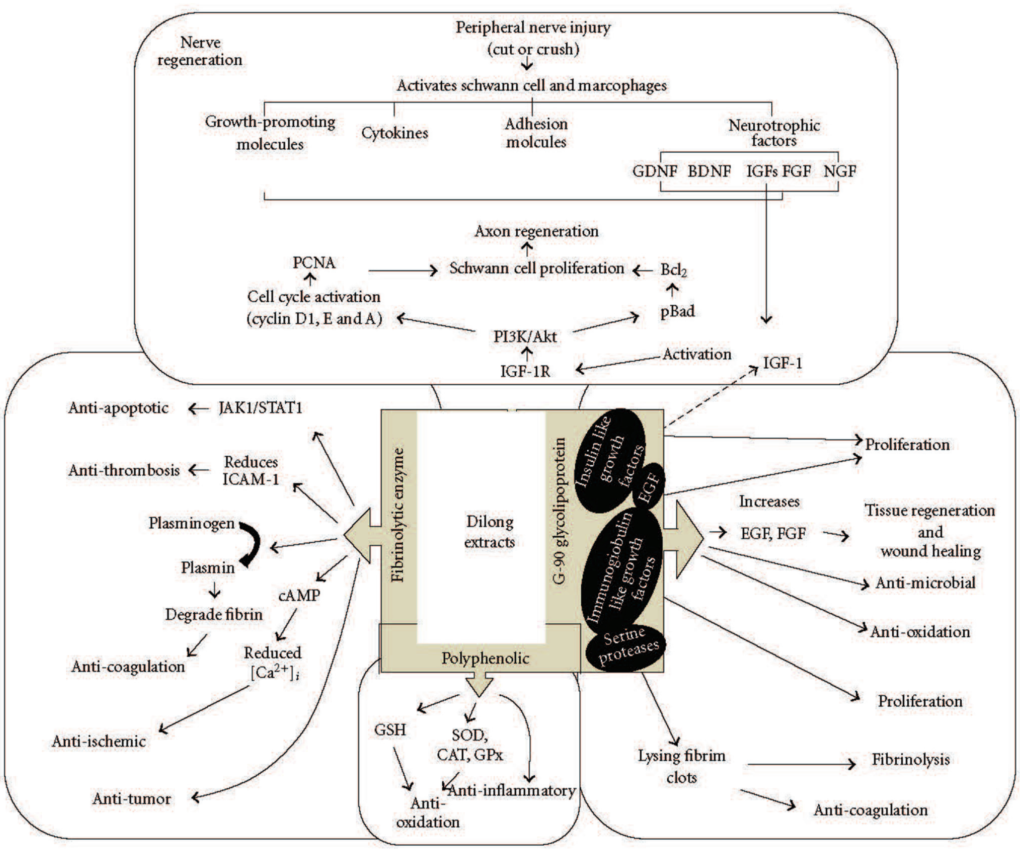


Figure 3. A summary of the various therapeutic effects exerted by the application of earthworm extracts. (From: Chang Y, Kuo W, Lai TY, Shih YT, Tsai FJ, Tsai CH, Shu WT, Chen YY, Chen YS, Kuo WW, Huang CY. 2009. RSC96 Schwann cell proliferation and survival induced by Dilong through PI3K/Akt signaling mediated by IGF-I. Evidence Based Complementary and Alternative Medicine 2011:1-9)

activity and hemolytic properties by the mechanism of binding sphingomyelin in cellular membranes.[65,66]

CONCLUSION: A NECESSITY FOR INCREASED RESEARCH CONCERNING MEDICINAL BENEFITS OF EARTHWORMS

Much of the research done on earthworms (蚯蚓 Qiū Yǐn; *Pheretima*) has focused on their immune capacity and ecological impact, specifically on soil. As we turn to the earthworms' use as a modern source of food and as a medicine, we note their high protein content, and accordingly their consumption by many organisms denotes considerable nutritive value. However, not only do they provide valuable dietary components, but also they possess medicinal properties. Alves and Ierecê call this discipline "zootherapy" and stress its importance in a wide range of other disciplines such as ecology, culture, economy, and public health.[67] The limited biomedical approaches presented herein offer an incredible starting point from where we must continue using these amazing invertebrates. It is in this realm that we must forge on and discover new ways to utilize and appreciate the enormous potential of this animal.

PERSPECTIVES AND FUTURE DIRECTIONS

While this paper focuses on the nutritional and immunological benefits of invertebrates, especially the earthworm, other animals such as insects, fish, and mice are widely utilized as research models. A recent statement published by the *BBC* explains the significant usage of these models because of their rapid reproduction, simplicity, and genetic similarity to humans.[68] These animals have helped not only to shed light on an incredible amount of genetic, developmental, and environmental understanding that they afford, but also for appreciating similar biological mechanisms in humans as well. The utility of experimentation using varied animal models cannot be overstated. Leeches, honeybees, maggots, and tunicates have also proven to be highly useful in biomedical research.[69]

Similarly, the UN's Food and Agriculture Organization (FAO) recently released a statement endorsing the use of insects as nutrients in places of the world where malnutrition runs rampantly. The FAO boasts that insects contain significant amounts of vital nutrients and minerals such as protein, fiber, calcium, copper, iron, magnesium, manganese, phosphorus, selenium, and zinc. Besides their nutritive benefits, they also offer environmental benefits surpassing the more common source of protein, e.g. red meat. Insects produce less greenhouse gases, are more efficient in their conversion of the food they eat into their own flesh that their predators consume, and reproduce quickly, making them incredible alternatives to beef, pork, and chicken.[70] In addition to being used as food for humans, they also serve to support the existing paradigm of protein consumption by their use as food for more common domestic animals that we prefer to consume.[71] Insects provide a renewable source of food even for chickens and cows which produce little environmentally taxing side effects. It should be remembered that food consumption is dependent upon culture. For example, we eat with great gusto arthropods such as crabs, shrimp, and lobsters, but think negatively of eating similar arthropods such as insects.

The scope of bioprospecting for these therapeutic applications of food should not only be limited to the animal kingdom, but also to all organisms. One large group that should also be explored includes numerous plants. Several positive immune effects have been demonstrated by the use of herbal products.[72] The molecules housed within these herbal products include indole alkaloids, curcuminoids, and ginsenosides that exert beneficial immune effects such as increasing the lymphocyte proliferation and inhibiting or promoting the production of proinflammatory cytokines. These immunologic substances can be found in virtually all major living groups, which warrant an immense amount of research into these sources of medicinal applications. Biodiversity in medical research offers significant potential not only for traditional medicine, but also for improving public and global health.[73]

Clearly, the benefits of using earthworms (蚯蚓 Qiū Yǐn; *Pheretima*) as nutritional and medicinal tools are still a secret to the general public, but as evidenced by the two publications noted above, this mood could change, with more constant reminders. There are some reminders within pop culture such as the children's book, *How to Eat Fried Worms*, which offers some recipes on how to enjoy worms with various condiments (ketchup, mustard, etc.).[74] Moreover, within the community of bloggers, this beneficial powerhouse of an invertebrate has gained notoriety. A blog post by Ervien Edwin touts the earthworm as having various uses such as treatment for diseases like typhus, thrombosis, and digestive tract infections.[75] Also, in Brazil, courses on the utilization of earthworms in vermiculture are being taught by *Minhobox,* a vermiculture product company.[76] The *New York Times* advocates for their use in keeping a well-nourished garden.[77] *The Reader's Digest* has featured several publications of earthworms for both entertainment and education.[78-80] No longer is the knowledge about the benefits of earthworms limited to the biomedical community, but is now becoming better known to the lay public as well.

So, if we are advocating the use of earthworms as sources of nutrition, what about their taste? When one thinks of fine dining or delicious comfort food, earthworms surely are not the first dish that comes to mind. Kai Kupferschmidt, a food science journalist, who published in *Science,* recently wrote about Per Møller, a Danish food scientist who explores the pathways and mechanisms by which humans perceive taste.[81] He finds that preferences in taste depend largely on differences in genetics as well as environmental stimuli during critical developmental periods. These are incredibly relevant areas of research for any initiative that proposes usages that utilize food as therapeutic agents. Similarly, the Nordic Food Lab enlists the help of scientists and chefs alike in order to analyze molecular gastronomy.[82] They commonly concoct eccentric recipes like ground grasshoppers (arthropods!) and fermented pears. This may be a most viable strategy for using and potentially convincing strange foods like earthworms to come into vogue with popular and high-class cuisine.

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