Sahel Journal of Life Sciences FUDMA (SAJOLS)
March 2025 Vol. 3(1): 555-562
ISSN: 3027-0456 (Print)
ISSN: 1595-5915 (Online)
DOI: https://doi.org/10.33003/sajols-2025-0301-67

Review Article

Wolbachia at the Crossroads of Symbiosis and Public Health: A Comparative Analysis of Arthropod and Nematode Hosts

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ABSTRACT

Wolbachia is a maternally inherited intracellular bacterium that is widely distributed among arthropods and filarial nematodes, where it plays diverse roles ranging from reproductive manipulation to essential symbiosis. In insects, *Wolbachia* alters host reproduction through mechanisms such as cytoplasmic incompatibility, parthenogenesis, and feminization, while also enhancing antiviral defense. These properties have made it a valuable tool in biocontrol programs, particularly for reducing the transmission of mosquito-borne diseases. In filarial nematodes, especially *Onchocerca* species responsible for river blindness, *Wolbachia* is essential for parasite development, survival, and host immune modulation. This dependency has positioned the bacterium as a promising chemotherapeutic target. Antibiotics like doxycycline have proven effective in depleting *Wolbachia*, reducing worm viability and providing an alternative to conventional drugs such as ivermectin, which faces challenges due to emerging parasite resistance. Additionally, the presence of bacteriophage WO within *Wolbachia* genomes facilitates horizontal gene transfer and may influence host interactions and bacterial evolution. While current interventions show promise, concerns regarding the potential emergence of resistance to anti-*Wolbachia* therapies underscore the need for continued research into novel treatment strategies, including combination therapies. This review synthesizes existing knowledge on *Wolbachia*'s biological roles, host interactions, and implications for integrated control of vector-borne and helminthic diseases. By exploring *Wolbachia*'s dual function as both a reproductive manipulator and a mutualistic endosymbiont, the review highlights its growing relevance in One Health approaches to improve global public health.

Keywords: Arthropods; Endosymbiont; Filarial Nematodes; One Health; *Wolbachia*

Citation: Fadiji, O.S., Rabiu, A.G., Bale, M.I., Ebere, C.U., Marcus, A. J[2], Jimoh, S.O. & Adeleke, M.A. (2025). *Wolbachia* at the Crossroads of Symbiosis and Public Health: A Comparative Analysis of Arthropod and Nematode Hosts. *Sahel Journal of Life Sciences FUDMA*, 3(1): 555-562. DOI: https://doi.org/10.33003/sajols-2025-0301-67

INTRODUCTION

Wolbachia is an obligate intracellular, Gram-negative α-proteobacterium that belongs to the order *Rickettsiales* and the family *Anaplasmataceae*. First discovered in *Culex pipiens* mosquitoes in 1924, it is among the most widespread endosymbionts, infecting approximately 52% of arthropod species globally, including insects, mites, spiders, and various nematode taxa (Kaur *et al*., 2021; Ramalho *et al*., 2021). Its extensive distribution and effects on host biology have made it a focal point for research in symbiosis, vector control, and parasitic diseases.

Molecular advances, such as whole-genome sequencing and phylogenetics, have deepened the understanding of *Wolbachia*'s diversity and evolutionary research point (Pimentel *et al*., 2021). It is divided into 17 supergroups (A–F, H–Q), with groups A and B predominantly found in arthropods (Fallon, 2021; Manoj *et al*., 2021). These maternally inherited bacteria influence their hosts through mechanisms ranging from parasitism to mutualism. In arthropods, *Wolbachia* induces cytoplasmic incompatibility, feminization, male killing, and parthenogenesis (Ramalho *et al*., 2021; Pimentel *et al*., 2021).

In filarial nematodes such as *Onchocerca volvulus* and *Brugia malayi*, *Wolbachia* acts mutualistically, promoting development, embryogenesis, and survival (Kaur *et al*., 2021). These nematodes, responsible for onchocerciasis and lymphatic filariasis, pose significant public health challenges, particularly in Sub-Saharan Africa. *Wolbachia* inhabits lateral cords and female reproductive tissues and affects host immunity (Tamarozzi *et al*., 2011; Bouchery *et al*., 2013).

Bacteriophage WO in *Wolbachia*, which carries eukaryotic-like genes, may enhance horizontal gene transfer and host interactions. Additionally, *Wolbachia* can protect arthropods from viral pathogens, presenting opportunities for disease control.

Given its dual role as a reproductive manipulator in arthropods and a mutualist in nematodes, *Wolbachia* serves as a target for biological and therapeutic interventions. Despite growing research, knowledge remains disjointed across hosts and locations, warranting an inclusive and systematic evaluation. This review aims to consolidate findings on *Wolbachia* in arthropods and filarial nematodes while examining implications for disease ecology and control.

Wolbachia in Arthropods

Host Manipulation

Wolbachia alters arthropod reproduction to enhance maternal transmission, as shown in Fig. 1. Cytoplasmic incompatibility (CI) causes embryo lethality when infected males mate with uninfected females, increasing the prevalence of infected females (Werren *et al*., 2008). Feminization, male killing, and parthenogenesis further bias reproduction towards infected female offspring (Bourtzis *et al*., 2014).

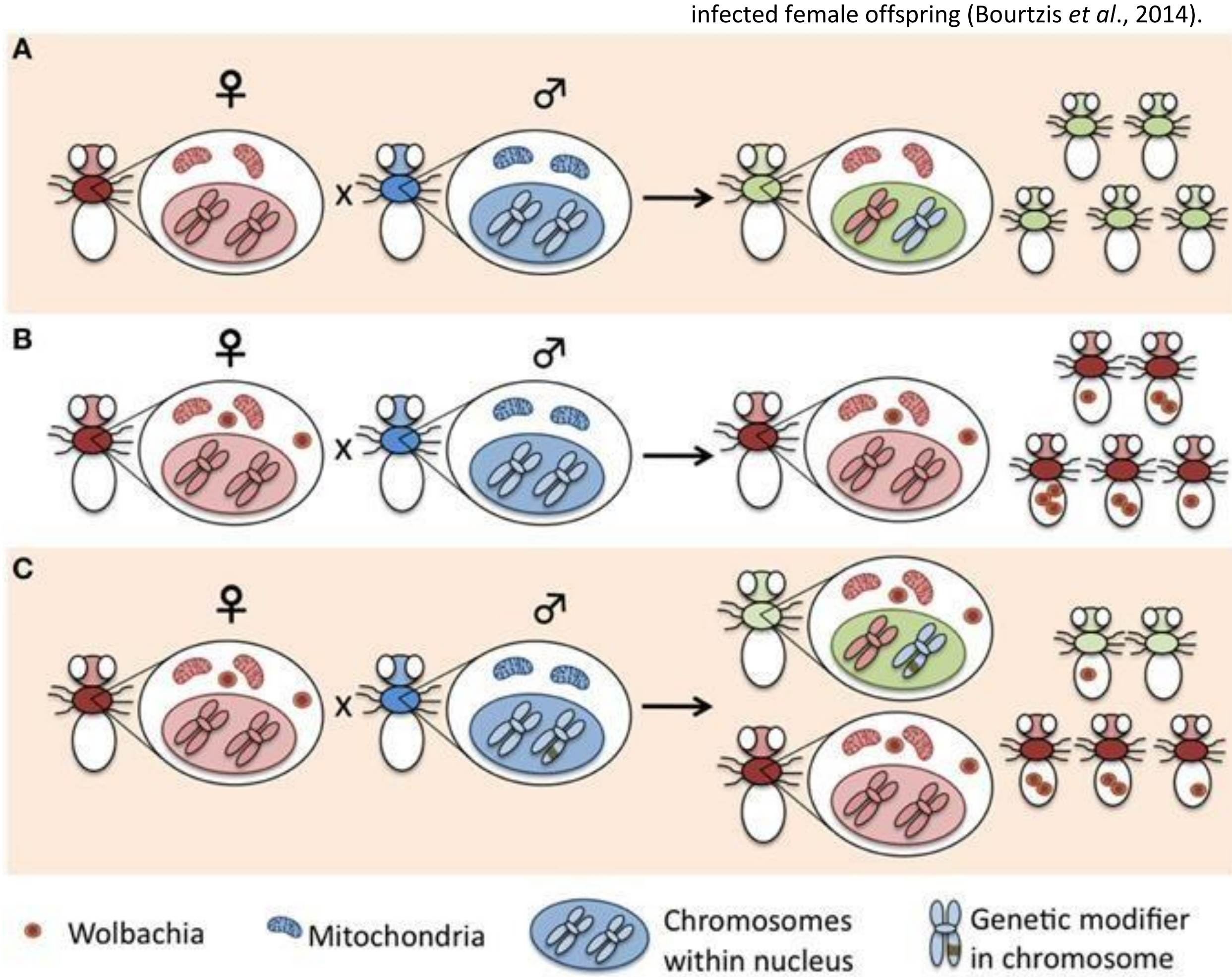

Figure 1. Conceptual illustration of Wolbachia-induced sex ratio distortion in insect populations

This diagram presents a simplified representation of how *Wolbachia* distorts sex ratios to enhance its transmission within an insect population. As a maternally inherited, cytoplasmic symbiont, *Wolbachia* promotes its spread by manipulating host reproductive mechanisms, often to the detriment of the host's nuclear genome. (A) In a non-infected population, males and females contribute equally to the gene pool through nuclear inheritance. (B) When

Wolbachia is present, it boosts the reproductive success of infected females through mechanisms like feminization and male killing, thereby reducing the relative genetic contribution of males. (C) Over time, as male numbers decline, natural selection favors host nuclear genes that suppress or mitigate the effects of *Wolbachia*-induced reproductive manipulation. Individuals carrying such modifier genes possess a reproductive advantage, leading to the population's gradual spread of suppressor alleles (Kaur *et al*., 2021).

Viral Pathogen Interference

Wolbachia resists viral infections in certain arthropods, particularly diminishing replication and transmission of dengue, Zika, and chikungunya viruses in *Aedes aegypti*. This antiviral effect is utilized in vector control programs (Hoffmann *et al*., 2011).

Population Replacement and Suppression

Field releases of *Wolbachia*-infected mosquitoes aim to suppress or replace wild populations with virus-resistant strains. Successful trials in Australia, Indonesia, and Brazil indicate a reduced incidence of mosquito-borne diseases (Ryan *et al*., 2020).

Evolutionary and Ecological Considerations

Wolbachia can influence host speciation by causing reproductive isolation and altering gene flow. It also shapes host microbiomes, physiology, and immunity (Engelstädter and Hurst, 2009), and Table 1 highlights the factors contributing to its evolutionary success.

Table 1: Factors Contributing to the Evolutionary Success of Wolbachia (Correa and Ballard, 2016)

Scale	Factors	Strategies	Observations
Ecological Timescale	Vertical transmission and maintenance of infection in individual hosts	Correct bacterial replication	Bacterial cell cycles synchronize with the development of organisms. Evidence suggests the presence of a functional gene involved in the bacterial cell cycle.
		Avoidance of the host's immune system	Wolbachia triggered neither the induction nor the suppression of antimicrobial peptides. Wolbachia resides phagosome-like structures of host origin.
		Precise bacterial localization	Localized preference of bacteria within the oocyte during oogenesis. Leveraging microtubule-driven mechanisms for movement in embryonic development
	Maintenance of infection in the host population	Increased fitness of infected matrilines	Inducing parasitic traits that remove non-transmitting individuals from the population: Cytoplasmic incompatibility (CI), male killing (MK), parthenogenesis induction (PI), and feminization. Physiological advantages of infection: supplying metabolites and parasite protection.
Macroevolutionary timescale	Spread of infection across species	Ability to infect new hosts	Wolbachia can survive outside of cells for long periods. The capacity to colonize a naive female germline from adjacent tissues. Host species in close ecological contact have been observed to carry closely related Wolbachia.
		Escape/counter Muller's ratchet.	Genomes that contain mobile and repetitive DNA facilitate recombination and adaptive evolution, such as insertion sequences and phages. Evidence of extensive intra- and intergenic recombination.

***Wolbachia* in Filarial Nematodes**

Mutualism and Development

Wolbachia is crucial for survival and reproduction in nematodes. It is found in the lateral cords, ovaries, and embryos. Eliminating *Wolbachia* through antibiotics results in halted development and sterility, confirming its mutualistic role (Taylor *et al*., 2005). In Fig. 2, we highlight the role of *Wolbachia* in the onchocercid nematode infection.

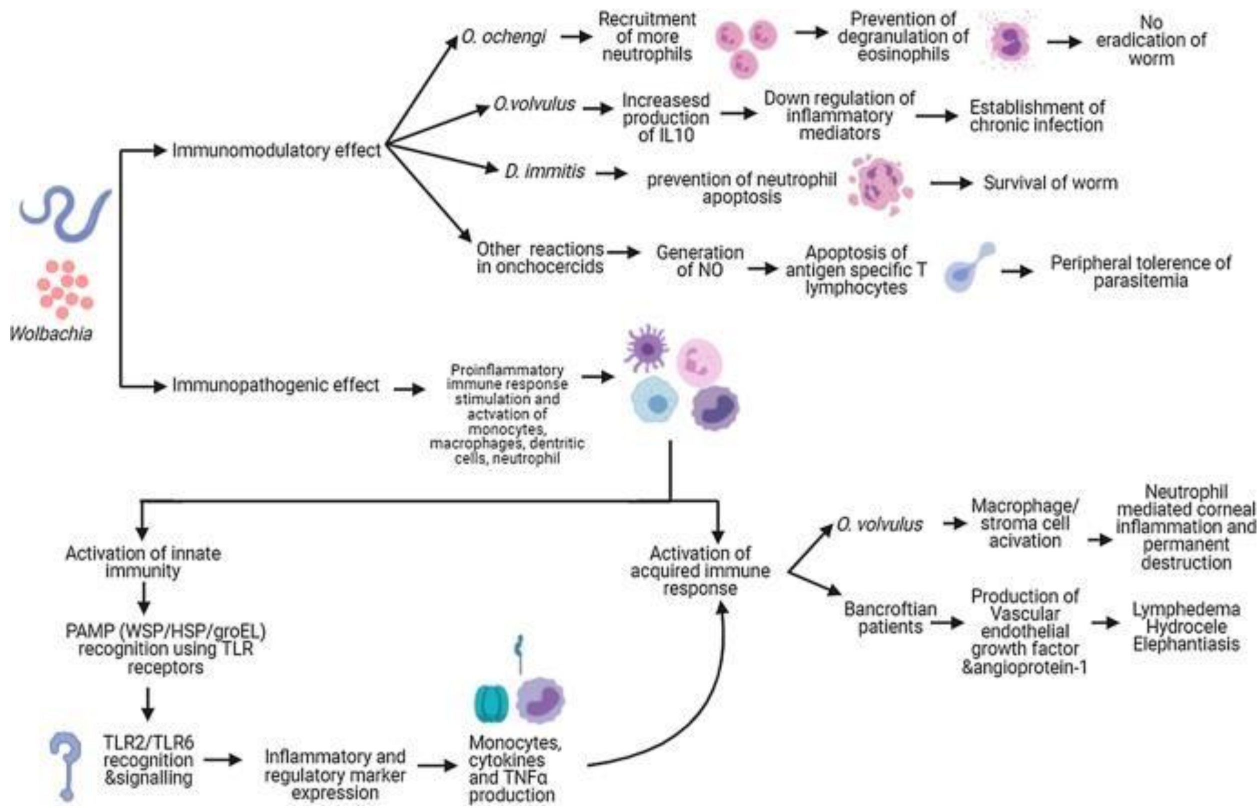

Figure 2. Immunological role of *Wolbachia* in onchocercid nematode infections

This diagram summarizes the role of *Wolbachia* in modulating the host immune response during filarial nematode infections. *Wolbachia* aids parasite survival through immune evasion and modulation, while its molecules, such as surface proteins and DNA, can activate host immune responses that lead to inflammation. This dual role underlies the immunopathology in diseases like onchocerciasis and lymphatic filariasis. The figure illustrates the stages of immune activation and the development of pathology, demonstrating how *Wolbachia* affects the host-parasite interaction throughout the infection process (Manoj *et al*., 2021).

Immunopathology

Wolbachia molecules, such as lipoproteins and DNA, stimulate host immune responses. In onchocerciasis, *Wolbachia* contributes to the inflammatory pathology associated with the death of microfilariae (Saint André *et al*., 2002). Figure 3 showcases the role of Wolbachia in river blindness.

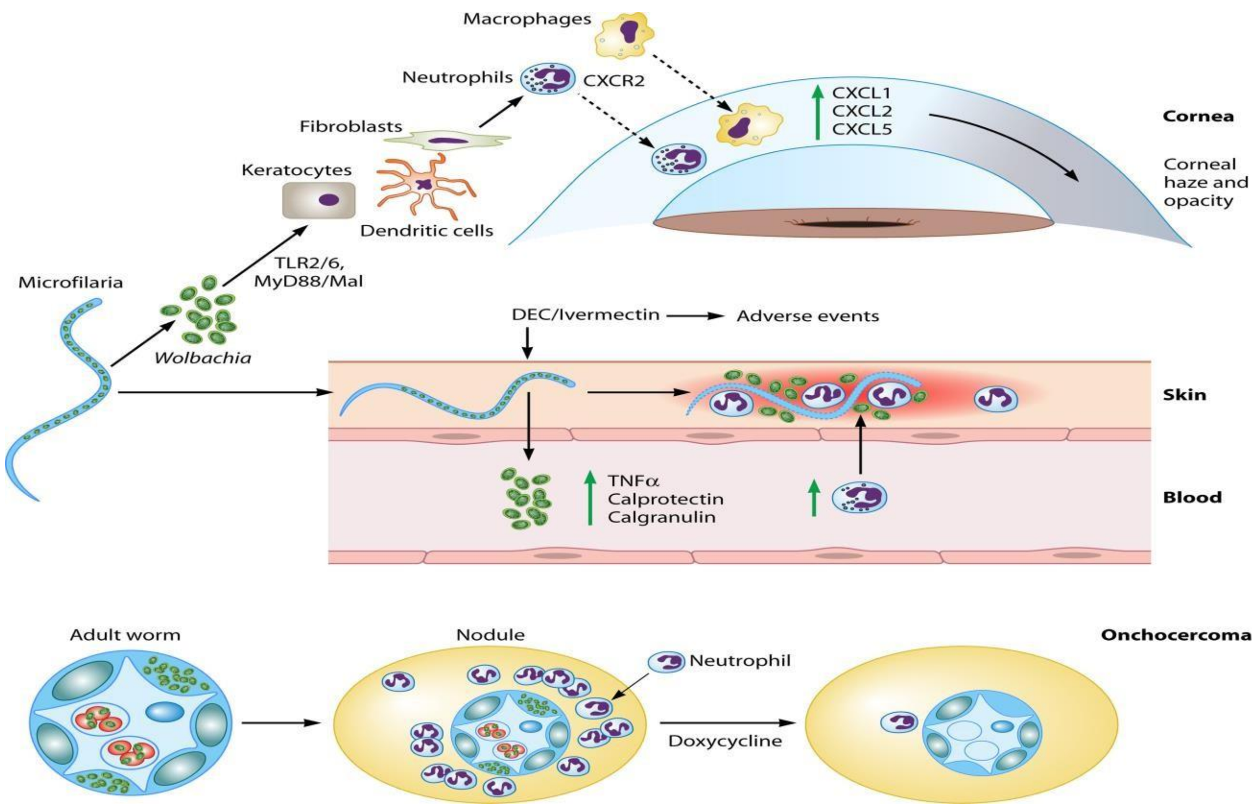

Figure 3. Wolbachia's role in the immunopathogenesis of river blindness

This illustration summarizes how *Wolbachia* contributes to developing ocular and systemic pathology in onchocerciasis (river blindness). When microfilariae die in ocular tissues, *Wolbachia* antigens are released, triggering the infiltration and activation of neutrophils and macrophages in the corneal stroma. This inflammatory cascade, mediated via TLR2-MyD88 signaling and CXC chemokine production, leads to corneal edema and opacity. Keratocytes and bone marrow-derived cells initiate this immune response, which is sustained by recruited inflammatory cells. In systemic and cutaneous tissues, microfilaricidal treatment causes the release of large quantities of *Wolbachia*, resulting in adverse effects such as fever, tachycardia, hypotension, lymphadenopathy, and pruritus. Neutrophils are the first responders in the skin, contributing to dermal inflammation. These pathological effects are associated with increased levels of proinflammatory cytokines, neutrophilia, antimicrobial peptides (e.g., calprotectin and calgranulin), circulating Wolbachia DNA, and overall bacterial burden. *Wolbachia* is consistently linked to neutrophilic infiltration in the skin, cornea, and onchocercomas (Tamarozzi *et al*., 2011).

Target for Chemotherapy

Antibiotics such as doxycycline target *Wolbachia*, decreasing the longevity of adult worms and the production of microfilariae. *Wolbachia*-targeted therapy presents a promising alternative to ivermectin, especially in regions where *Loa loa* is endemic and ivermectin is contraindicated (Taylor *et al*., 2010). Similarly, we also present the resistance of *Wolbachia* to antimicrobial agents (Table 2).

Table 2: Resistance of *Wolbachia* to Antimicrobial Agents

Factors	Characteristics
Mechanisms of Resistance	- Genetic mutations: Wolbachia's genetic structure changes could decrease susceptibility to antimicrobial agents. - Efflux pumps: Wolbachia might develop or upregulate efflux pumps, which reduce antibiotic accumulation. - Altered drug targets: Mutations in ribosomal or metabolic pathways that antibiotics typically target, leading to reduced drug binding or effectiveness.
Antibiotics in Use	- Doxycycline: The most extensively studied antibiotic inhibits protein synthesis in *Wolbachia*. - Rifampicin: It has also been shown to reduce the Wolbachia load, potentially allowing for shorter treatment duration. - Minocycline: A tetracycline alternative that has similar effects to doxycycline. - Macrolides: Investigated for their ability to target *Wolbachia* in some nematodes.
Evidence of Resistance	- There are a few documented cases of Wolbachia resistance, but potential exists due to extended treatment regimens. - Cross-resistance: Resistance to one antimicrobial agent (e.g., doxycycline) could decrease the effectiveness of other antibiotics.
Challenges with Resistance	- Long-term treatment: Prolonged use of antibiotics (e.g., doxycycline for 4–6 weeks) raises the risk of developing resistance. - Lack of alternative treatments: Resistance could undermine *Wolbachia*-targeted therapies, especially in areas with high antibiotic pressure.
Strategies to Mitigate Resistance	- Combination therapies: Utilizing multiple antimicrobial agents to target various Wolbachia pathways could decrease the risk of resistance. - Novel antibiotics: The development of new drugs that specifically and effectively target Wolbachia. - Surveillance and monitoring: Genetic tracking of Wolbachia populations for resistance markers.
Future Directions	- Understanding genetic basis: Investigate the genetic mechanisms behind *Wolbachia* resistance to develop better strategies. - Development of shorter-duration therapies: Focusing on more efficient antibiotics that can achieve the same therapeutic effects in less time. - Reducing reliance on antibiotics: Explore non-antibiotic approaches, such as gene silencing or immune modulation, to target *Wolbachia*.

Genetic Insights

Wolbachia genome sequencing reveals genes essential for heme, riboflavin, and nucleotide biosynthesis—functions crucial to host metabolism. This dependence highlights its significance in nematode physiology (Foster *et al*., 2005).

Bacteriophage WO and Horizontal Gene Transfer

Structure and Function

Phage WO is integrated into the *Wolbachia* genome and can influence host-symbiont dynamics. It carries eukaryotic-like genes, possibly facilitating host manipulation (LePage *et al*., 2017).

Genetic Exchange and Evolution

Evidence of lateral gene transfer between *Wolbachia* and hosts, mediated by phage WO, suggests an evolutionary mechanism for adaptation and symbiosis reinforcement (Bordenstein and Bordenstein, 2016).

Implications for Disease Control

Integrated Vector Management

Wolbachia's role in biocontrol aligns with integrated vector management (IVM) strategies. Releases of infected mosquitoes reduce arbovirus transmission sustainably and with community engagement.

Anti-filarial Therapies

Wolbachia-targeted chemotherapy offers long-term effects, interrupting transmission cycles. It presents a feasible complement to mass drug administration programs (Hoerauf *et al*., 2008).

One Health and Future Directions
Wolbachia's cross-kingdom relevance underscores its utility in One Health approaches. Future research should explore co-evolution, ecological impact, and resistance potential.

CONCLUSION

Wolbachia exemplifies the complexity of host-microbe interactions, functioning as both a reproductive parasite and a mutualist. Its influence on host biology and potential for disease control render it a valuable target in global health initiatives. Continued interdisciplinary research will further unveil its biology and improve its application in disease ecology and management.

Conflict of Interest
The authors declare no conflict of interest.

Funding for the Project
The research received no specific grant from funding agencies in the public, commercial, or non-profit sectors.

Author Contributions
Fadiji Oyinkansola S. and Rabiu Akeem G. designed the scope of the review. Together, we wrote the first draft, synergizing ideas and information. Bale Muritala I., Ebere Christian U., and Marcus Abidemi J. reviewed different sections and drafts of the manuscript, introducing tables and figures where necessary. Simiat Jimoh O. proofread all drafts of the manuscript, making corrections and suggestions to enhance it. Monsuru Adeleke A. is the expert on onchocerciasis consulted throughout this review.

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