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Review

THE FREE-LIVING NON-PARASITIC NEMATODE *CAENORHABDITIS ELEGANS* AS AN ALTERNATIVE MODEL IN BIOMEDICAL RESEARCH

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Abstract

Caenorhabditis elegans is a nematode that is known as an alternative model for research. Adult forms are about 1mm long, while larvae reach a length of 0.25 mm. This nematode is easily grown in laboratories in a special nematode growth medium (NGM) with a layer of the bacterium *Escherichia coli*, on which *C. elegans* feeds. The worms exist in two natural sexes. *C. elegans* is one of the most frequently used experimental model organisms in biomedicine. The main advantages of *C. elegans* as a model organism are its small size, high reproductive capacity, simple cultivation, low maintenance costs, the possibility of long preservation at low temperatures, very short reproductive time and good visibility. *C. elegans* has been used for analysis of toxicants, investigation of cancer, discovery of antiparasitics and anticancer drugs, and investigation of the functions of the neuromuscular system. The *C. elegans* model is successful for identifying and characterizing molecular drug targets of all classes of anthelmintics acting on the nervous system. All these characteristics make *C. elegans* a valuable and prospective model organism in biomedical research. This review article primarily focuses on the utility of *C. elegans* as a model organism in the evaluation of anthelmintic substances, with particular emphasis on essential oils and natural products, while briefly highlighting

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its general biomedical applications. The main goal of this paper is to demonstrate our application of this model in some antinematodal research.

Key words: *C. elegans, E. coli,* genome, nematode, antiparasitic drug

INTRODUCTION

Caenorhabditis elegans was first mentioned in the early 1960s when biologist Sidney Brenner announced the potential use of this nematode in the study of nervous system development. Interestingly, Brenner shared the 2002 Nobel Prize in Physiology or Medicine with H. Robert Horwitz and John E. Sulston. In his Nobel lecture, Brenner honored *C. elegans* and said, the fourth Nobel Prize winner this year is *C. elegans* because most of the research was done on this nematode. So far, three different Nobel Prizes have been awarded to six researchers working on these worms. *C. elegans* is a non-parasitic, free-living nematode. Adult forms are about 1mm long, while larvae are four times shorter. Worms are easily seen, observed and examined using a dissecting microscope directly in petri dishes, in which they are grown on nematode growth medium (NGM) or in liquid examination medium. The body of *C. elegans* is transparent, so good visualization of its individual cells, pharynx and even subcellular structures is possible. *C. elegans* has a fast development cycle, so this characteristic of its very intensive reproduction makes this nematode an excellent model for various biomedical research, including genetic studies. The worm has a fixed number of cells, about 1000 somatic cells and 1000-2000 germ cells, so it is possible to follow each individual cell from fertilization to the adult stage, creating a complete cell lineage map (Sulston and Horvitz, 1977). Significantly, humans and *C. elegans* share a common ancestor that lived about 500 million years ago, so some genes are still similar between humans and these nematodes. The complete genome of *C. elegans* was sequenced in 1998, making it the first multicellular organism whose genome was completely known. There is great similarity in the *C. elegans* and human genomes, and some authors report that at least 38% of *C. elegans* protein-coding genes predict orthologs in the human genome. On the other hand, the fact that the *C. elegans genome* is well known allows the use of this nematode in the study of diseases with genetic causes (Kaletta and Hengartner, 2006). The aim of this review article is to highlight the biological features that make *C. elegans* a powerful tool for biomedical studies, with a particular focus on its application in anthelmintic drug research and discovery.

Basic information

The free-living nematode *C. elegans* exists in the two natural sexes, the hermaphrodite with XX chromosomes and the male with one X chromosome, so this nematode does not have a Y chromosome. The hermaphrodites are somatically female, but can reproduce either by self-fertilization or by mating with males (Zarkower, 2006). The gonads of hermaphrodites perform the ovotestis function, meaning they are capable of producing both male and female gametes. Initially, they produce haploid amoeboid

sperm that are stored in the spermatheca during the L4 stage of development. As the worm's body matures and approaches adulthood, the gonads switch to oocyte production. Self-fertilization generally produces hermaphroditic offspring, with less than 0.2% males.

Hermaphrodites that have the ability to self-fertilize ("selfing") are particularly suitable for genetic analysis. Self-fertilization facilitates strain maintenance, because only one individual can generate an entire population. Hermaphrodite populations naturally lose heterozygosity over generations (since hermaphrodites cannot mate with each other), causing them to become homozygous. On the other hand, the existence of males in the population is essential for the exchange of genetic material, i.e., to ensure the creation of animals with different genetic material. In fact, the nematode has been seen to utilize the males and use sperm to reproduce rather than relying on hermaphroditic gonad seed (Ward and Carrel, 1979).

Life cycle. This nematode has a very rapid life cycle which takes only 3 days from egg to adult, at 25 ºC. The data show that at 20 ºC, embryogenesis of *C. elegans* lasts about 16 hours. After fertilization, the protective shell of the egg is formed, which ensures that the embryo can safely develop independently of the mother. The hermaphrodite embryo hatches into the first larval stage (L1) and larvae begin feeding immediately. The continuation of the development cycle goes through four stages (L1-L4) (Figure 1).

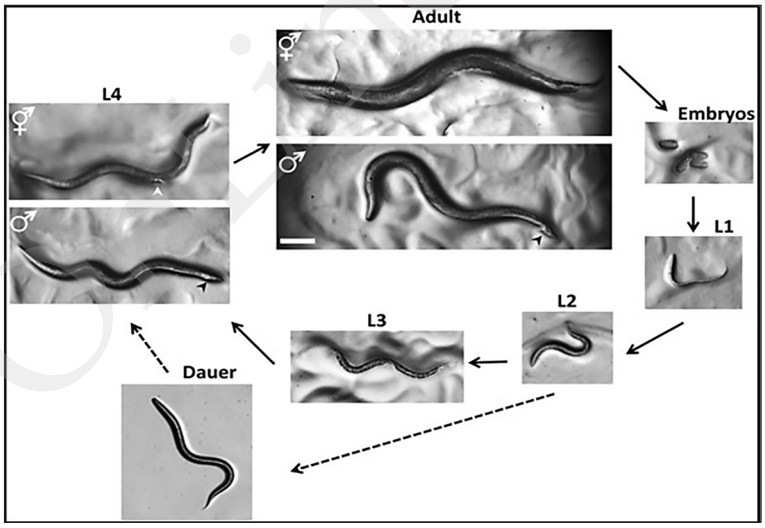

Figure 1. *C. elegans* life cycle, from embryos to adult hermaphrodites and males (http://www.wormbook.org/chapters/www_celegansintro/celegansintro_fig2.jpg), Figures reproduced from: Corsi A.K., Wightman B., and Chalfie M. A Transparent window into biology: A primeron *Caenorhabditis elegans* (June18,2015), WormBook, ed. The *C.elegans* Research Community, WormBook, doi/10.1895/wormbook.1.177.1, http://www.wormbook.org., Copyright:©2015 Ann K. Corsi, Bruce Wightman, and Martin Chalfie.

The L1 stage lasts about 16 hours, while each subsequent stage of worm development lasts about 12 hours. The new cuticle (collagenous layer covering the larvae from the outside) is produced and the larvae enter a period of rest, known as lethargy (Raizen et al., 2008). This period ends when the old cuticle is replaced by a new one. When it comes to L4 larvae, 12 hours after discarding the old cuticle, adult hermaphrodites start producing offspring for the next 2-3 days, as long as they have self-produced sperm. After that, if they have food, the hermaphrodites can live for a few more weeks before they die.

Evolution has enabled *C. elegans* to adapt to various circumstances. When there is not enough bacteria so food becomes scarce, or if population density increases, *C. elegans* L2 larvae enter an alternative developmental pathway, transitioning to a specialized L3 stage known as the dauer larva (Hu, 2007). The dauer larva forms a protective cuticle that completely surrounds the body, including the mouth, preventing feeding and further development. This cuticle is highly resistant to chemicals, providing additional protection against environmental stressors and harmful agents. In this form, the larva is able to live for several weeks or months. In good conditions, which means the presence of bacteria on which they feed, the dauer larvae discard the plugs from their mouths, discard the cuticle, and continue their development as a modified L4 stage.

C. elegans tissues

Epidermis. The nematode is protected from the outside by the cuticle, a special extracellular matrix, the coat of which consists of lipids, glycoproteins and collagen. Collagen is created by large syncytial epidermal cells, which in embryos are formed by changes and fusions of the epidermis. The cuticle is actually a special extracellular matrix (ECM), which in addition to protecting the worm plays a crucial role in shaping the body and by connecting the epidermis to muscles, acts as an anchoring structure for muscle contractions (Chisholm and Hardin, 2005; Page and Johnstone, 2007). Finally, the cuticle serves as a model for ECM formation and function, with many molecules and pathways involved in its biogenesis conserved in vertebrates (Page and Johnstone, 2007). Some mutations in genes needed for cuticle formation produce a variety of phenotypes. Mutations in collagen genes can result in animals that are shorter than normal [the Dumpy (Dpy) phenotype] or that move like corkscrew [the Roller (Rol) phenotype]. Research on the epidermis of *C. elegans* allowed us to learn about how cells move and heal. Upon injury, this epidermis activates Ca^{2+} channels to drive actin polymerization (Xu et al., 2012). Studies on multinucleate epidermis formation have highlighted the significance of both promoting and repressing cell fusion for proper development (Podbilewicz, 2006).

Muscles. On the inner side of epidermis, the body-wall muscles connected to it and separated into four quadrants, each of which comprises 95 cells. These somatic muscles are striated, but in an unusual oblique pattern. Unlike in vertebrates, the muscle cells remain mononucleate without fusing, and each cell contains multiple sarcomeres

(Moerman and Fire, 1997). Contraction and relaxation of these muscles provides the "elegant" sinusoidal movement of the worm. Nematode muscle innervation is unique and different from in vertebrates. Unlike vertebrates, where muscles are innervated via the axons of nerve cells, the muscle cells in nematodes extend "arms" to the dorsal or ventral nerve cord and form synapses with motor neurons. Also, specific interneurons occur in those synapses, whose role is particularly intriguing (White et al., 1976). The entire muscular system in *C. elegans* is specific. In addition to the somatic muscles, the nematode's body also contains the pharynx, a specific muscle organ responsible for feeding, then the vulval and uterine muscles responsible for laying eggs, a specific muscle on the tail of the male that enables mating, and intestinal muscles that enable defecation. The importance of the genetic studies in which the gene coding for myosin synthesis, designated as *unc-54*, was sequenced and cloned for the first time is specially highlighted. This discovery enabled the subsequent analysis of the structure of all myosins (MacLeod et al., 1981). The basic functional unit of the muscle is the sarcomere. Research on this nematode muscle is significant in understanding certain muscular dystrophies and cardiomyopathies.

The digestive system. The digestive tract of *C. elegans* begins with the mouth where bacteria or other food particles enter and pass through the pharynx. The pharynx is a muscular pump, which pulls in and grinds food, and then passes it into the intestine where it is further digested (Avery and You, 2012). The pharynx pumps constantly, and the pumping speed depends on the food, its availability and type, but also on whether the nematode is hungry or satiated (Avery and Shtonda, 2003). The pharynx connects to the intestine, which is made up of 20 large, paired epithelial cells forming a tube that runs to the end of the animal's body. As the individual grows and its metabolic demands increase, these intestinal cells divide their nuclei once during the L1 stage, and later replicate their DNA again without dividing the nucleus (Hedgecock and White, 1985). Our knowledge on the gut microbial diversity on *C. elegans* in their natural environment and the effect of host genetics on their core gut microbiota is important (Kumar et al., 2020).

Reproductive tissue. *C. elegans* males and hermaphrodites differ in body size, gonad structure, and secondary sexual features. The gonad, located near the intestine in the middle of the body, has a different shape depending on the sex. The hermaphrodites have two U-shaped gonad arms, while males have only one. Both types contain the germline, where eggs and sperm are formed (Hubbard and Greenstein, 2005). Secondary sexual traits include the vulva in hermaphrodites and the fan-shaped tail in males (Emmons, 2005; Herman, 2006). In hermaphrodites, the vulva forms in the center of the belly side and allows sperm to enter and eggs to exit the body (Sternberg, 2005). The males have a thin, flat tail made of cuticle material. As their gonad is smaller, males are slimmer than hermaphrodites.

The nervous system. *C. elegans* has emerged as a key model organism for exploring various neurobiological questions. Numerous genes have been uncovered, along with molecular pathways involved in processes such as neuronal development and

specification, programmed cell death, migration of neural precursors, synaptogenesis, sensory transduction (both chemical and mechanical), neurodegeneration, neurite repair, and the function of glial cells (Driscoll and Chalfie, 1992; Silhankova and Korswagen, 2007; Hammarlund and Jin, 2014; Shaham, 2015). Additionally, a wide range of behaviors ranging from simple to more complex have been studied in this nematode (Bargmann, 2006; Hart, 2006; Barr and Garcia, 2006; Ardiel and Rankin, 2010). *C. elegans* also undergoes quiescent states resembling certain characteristics of mammalian sleep (Raizen et al., 2008).

The adult nematode has a nervous system made up of 302 neurons (Sulston and Horvitz, 1977), while the adult male has 383 neurons, with most of the extra ones found in the specialized tail region. Neuronal cell bodies are mainly grouped in ganglia located in the head, along the ventral nerve cord, and in the tail. Most neurons have a simple shape, usually extending one or two projections from the cell body. However, some touch-sensitive neurons, like FLP and PVD, have complex, branched structures (Dong et al., 2013). In *C. elegans*, most neuronal extensions cannot be clearly classified as neuronal structures since they both send and receive signals, but they are often called "axons" for convenience. The nervous system is divided into four main areas where all synapses occur: the nerve ring around the pharynx, the dorsal and ventral nerve cords, and the tail neuropil. This nematode also has a small number of glia-like support cells, mainly linked to sensory neurons, but far fewer than in vertebrate animals (Oikonomou and Shaham, 2010).

Why choose *C. elegans* for research?

Beyond its strength as a genetic model, *C. elegans* offers several inherent advantages for studying the biological characteristics of eukaryotic organisms. The main advantages of *C. elegans* as a model organism are its small size, high reproductive capacity, simple cultivation, low maintenance costs, the possibility of storing it in low temperature ice, the short time between adult to adult stage and the possibility of producing knock-down gene variants. An often-overlooked advantage of *C. elegans* is its harmlessness to humans. Notably, because it cannot survive at body temperature, it is incapable of infecting humans. In contrast, some nematodes, besides being parasites (e.g., *Ascaris suum*), can trigger severe allergic reactions and require work in special ventilation conditions (Kennedy, 2013).

The transparency of *C. elegans*' body is a major advantage in cell and developmental biology research, allowing scientists to observe development and environmental or genetic changes in cells within a living organism. Transparency also facilitates live-animal studies using fluorescent protein reporters. Labeling the worm cells enables the monitoring of gene mutations as well as electrophysiological changes, such as calcium efflux *in vivo* (Kerr, 2006). Transparency also enhances the effectiveness of optogenetic tools, which allow precise manipulation of neuronal activity (Husson et al., 2013).

C. elegans is very often used as a model organism for the study of the nervous system and human diseases as well as being a model for the discovery of antiparasitic drugs. The pharmaceutical industry uses this nematode as a platform in the research of new therapeutic compounds. *C. elegans* is a reasonable model for the discovery of anthelmintic drugs and for research on the mechanism of action of anthelmintics. Also, important information on mechanisms of anthelmintic resistance has been obtained from studies on *C. elegans*. The two largest groups of modern anthelmintic drugs, imidazothiazoles and avermectins, act on the nervous system of parasites. The essence of their action is in selective toxicity, and to explain such an effect, knowledge about the mechanism of action is needed (El-Shafeey et al., 2019). Mutations that alter drug permeability across primary nematode barriers have been identified as potential resistance mechanisms using *C. elegans* (Rehborg et al., 2023).

The main types of anthelmintic drugs target either nicotinic acetylcholine receptors (nAChRs), such as imidazothiazoles and tetrahydropyrimidines, or glutamate-gated chloride channels (GluCl), like avermectins and milbemycins. Both, nAChRs and GluCl are part of the Cis-loop receptor family, a large group of five-subunit, ligand-gated ion channels that produce fast electrical responses in both vertebrates and invertebrates. These receptor subunits can combine in various ways to form receptors made of identical (homomeric) or different (heteromeric) subunits, resulting in diverse types with unique functions, drug responses, locations, and roles in the body. In *C. elegans*, scientists have identified around 100 genes coding for Cis-loop receptor subunits, twice as many as in humans. Some of these receptors exist only in invertebrates, and a few are unique to nematodes. Although only a limited number have been studied in detail, several still have no known activating molecule or defined role. Besides nAChRs and GABAA-like receptors, this group also includes chloride channels activated by glutamate, acetylcholine, dopamine, and serotonin, as well as others triggered by ligands absent in vertebrates, like tyramine and betaine. Because of this diversity, *C. elegans* serves as an excellent model for studying the biology, pharmacology, and therapeutic potential of Cis-loop receptors (Hernando et al., 2023). This means *C. elegans* is an effective and cost-efficient model system for anthelmintic discovery (Burns et al., 2015). Because of its simplicity and well-characterized biology, *C. elegans* is considered an excellent alternative model for testing substances with potential antinematodal activity (D'Addabbo et al., 2021). *C. elegans* has proved to be a valuable model as a result of its genetic and physiological similarities to higher organisms, fully sequenced genome, short life cycle, and transparency. These features enable high-throughput screening, molecular pathway analysis, and lifespan and healthspan assays (Deji-Oloruntoba et al., 2025).

In our study, we used wild-type *C. elegans* to evaluate the nematocidal effects of active compounds found in plant essential oils. By dissolving these substances in NGM, we created various concentrations and then observed the worms' movement and pharyngeal activity. The stopping of pharyngeal pumping and movement was used as a key indicator of the antiparasitic effect (Marjanović et al., 2018; Medić and Marjanović,

2023; Stojković et al., 2024). Based on the body posture of the nematode after death, we could distinguish between spastic and flaccid paralysis (Figure 2), which reflects the mechanism of action of the tested antiparasitic agent (Stojković et al., 2024).

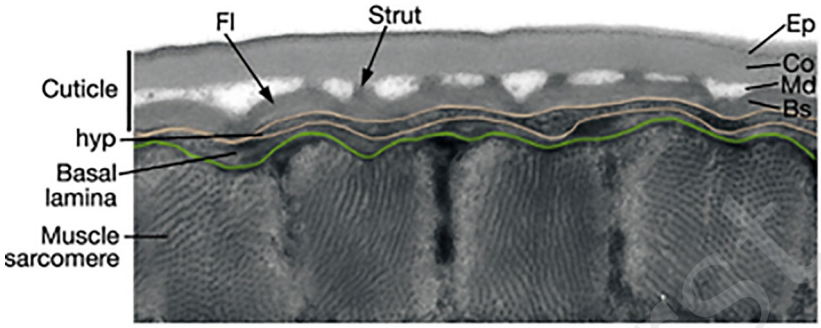

Figure 2. Epidermis layout (https://www.wormatlas.org/dauer/cuticle/mainframe.htm). (hyp) Hypodermis; (Fl) Fibrous layers in the basal zone; (Struts) Cuticle struts; (Ep) Epicuticle; (Co) Cortical zone; (Md) Medial zone; (Bs) Basal zone. Figures reproduces from: CorsiA.K., WightmanB., and Chalfie M. A Transparent window into biology: A primeron Caenorhabditis elegans (June 18, 2015), WormBook, ed. The C.elegans Research Community, WormBook, doi/10.1895/wormbook.1.177.1,http://www.wormbook.org., Copyright:©2015 Ann K. Corsi, Bruce Wightman, and Martin Chalfie

The results from *C. elegans* can later be compared with the muscle contractions and relaxations seen in the neuromuscular system of the parasitic worm *A. suum* (Marjanović et al., 2021). Strains of *Bacillus thuringiensis* (Bt) can produce a range of nematocidal proteins. Among these, the most researched are crystal (Cry) proteins, part of the δ-endotoxin group, which are highly toxic to invertebrates but harmless to plants, humans, and other vertebrates. We screened 17 natural Bt isolates for the presence of nematocidal genes (Cry1, Cry5, Cry6, Cry12, Cry13, Cry14, and Cry21) and their activity against *C. elegans*. Most of the strains tested were positive for Cry1 and at least one additional Cry gene. Moreover, 82.35% of the strains showed nematocidal activity against *C. elegans*, which is significantly higher than the percentages reported in earlier studies of similar bacterial collections (Atanasković et al., 2020). The observed damage in *C. elegans* was located in the intestinal region. Because of this, we further examined the effect of Cry proteins on *A. suum*. All tested Bt strains (SS_26.2, SS_29.2, SS_35.1, SS_37.7) caused structural damage in the intestines of *A. suum*. Although there are differences between free-living and parasitic nematodes, our findings confirm that Cry proteins are effective against both groups (Atanasković et al., 2025).

In our research with *C. elegans*, we now use the WMicrotracker® SMART (Phylumtech S.A., Argentina). The system is optimized to quantify the speed and trajectory of worms cultured in 35 mm Petri dishes, and to obtain data on average speed [mm/s], travel distance, [mm/worm], motility score and rotation index. This system allows continuous monitoring of these motility parameters. Figure 3 shows a petri dish with the trajectory of tracked *C. elegans* individuals. As the majority of anthelmintics and

substances with potential anthelmintic effect act on the neuromuscular system of nematodes (Marjanović et al., 2021), this type of equipment enables rapid preliminary tests to be carried out on the mode of action of the investigated substances. At the same time, it is effective and provides objective data on whether the substance being tested has an inhibitory or excitatory effect on worm motility.

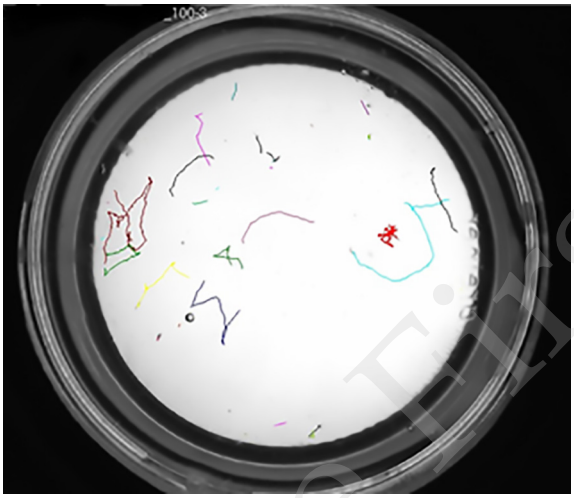

Figure 3. Petri dish with the marked trajectory of tracked *C. elegans* (our nonpublished data).

CONCLUSION

The non-parasitic nematode *C. elegans* has become a frequently used alternative model in biomedical research. Among the features that make *C. elegans* an attractive and effective model organism are that it is easy to work with in the laboratory, its nutritional needs are easy to provide, it produces a large number of offspring by self-fertilization within a few days, and its life cycle is short. This nematode was the first complex organism to have its entire genome sequenced. In particular, the community of worm researchers is highly interactive and collaborative, making it easy for newcomers to the field to organize research quickly. *C. elegans* has been used for analysis of toxicants, investigation of cancer, the discovery of antiparasitics and anticancer drugs, and investigation of the nervous system functions, as it shares ~~molecules~~ molecular pathways and genes with vertebrates. The *C. elegans* model is successful in identifying and characterizing molecular drug targets of all classes of anthelmintics targeting the nervous system. All these characteristics make *C. elegans* a valuable and prospective model organism in biomedical research. In our studies, *C. elegans* proved to be an efficient and ethical alternative model for evaluating the nematocidal potential of natural products, such as plant essential oils and Bt toxins. The application of automated motility tracking (WMicrotracker® SMART system) has further improved data accuracy and throughput in drug screening, confirming the

nematode's importance in preclinical testing of antiparasitic compounds. Together, these findings underscore the relevance and reliability of *C. elegans* as a cost-effective, informative, and scalable model for modern biomedical and pharmaceutical research.

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Authors' contributions

ĐSM wrote the manuscript with input from all authors. TM prepared initial draft of the text. DM prepared figures. SMT finalized the manuscript for submission. SM, MJ critical revision.

Competing interests

The authors confirm that they have no conflicts of interest.

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SLOBODNO ŽIVEĆA NEPARAZITSKA NEMATODA *CAENORHABDITIS ELEGANS* KAO ALTERNATIVNI MODEL U BIOMEDICINSKIM ISTRAŽIVANJIMA

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Kratak sadržaj

Caenorhabditis elegans je neparazitska, slobodnoživeća nematoda. Odrasli oblici su dugi oko 1 mm, dok larve dostižu dužinu od 0,25 mm. Ova nematoda se lako uzgaja u laboratorijama u specijalnom medijumu (NGM) sa slojem bakterije *Escherichia coli*, kojom se hrani. Crvi postoje u dva pola, hermafroditnom i muškom. *C. elegans* je jedan od najčešće korišćenih eksperimentalnih model-organizama u biomedicini. Njegove glavne prednosti kao eksperimentalnog modela su mala veličina, visok reproduktivni kapacitet, jednostavan uzgoj, niski troškovi održavanja, mogućnost dugotrajne krioprezervacije, kratko generacijsko vreme i transparentnost tela. Štaviše, ova nematoda je bila prvi višećelijski organizam čiji je ceo genom sekvenciran. *C. elegans* se koristi za analizu toksikanata, istraživanje karcinoma, otkrivanje antiparazitika i lekova protiv raka, istraživanje funkcija nervnog sistema. Ovaj eksperimentalni model je efikasan za identifikaciju i karakterizaciju molekularnih meta za sve klase anthelmintika koji deluju na nervni sistem nematoda. Sve ove karakteristike čine *C. elegans* vrednim i perspektivnim model-organizmom u biomedicinskim istraživanjima. Cilj ovog preglednog članka je da istakne biološke karakteristike koje čine *C. elegans* gotovo idealnim modelom za biomedicinske studije, sa posebnim fokusom na njegovu primenu u istraživanjima i testiranju novih antihelmintika.

Ključne reči: *C. elegans, E. coli,* genom, nematoda, antiparazitski lekovi