

Earthworms (Annelida: Oligochæta) as Emerging Bioactive Resources in Modern Medicine: A Comprehensive Review

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Abstract

Earthworms have gained increasing attention as a source of bioactive compounds with potential applications in modern medicine. Molecules isolated from *Lumbricus rubellus*, *Eisenia fetida*, and related species exhibit fibrinolytic, antimicrobial, anti-inflammatory, antioxidant, and regenerative properties. Lumbrokinase, a fibrinolytic enzyme complex, is the most clinically advanced earthworm-derived therapeutic and has been evaluated for ischemic stroke, thrombosis, and microcirculatory disorders. Additional compounds—including antimicrobial peptides and coelomic fluid proteins—demonstrate promising activity in wound healing, infection control, and cancer research. This review summarizes current evidence, highlights translational challenges, and outlines future directions for integrating earthworm-derived biomolecules into biomedical practice.

Keywords: Earthworms; Lumbrokinase; Fibrinolysis; Antimicrobial peptides; Regenerative medicine; Coelomic fluid; Biotherapeutics

Introduction

Earthworms (Phylum Annelida) have historically been used in traditional medical systems, particularly in East Asia, where preparations such as Di Long were employed to treat fever, convulsions, and circulatory disorders. Modern analytical techniques have revealed that earthworms contain a diverse array of bioactive proteins, peptides, and polysaccharides with potential therapeutic value. These discoveries have prompted renewed interest in earthworms as a source of novel biotherapeutics relevant to surgery, wound care, and systemic disease.

Lumbrokinase and Cardiovascular Therapeutics

Biochemical Characteristics

Lumbrokinase is a collective term for multiple serine proteases isolated from *Lumbricus rubellus* and *Eisenia fetida*. These enzymes exhibit potent fibrinolytic activity and demonstrate substrate specificity for fibrin over fibrinogen, a property that may reduce hemorrhagic complications relative to conventional thrombolytics (Table 1) (Mihara et al., 1991; Nakajima et al., 1991) [1, 2].

Compound Class	Representative Molecules	Primary Effects	Key References
Fibrinolytic enzymes	Lumbrokinase	Fibrinolysis, antithrombotic activity	[1-3, 10]
Antimicrobial peptides	Lysenin, Eiseniapore, Fetidin	Broad-spectrum antimicrobial activity	[4, 5]
Coelomic fluid proteins	Various glycoproteins	Wound healing, angiogenesis	[4, 6]
Polysaccharides	EF polysaccharides	Antioxidant activity	[9]
Crude extracts	Mixed proteins/peptides	Cytotoxicity against cancer cells	[7, 8]

Table 1: Major Bioactive Compounds Isolated from Earthworms.

Mechanisms of Action

Lumbrokinase enhances fibrinolysis through:

1. Direct fibrin degradation;
2. Activation of plasminogen;
3. Reduction of whole-blood viscosity; and
4. Improvement of microcirculatory flow (Zhang et al., 2020) [3].

Clinical Applications

Clinical studies, primarily in Asia, have evaluated lumbrokinase for:

1. Ischemic stroke;
2. Deep vein thrombosis;
3. Hypercoagulable states; and
4. Atherosclerotic microcirculatory dysfunction.

A randomized clinical trial reported improved neurological outcomes in ischemic stroke patients receiving lumbrokinase compared with standard therapy (Table 2) (Zhang et al., 2010) [10].

Application Area	Evidence Type	Key Findings	Strength of Evidence
Fibrinolysis	Clinical trials, in vivo studies	Improved microcirculation, reduced clot burden	Moderate
Antimicrobial therapy	In vitro, in vivo	Effective against Gram+ and Gram- bacteria	Moderate
Wound healing	Animal models	Accelerated closure, enhanced collagen deposition	Moderate
Anticancer activity	In vitro	Apoptosis induction in cancer cell lines	Preliminary
Antioxidant therapy	In vitro, in vivo	Reduced ROS and lipid peroxidation	Moderate

Table 2: Summary of Therapeutic Applications and Evidence Levels.

Antimicrobial and Anti Inflammatory Activities

Antimicrobial Peptides

Earthworm coelomic fluid contains antimicrobial peptides (AMPs) such as lysenin, eiseniapore, and fetidin. These AMPs demonstrate activity against Gram-positive and Gram-negative bacteria, fungi, and protozoa through membrane pore formation and lipid raft disruption (Cooper et al., 2008; Wang et al., 2007) [4, 5].

Anti Inflammatory Effects

Earthworm extracts suppress pro inflammatory cytokines including TNF α , IL 1 β , and IL 6, and inhibit NF κ B signaling pathways. These properties support their potential use in wound healing and inflammatory skin conditions (Cooper et al., 2008; Balamurgan et al., 2007) [4, 6].

Regenerative and Wound Healing Properties

Earthworm-derived compounds accelerate wound healing in animal models by promoting fibroblast proliferation, enhancing angiogenesis, and increasing collagen deposition (Cooper et al., 2008) [4]. Coelomic fluid proteins have been incorporated into biomaterial scaffolds to improve tissue integration, suggesting potential applications in surgical reconstruction and chronic wound management.

Antioxidant and Anticancer Activities

Antioxidant Effects

Polysaccharides isolated from *Eisenia fetida* exhibit strong antioxidant activity, reducing reactive oxygen species and lipid peroxidation markers *in vitro* and *in vivo* (Wang et al., 2010) [9].

Anticancer Potential

Extracts from *Lumbricus rubellus* and *Eisenia fetida* demonstrate cytotoxicity against hepatocellular carcinoma, breast cancer, and leukemia cell lines. Proposed mechanisms include caspase-mediated apoptosis and inhibition of tumor angiogenesis (Cho et al., 2010; Cooper, 2012) [7, 8]. These findings remain preliminary but highlight promising avenues for oncologic research.

Challenges and Future Directions

Despite encouraging results, several limitations hinder clinical translation:

1. Lack of standardized extraction and purification protocols;
2. Variability in enzyme composition across species and environmental conditions;
3. Limited large-scale randomized clinical trials;
4. Potential immunogenicity of earthworm proteins; and
5. Regulatory challenges for complex biological mixtures.

Future research should prioritize recombinant production, structural characterization, and controlled clinical evaluation to support regulatory approval and integration into surgical and medical practice.

Conclusion

Earthworms represent a valuable but underexplored source of bioactive molecules with significant potential in modern medicine. Lumbricinase is the most clinically advanced earthworm-derived therapeutic, while antimicrobial peptides, coelomic fluid proteins, and polysaccharides offer additional promise in wound healing, infection control, and cancer therapy. Continued interdisciplinary research will be essential to translate these findings into clinically viable biotherapeutics.

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