Review

Biotechnological Potential of Microorganisms for Mosquito Population Control and Reduction of Vector Competence

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Biotechnological potential of microorganisms for mosquito population control and reduction of vector competence

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Simple Summary: Mosquitoes carry pathogens that can cause diseases like malaria, dengue fever, chikungunya, yellow fever, and Zika fever, causing more than 700,000 deaths each year around the world. Chemical pesticides kill mosquitoes effectively, minimizing the spread of illnesses. However, these chemicals have disadvantages such as high production costs and negative impacts on the environment and other organisms, including humans. Furthermore, mosquitoes are becoming more resistant to chemical pesticides. Therefore, alternatives to commonly used insecticides are urgently required. In this review, we highlight the biotechnological potential of microorganisms to control vector mosquitos and reduce disease transmission. In addition, we emphasize the importance of more basic research and improved translational research methods to bridge the gap between academic research on biopesticides and public health interventions.

Abstract: Mosquitoes transmit pathogens that cause human diseases such as malaria, Dengue fever, Chikungunya, yellow fever, Zika fever, and filariasis. Chemical pesticides are effective instruments for reducing disease transmission and managing mosquito populations. However, these chemicals have drawbacks such as high production costs and negative effects on the environment and non-target organisms. Furthermore, as mosquitoes develop resistance to chemical insecticides, they become less effective. As a result, researchers are investigating novel insecticides. Advances in microbial biotechnology have resulted in a wide range of value-added products, including biopesticides for agricultural and public health purposes. In this review, we highlight the mainly untapped biotechnological potential of microorganisms for vector mosquito control and disease transmission reduction. Also, we underline the importance of more basic research and improved translational research methodologies, encouraging efforts to bridge the gap between academic research on biopesticides and public health interventions.

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1. Introduction

Microorganisms constitute a large group of genetically diverse biological entities found in a wide range of terrestrial and aquatic habitats, playing crucial roles in the balance of ecosystems [1–3]. Advances in microbiology, molecular biology, and genomics enabled the biotechnological exploration of microbes, allowing the discovery and production of antibiotics [4,5], foods [6,7], alcoholic beverages [8], bioremediators [9,10], fertilizers [11], and biopesticides [12,13]. The microorganisms associated with mosquitoes have drawn special attention for their potential applications in public health (Figure 1) [14–16]. In this review, we highlight the largely unexplored

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potential of microbes for the control of mosquito-borne diseases and the need for better translational research strategies, encouraging efforts toward bridging the gap between academic research and public health interventions.

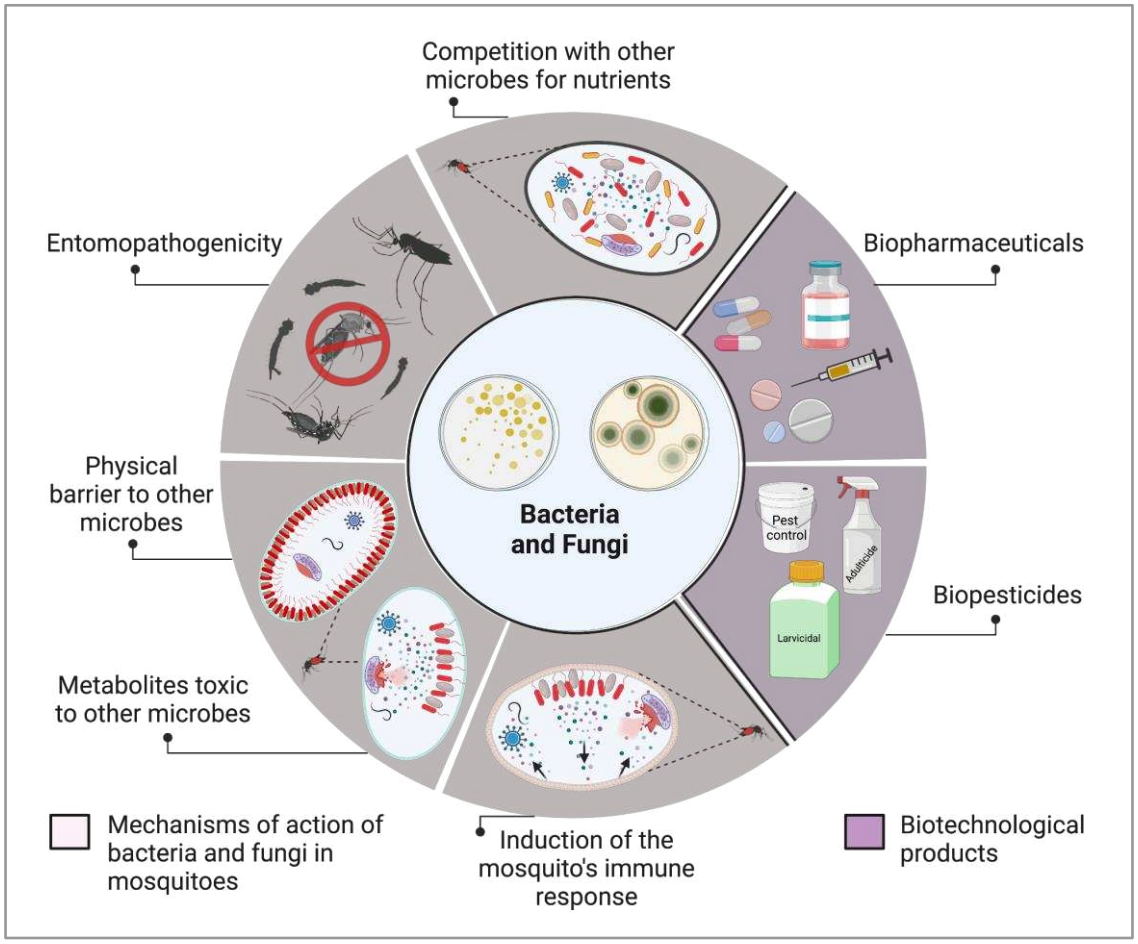

Figure 1. Environmental and symbiotic fungi and bacteria interact with mosquitoes and the mosquito microbiota, modulating the survival and development of both pathogenic microorganisms and the mosquito. Research that elucidates these interactions is essential for the development of novel biotechnological products for vector control and reduction of disease transmission. Created with BioRender.com.

2. Bacteria for biological control of medically important mosquitoes

Today, chemical insecticides are used as the main tool for mosquito control [17,18], but are no longer as effective as in the past due to the selection of insecticide resistant individuals in mosquito populations worldwide [19–22]. Furthermore, chemical insecticides harm the environment, contaminating groundwater systems through infiltration into the soil, reaching riverbeds, accumulating in fish and other animals [23], and through spraying, contaminating the air, affecting human health [24,25]. These facts emphasize the prominent need to develop new, efficient, and environmentally safe tools for the control of vector mosquitoes and the diseases they transmit.

Bacteria of the Bacillaceae family infect insects and produce toxins with insecticidal properties. *Bacillus thuringiensis israelensis* (Bti) and *Lysinibacillus sphaericus* (Lbs), the latter formerly known as *Bacillus sphaericus*, are widely known for their larvicidal activity against several species of mosquitoes [26–30]. Due to their high efficacy, safety, and the well-characterized mechanisms of action of their toxins, several strains of Bti and Lbs are included in commercially available biological larvicide formulations endorsed by organizations such as the World Health Organization [31] and the Environmental Protection Agency (EPA) in the United States of America (www.epa.gov/mosquitocontrol/bti-mosquito-control).

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The toxins of Bti and Lbs and the mechanisms associated with mosquito mortality have been extensively studied [32,33]. Briefly, in Bti, the molecules responsible for the entomopathogenic action are mainly the crystal toxins Cry4Aa, Cry4Ba, Cry10Aa, and Cry11Aa, the cytolytic toxins Cyt1Aa, and Cyt2Ba, and the P19 and P20 proteins [34,35]. Cry and Cyt toxins, also known as δ-endotoxins, when present in the midgut of mosquito larvae, are proteolytically activated by digestive proteases, bind to specific receptors on the host cell membranes, and cause cell rupture, resulting in death of infected larvae [36]. The Lbs Bin toxins [37–39], Mtx [40], Cry48Aa and Cry49Aa [41], display entomopathogenic mechanisms similar to those described above for the Bti toxins [42]. Acting synergistically, these toxins result in effective and potent toxic activity against mosquitoes [43–45].

Finding new microbes with larvicidal activities similar to those of Bti and Lbs has been the goal of several research groups around the world. However, this endeavor has been limited by the fact that culture media do not always meet the requirements for the growth of many species of bacteria [46]. Therefore, the search for entomopathogenic bacteria is often limited to those that grow in commercially available culture media. Despite these limitations, bacterial strains that are suitable for cultivation and have larvicidal activity have been identified. Unfortunately, most of them have not been further investigated, developed to applicable products, or tested under field or semi-field conditions. Additional research to understand their mechanisms of action, effects on non-target organisms and potential for large-scale production is needed.

Toward these goals, live bacteria, deactivated bacteria, and fractionated cells or culture media have been tested for their larvicidal activities. For example, *Bacillus safensis*, *Bacillus paranthracis*, and *Bacillus velezensis* culture supernatants and crude lipopeptide extracts were shown to be toxic to *Aedes aegypti* [47]. Whole genome sequencing and mass spectrometry analysis of those isolated bacteria strains revealed that these microorganisms synthesize bacteriocin, beta-lactone, and terpenes potentially toxic to mosquito larvae [47]. Nineteen *Bacillus sp*. strains and two strains of *Brevibacillus halotolerans* isolated from Amazonian environments showed larvicidal activity against *Ae. aegypti* [48]. The supernatant and pellet fractions of those strains were tested separately, revealing that cellular and secreted metabolites are toxic to mosquito larvae. *Bacillus mojavensis* kills *Ae. aegypti* larvae and its action was provisionally attributed to the biosurfactant surfactin thioesterase [49]. The testing of whole or fractionated bacteria and culture media is useful for defining procedures and formulation of new and promising biolarvicides. The identification of bacteria with mosquito larvicidal activities, in addition to Bti and Lbs (Table 1,) instigates their exploration as potential tools for mosquito control.

Table 1. Bacterial strains toxic to *Aedes*, *Culex* and/or *Anopheles* mosquito larvae.

Bacterium	Toxic formulation	Target mosquito genera			Refs
		Aedes	*Culex*	*Anopheles*	
Bacillus thuringiensis var. israelensis (Bti)	Extract (spores and crystals)	+	-	-	[50]
	Sporulated culture powder (Tablet formulation XL-47)	+	-	-	[51]
	Spores and crystals tablet	+	-	-	[52]
	Spores and crystals tablet	+	-	-	[53]
	VectoBac WG	+	-	-	[54]
	Formulated product	-	+	-	[55]
	Binary mixtures (Bti plus Deltamethrin)	-	+	-	[56]
	Cry2Aa and Cyt1Aa crystals	-	+	-	[57]

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	Crystallogenic variants.	+	+	-	[58]
	Two recombinant proteins (Cry10Aa and Cyt2Ba)	+	-	-	[59]
	Xpp81Aa toxin combined with Cry2Aa and Cry4Aa	+	-	-	[35]
	Kappa-carrageenan and Vectobac 12 AS hydrogels	+	-	-	[60]
	Bti extracts	+	-	-	[61]
	Vectobac® AS	-	+	-	[62]
	Granular formulation (Vectobac G)	-	-	+	[63]
	Dispersible granule (strain AM65-52)	+	+	+	[64]
	Bti strain Becker Microbial Products (BMP)	-	+	+	[65]
	Bti product VECTOBAC TP® sprayed	-	-	+	[66]
	Bti Water Dispersible Granular (WDG) formulation	-	-	+	[67]
	Water dispersible granule (Bti strain AM65-52 formulation, VectoBac® WDG)	-	-	+	[68]
	Water-dispersible granule Bti VectoBac (WDG)	-	-	+	[69]
	Bti VectoBac® WG, AM65-52 strain	-	-	+	[70]
Bacillus thuringiensis (Other strains)	Total and lyophilised culture	+	+	-	[71]
	Bacterial cultures	+	+	+	[72]
	Bacterial suspensions (spores and crystals)	+	-	-	[73]
	Spores	+	+	+	[74,75]
	Parasporal crystalline inclusion bodies	+	-	-	[35]
	Culture supernatant	+	-	+	[29]
	Synergistic interaction (Purified Cry11Aa and Cyt1Aa Toxins)	+	-	-	[76]
	Synergistic action of the Cry and Cyt proteins	-	-	+	[77]
Lysinibacillus sphaericus (Lbs)	Culture supernatant	+	-	+	[29]

	Spores and vegetative cells	+	+	-	[30]
	Cell suspension plus glyphosate	+	-	-	[78]
	Spore crystals (lyophilized powder)	+	+	+	[79]
	Spores	-	+	-	[80]
	Granular formulation (Vectobac G)	-	+	+	[63]
	Vectolex G	-	+	-	[81]
	S-layer protein	-	+	-	[82]
	Purified BinA and BinB proteins	-	+	+	[83,84]
	Spore-crystals and purified S-layers protein	-	+	+	[85]
	Synergy of Mtx and Cry proteins	-	+	-	[44]
	Purified BinA and BinB proteins	-	+	-	[39]
	VectoLex® WG plus Pyrethroid Resigen®	-	+	-	[86]
	Cry48Aa and Cry49Aa proteins combined	-	+	-	[87]
	Synergistic interaction (S-Layer and spores/crystals)	-	+	-	[88]
	VectoLex (ABG-6185)	-	-	+	[89]
	Suspension (Lyophilized bacteria)	-	-	+	[90]
	VectoLex® CG	-	-	+	[91]
	Bin toxin proteins	-	-	+	[92]
Acidovorax sp.	Cell-Free Supernatant	+	-	-	[93]
Aneurinibacillus aneurinilyticus	Bacterial suspension	+	+	+	[94]
Bacillus amyloliquefaciens	Biosurfactant	+	+	+	[95]
Bacillus cereus	Culture supernatant	+	-	+	[29]
Bacillus circulans	Spores	+	+	+	[96]
Brevibacillus halotolerans	Supernatant and pellet fractions of bacterial cultures	+	-	-	[48]
Bacillus licheniformis	Dahb1 exopolysaccharide (Bl-EPS)	+	-	+	[97]
Brevibacillus laterosporus	Suspension of sporulated cells	+	-	+	[98]

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	Spore and the canoe-shaped parasporal body (CSPB) structure	+	-	-	[99]
	Purified protein crystals	+	-	+	[100]
	Pellets (cells and spores)	+	-	-	[101]
	Spores	+	-	-	[102]
Bacillus paranthracis	Pellets (cells)	+	-	-	[47]
Bacillus safensis	Supernatant and pellet fractions of bacterial cultures	+	-	-	[48]
	Pellets (cells)	+	-	-	[47]
Bacillus subtilis	Culture supernatant	+	-	+	[29]
	Crude cyclic lipopeptides (CLPs)	-	+	-	[103]
	Crude surfactin	-	-	+	[104]
	Bacterial biomass	+	-	-	[105]
	Biosurfactants	-	-	+	[106,107]
Bacillus megaterium	Bacterial culture	+	-	-	[48]
Bacillus nealsonii	Secondary metabolites	+	-	-	[108]
Bacillus tequilensis	Cyclic Lipopeptide Biosurfactant	-	-	+	[109]
Bacillus velezensis	Bacterial culture	+	-	-	[48]
	Pellets (cells)	+	-	-	[47]
Chromobacterium sp.	Hydrogen cyanide	+	-	+	[110,111]
Chromobacterium anophelis	Bacterial suspension	-	-	+	[112]
Pantoea stewartii	Silver nanoparticles	+	+	+	[113]
Paraclostridium bifermentans	Clostridial neurotoxin	-	-	+	[114]
Peanibacillus macerans	Bacterial biomass	+	-	-	[105]
Photorhabdus luminescens	Secondary metabolites (Culture fluids)	+	-	-	[115]
	Secondary metabolites	+	-	-	[116]
Photorhabdus luminescens subsp. akhurstii	Bacterial cell suspension	+	-	-	[117]
Pseudomonas sp.	Bacterial cell suspension	-	+	-	[84]
Priestia aryabhattai	Silver nanoparticles	+	+	+	[113]
Serratia marcescens	Prodigiosin	+	-	+	[118,119]
	Bacterial suspension	+	-	-	[120]

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Serratia nematodiphila	Bacterial cultures	+	+	+	[72]
Saccharopolyspora spinosa	Spinosad (Tracer®)	+	-	+	[121]
	Spinosad formulation	+	+	+	[122]
	Spinosad-based product (Laser®)	+	+	+	[123]
	Spinosad	+	-	-	[124]
	Spinosad - Tablet (DT) and granules (GR)	+	-	-	[125]
	Spinosad powder	-	+	-	[126]
	Spinosad formulation	-	-	+	[127,128]
	Natular T-30 formulation	-	+	-	[129]
	Formulation Emulsifiable Concentrate	-	+	-	[130]
Streptomyces sp.	Secondary metabolites	+	-	-	[108,131]
Xenorhabdus indica	Bacterial cell suspension	+	-	-	[117]
Xenorhabdus nematophila	Secondary metabolites	+	-	-	[116]
	Secondary metabolites (Culture fluids)	+	-	-	[115]
Xenorhabdus stockiae	Bacterial cell suspension	+	-	-	[117]

This list is not exhaustive but provides ideas for future research and product development opportunities.

3. Fungi as vector mosquito biocontrol agents

Fungi, and their metabolites are also potentially useful for the control of medically important mosquitoes [132–137]. In fact, fungal strains have already been applied as complementary measures for the control of vector mosquitoes [138–141].

Beauveria bassiana strains infect and kill a variety of insects, including mosquitoes. Application of *B. bassiana* spores on surfaces where mosquitoes rest [142], the impregnation of spores in traps [143], association of the fungus with insecticides, such as the combination of *B. bassiana* and permethrin [144] and the spread of the fungus by females mating with pre-inoculated males [145] have been proposed as means of field applications of *B. bassiana* against mosquitoes. The attraction of *An. stephensi* to spores of *B. bassiana* present in dead and dying caterpillars infected with the fungus [146], has been proposed as a useful alternative to infect mosquitoes. Furthermore, experimental evolution has been applied successfully to increase the efficacy of *B. bassiana* to *Anopheles coluzzii* [147].

Exposure to lethal and sublethal doses of *B. bassiana* spores decreases *Ae. aegypti* and *Ae. albopictus* host-seeking behavior and fecundity [132,148]. Infected mosquitoes, while still alive, spread the fungus through the vector population. *Beauveria bassiana* spores and extracts are also effective against mosquito larvae [149–151]. As a result of this evidence, several strains of *B. bassiana* are authorized for use as biological insecticides, against vector mosquitoes, by regulatory agencies such as the EPA [152] and ANVISA in Brazil [153].

Metarhizium anisopliae is another fungus with biotechnological potential for mosquito control [154]. Its entomopathogenic mechanism is similar to that of *B. bassiana*. After contact, the spores germinate, producing hyphae, which in turn penetrate the insect exoskeleton, developing inside the host's body [155,156].

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Metarhizium anisopliae CN6S1W1 is effective against *Ae. albopictus* and *Cx. pipiens* [157]. The fungus also affects the behavior of *An. gambiae* mosquitoes by inhibiting blood feeding and reducing fecundity and oviposition [158]. Concurrent infections with both *M. anisopliae* and *B. bassiana* shorten the lifespan of *Ae. aegypti* [142,159]. The synergistic actions of *M. anisopliae* and *B. bassiana*, together with the imidacloprid immunosuppressant, showed a greater larvicidal activity against *Cx. quinquefasciatus* than the respective entomopathogens alone [160]. The metabolites isolated from *M. anisopliae* are also active against *Ae. aegypti*, *An. stephensi,* and *Cx. quinquefasciatus* [135]. These metabolites represent a solution for mosquito larvae control, since *M. anisopliae* conidia are not effective in the aquatic environment [161].

In addition to *B. bassiana* and *M. anisopliae*, other fungi have been reported with high biotechnological potential for mosquito control. The killing activity of *Aspergillus nomius* spores toward adult *Ae. albopictus* was comparable to those of *B. bassiana* [162]. Crude and purified extracellular extracts of *Aspergillus* with larvicidal action against *An. stephensi*, *Cx. quinquefasciatus,* and *Ae. aegypti* were reported [163]. Di-N-Octyl phthalate, (1H-Benzoimidazole-2-Yl)-[4-(4-Methyl-Piperazin-1-Yl)-Phenyl]-Amine, and 6,8-Dimethyl-5-Oxo-2,3,5,8-Tetrahydroimidazo [1,2-A] Pyrimidine, secondary metabolites of *Aspergillus flavus* and *Aspergillus fumigatus* [164] and preg-4-en-3-one, 17. α-hydroxy-17. β-cyano-, trans-3-undecene-1,5-diyne, and pentane, 1,1,1,5-tetrachloro-, from *Aspergillus tamarii* have been suggested to be responsible for larvicidal activity [165]. The biosafety of products derived from *Aspergillus spp*, or the fungus itself, still needs to be investigated. Suspensions of *A. flavus* conidia exhibited considerable toxicity against non-target organisms present in aquatic environments of mosquito larvae [166].

Species of the genus *Isaria* also have entomopathogenic characteristics for mosquito control. *Isaria tenuipes* [167], *Isaria javanica* ARSEF 5874 and *Isaria cateniannulata* ARSEF 6241 strains showed high levels of pathogenicity toward *Ae. aegypti* [134]. Larvicidal activity against *Cx. quinquefasciatus* and *Ae. aegypti* were demonstrated with silver nanoparticles (AgNps), with secondary metabolites of *Isaria fumosorosea* (Ifr) [168]. Other fungal species of interest that may be useful for vector control include *Trichoderma asperellum* [169] and *Hyalodendriella sp*. [170] which produce metabolites toxic to mosquitoes.

Table 2. Fungal strains toxic to *Aedes*, *Culex,* and/or *Anopheles* mosquito larvae.

Fungus	**Toxic formulation**	**Target mosquito genera**			**Refs**
		Aedes	*Culex*	*Anopheles*	
Beauveria bassiana	Fungal suspensions	+	-	-	[142]
	Surfaces treated with conidia	+	-	-	[145]
	Spores	+	-	-	[132]
	Oil-formulated spores	-	-	+	[146]
	Fungal suspensions	-	-	+	[149]
	Spores	-	-	+	[147]
	Fungal suspensions	+	+	-	[171]
Metarhizium anisopliae	Conidial suspension	-	+	-	[172]
	Fungal conidia	+	-	-	[173]
	Fungal suspensions	+	-	-	[142]

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	Conidial suspension	+	+	-	[157]
	Oil formulation	-	+	+	[174]
	Secondary metabolites	+	+	+	[175]
Aspergillus niger	Crude metabolites	+	+	+	[163]
Aspergillus flavus	Secondary metabolites	+	+	+	[164]
	Suspensions of conidia	+	-	-	[166]
	Culture filtrates	-	+	-	[176]
Aspergillus fumigatus	Secondary metabolites	+	+	+	[164]
Aspergillus parasiticus	Culture filtrates	-	+	-	[176]
Aspergillus tamarii	Endophytic Fungal Extracts	+	+	-	[165]
Aspergillus terreus	Mycelia (Ethyl acetate and methanol extracts)	+	+	+	[177]
	Emodin compound	+	+	+	[178]
Aspergillus nomius	Spores	+	-	-	[162]
Beauveria tenella	Blastospores suspensions	+	+	-	[179]
Cladophialophora bantiana	Secondary metabolites	+	+	-	[180]
Chrysosporium lobatum	Secondary metabolites	-	+	+	[181]
Chrysosporium tropicum	Secondary metabolites	+	+	+	[182]
Fusarium moniliforme	Isoquinoline type pigment	+	-	+	[183]
Fusarium oxysporum	Temephos + F. oxysporum extract	+	+	+	[184]
Fusarium vasinfectum	Culture filtrates	-	+	-	[176]
Isaria javanica	Conidial suspensions	+	-	-	[134]
Isaria cateniannulata	Conidial suspensions	+	-	-	[134]
Isaria tenuipes	Conidial suspensions	+	-	-	[167]
Isaria fumosorosea	Secondary metabolites	+	+	-	[168]
Paecilomyces sp.	Secondary metabolites	+	+	+	[131]
Penicillium daleae	Mycelium extract	+	+	-	[185]
Penicillium falicum	Culture filtrates	-	+	-	[176]
Penicillium marneffei	Spores	-	+	-	[186]
Penicillium sp.	Ethyl acetate extract	-	+	-	[187]

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	Ethyl acetate extract	+	+	-	[188]
Pestalotiopsis virgulata	Ethyl acetate mycelia (EAM) extracts and liquid culture media (LCM)	+	-	+	[189]
Podospora sp.	Sterigmatocystin compound	-	-	+	[190]
Pycnoporus sanguineus	Ethyl acetate mycelia (EAM) extracts and liquid culture media (LCM)	+	-	+	[189]
Trichoderma asperellum	Methanolic extract	-	-	+	[169]
Trichoderma harzianum	Mycosynthesized silver nanoparticles (Ag NPs)	+	-	-	[191]
Trichoderma viride	Culture filtrates	-	+	-	[176]
Hyalodendriella sp.	EtOAc extract	+	-	-	[170]
Verticilluim lecanii	Spores	-	+	-	[186]

This list is not exhaustive but provides ideas for future research and product development opportunities.

4. The role of insect-bacteria associations in vector competence

Associations between mosquitoes and their and microbiota have gained significant attention in scientific research due to their impact on vector competence [192–197]. Following, we discuss ways these associations can influence vector competence, including the blocking of pathogen infection through the distinctive properties of symbiotic microorganisms, stimulation of the vector's immune system, and the utilization of symbionts for paratransgenesis. Understanding these interactions is essential for developing effective vector-borne disease control strategies to reduce the impact of these diseases on public health.

4.1. Symbiotic bacteria and their potential against infectious agents

The mosquito microbiota influences host development, nutrition, reproduction, and immune responses to invading organisms [198–201]. While the composition of the mosquito microbiota is largely defined by the environment in which they live [202–204], resident bacteria can modulate the development and replication of parasites and viruses within their vectors [205–212]. Although this modulation can enhance or reduce the survival and replication of pathogens within mosquitoes, those mosquito-microbiota interactions that negatively affect pathogens offer innovative possibilities to control arthropod-borne diseases.

For example, the gram-negative bacteria, *Escherichia coli* H243, *E. coli* HB101, *Pseudomonas aeruginosa* and *Ewingella americana* inhibit the formation of *Plasmodium falciparum* oocysts, in *Anopheles stephensi* [213]. *Enterobacter sp.* (*Esp*_Z), isolated from the intestine of *Anopheles gambiae*, inhibited the development of malaria parasites when reintroduced into this same vector species [214,215]. *The formation of oocysts of Plasmodium berghei* was affected by the presence of *Serratia marcescens*-HB3 in *An. stephensi* [216]. In *Anopheles gambiae*, *Escherichia coli*, *S. marcescens*, and *Pseudomonas stutzeri reduced* the prevalence and intensity of *P. falciparum* infection [217]. The *Serratia* Y1 strain exerts inhibitory activity on *P. berghei* ookinetes by activation of the Toll immune pathway in *An. stephensi* [218]. *Serratia ureilytica* (Su_YN1) produces an antimalarial lipase (AmLip) that inhibits the formation of *P. falciparum* oocysts in *An. stephensi* and *An. gambiae* [219]. *Asaia* SF2.1 also inhibits *Plasmodium* development in anophelines [220].

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Virus replication in their vectors is also regulated by the mosquito microbiota. Bacteria of the genera *Proteus*, *Paenibacillus*, and *Chromobacterium* inhibited the replication of dengue virus serotype 2 (DENV-2) when administered to mosquitoes [110,221]. Some of the mechanisms by which symbiotic bacteria can hamper pathogen development have been elucidated and can be exploited to inhibit the spread of infectious agents by mosquitoes (Figure 2).

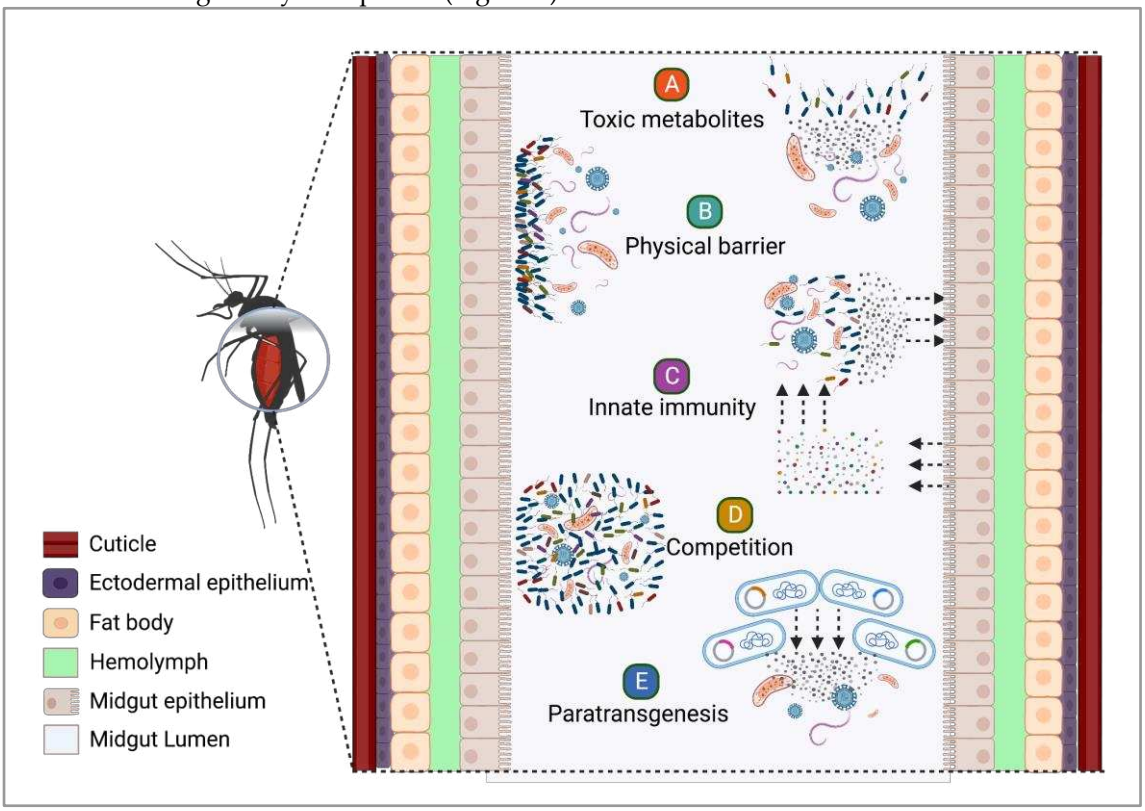

Figure 2. Biotechnological potential of mosquito symbiotic bacteria against infectious agents. **A**, Secretion of toxic substances that either kill or arrest the development and replication of viruses and parasites. **B**, formation of physical barriers through large population accumulation or rearrangements of molecules secreted into the midgut lumen, preventing the passage of parasites to organs essential for their successful development. **C**, activation of the mosquito immune system, which not only reduces the load of symbiotic bacteria but also leads to the elimination of invading parasites through the secretion of toxic molecules, preventing their propagation in the mosquito's body. **D**, competition with infectious agents for space and nutrients can have dire consequences for these pathogens as they must compete with a vastly larger population of symbiotic bacteria in the mosquito's midgut lumen. This results in limited resources for the pathogens, ultimately leading to their decreased survival and replication within the mosquito. **E**, paratransgenesis approach to synthesize and secrete antipathogen molecules. If this approach receives more attention and research funding from government agencies in endemic countries, it could have a significant impact on reducing the transmission of vector-borne diseases. This topic is further explored in topic 4.3 of this review. Created with BioRender.com.

The *w*Mel and *w*AlbB strains of *Wolbachia pipientis*, an intracellular bacterium, inhibit dengue, chikungunya, and Zika virus replication within mosquito cells [222–226]. However, another *Wolbachia* strain, *w*Pip, does not inhibit virus infection in *Ae. aegypti* [227] and the mechanism by which *Wolbachia* interferes with virus replication has not been fully elucidated. Current hypotheses include competition between *Wolbachia* and the virus for physical space within mosquito cells and metabolite resources [228,229] and *Wolbachia* induced modulation of the host's immune system and immune priming [230,231].

Despite the lack of a complete understanding of the mechanism or mechanisms involved in *Wolbachia*-associated modulation of viral suppression, the *Wolbachia*-carrying mosquito-based strategy has been deployed as a public health intervention to control dengue transmission (The World

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Mosquito Program https://www.worldmosquitoprogram.org/). A randomized study carried out in the city of Yogiakarta, Indonesia, compared the areas where *Ae. aegypti* infected *Wolbachia* was released with areas without *Wolbachia* and revealed a 77% lower incidence of dengue cases, in the Wolbachia-treated area [232]. Another study conducted in the city of Niterói, Rio de Janeiro, Brazil, reported a 69% reduction in dengue, 56% in chikungunya, and a 37% reduction in Zika incidence three years after the beginning of the release of *Ae. aegypti* with *Wolbachia* [233].

Although these results bring optimism regarding the use of *Wolbachia* for the control of dengue transmission, these bacteria can have variable effects on mosquito-borne viruses. For example, the *Wolbachia* strain *w*Mel strongly blocked Mayaro virus (MAYV) infections in *Ae. aegypti*, but another strain, *w*AlbB, did not influence on MAYV infection in this same vector. *Aedes aegypti* infected with *w*AlbB and *w*Mel showed enhanced Sindbis virus infection rates [234]. The variable effects of *Wolbachia* on vector competence bring into question the safety of the current release of *Wolbachia*-infected mosquitoes. Furthermore, the potential impact of these bacteria on biodiversity has not been thoroughly investigated [235,236], and the risk of the emergence of DENV variants that escape virus-specific inhibition in *Wolbachia* infected mosquitoes [237,238], underscores the importance of further research on interactions between *Wolbachia*, mosquitoes, viruses, and other organisms.

The intracellular bacterium *Wolbachia pipientis* has also been used to create conditional sterility between released males and wild-type females through cytoplasmic incompatibility [239]. Large-scale trials of *Ae. aegypti* population suppression carried out from 2017 to 2018 in California and based on the release of 7.5 million and 14.4 million *Wolbachia*-infected male mosquitoes, resulted in mosquito population suppression rates of 69% and 95%, respectively. Since 2011 in the United States, the Environmental Protection Agency (EPA) has regulated *Wolbachia* as a biopesticide [240].

4.2. Exploring the potential of fungi as anti-Plasmodium agents for malaria control

Fungi with potential antiparasitic properties, particularly against protozoa of the genus *Plasmodium*, have been researched as a potential tool to combat malaria. Endophytic fungi isolated from different organs of *Annona muricata*, a medicinal plant commonly used in traditional Cameroonian medicine against malaria, completely inhibited the growth of *P. falciparum in vitro*. Of the 152 fungi tested, 17.7% showed activities against different strains of the parasite, with the strongest effects from fungi belonging to the genus *Fusarium*, *Thricoderma*, *Aspergillus*, *Penicillium*, and *Neocosmopora* [241]. Compounds such as oxylipin and alternarlactones from *Penicillium herquei* and *Alternaria alternata* respectively, demonstrated *in vitro* antiplasmodial activity [242,243]. A killer toxin purified from *Wickerhamomyces anomalus*, a symbiotic yeast of insects, when supplemented in a mosquito diet interfered with the development of ookines in the *An. stephensi* midgut [244]. *Aspergillus* also showed antiplasmodial activity when supplemented in the mosquito diet. This activity was shown to be related to inhibition of the interaction between parasites and fibrinogen-related protein-1 (FREP1), an agonist of gametocytes and ookinetes [245]. These authors identified the fungal metabolite orlandin as a candidate reagent to inhibit *P. falciparum* infection in *An. gambiae*.

The topical application or spraying of *B. bassiana* on the mosquito cage mesh killed ~92% of *An. stephensi* on day 14 after exposure and reduced the number of *Plasmodium chabaudi* sporozoite positive mosquitoes. Although no impact on early stages of the parasite (gametocytes and oocyst stages) was noted, the combined effect of mosquito mortality and reduced sporozoite prevalence was estimated to result in the reduction of malaria transmission risk by a factor of about 80 [246]. However, other studies did not show an impact of *B. bassiana* or *M. anisopliae* on the development of *Plasmodium* species in *Anopheles* mosquitoes [247,248].

Metarhizium anisopliae has been genetically transformed to express anti-*Plasmodium* proteins. Mosquitos treated with transgenic *M. anisopliae* had 71-98% fewer sporozoites present in their salivary glands [248]. Scorpine, one of the molecules expressed by transgenic *M. anisopliae*, also affects negatively dengue virus replication, expanding the application of genetically transformed fungi to control arbovirus transmission [249]. This study supports the concept of engineering fungi to express proteins that can impact the development of pathogens in mosquitoes and further their use as biopesticides.

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4.3. Symbiotic microorganisms and paratransgenesis

Paratransgenesis involves the colonization of vector insects with genetically engineered symbiotic microorganisms that are effective in inhibiting parasite development [250–253]. Ideal symbionts for effective paratransgenesis are easily manipulated genetically, colonize mosquitoes efficiently, spread into mosquito populations (vertical and horizontal transmission), and are efficient in inhibiting pathogen development in mosquitoes [254]. Proof-of-principle experiments demonstrated that genetically modified bacteria expressing antipathogen molecules are capable of interfering or blocking the development of malaria parasites in mosquitoes [255–257]. Among the mosquito symbiotic bacteria, strains of *Asaia*, *Pantoea*, *Serratia*, *Pseudomonas,* and *Thorsellia* have been evaluated as candidates for paratransgenesis [258–262].

Advances toward deploying paratransgenesis as a tool for blocking pathogen transmission by mosquitoes include the identification of anti-pathogen effector peptides [251,256]. The secretion of effector molecules from the cytoplasm of bacteria into the lumen of the mosquito intestine has been engineered using the *Escherichia coli* hemolysin-A secretion system [263]. The discovery of mosquito symbiotic bacteria [256,264–266], viruses [267–270] and fungi [271] is an active area of research. Safety concerns about the release of engineered bacteria into the environment and any uncertain consequences that might occur still need to be addressed when considering paratransgenesis field tests. Self-limiting paratransgenesis [254] has been suggested as an alternative for initial field trials. This approach proposes the utilization of transient expression of antipathogen compounds from a plasmid that is gradually lost, reverting bacteria to their original wild type. Risk assessment still needs to be carried out and laws and regulations need to be created and enacted before paratransgenesis can be tested in field conditions. However, the processes by which genetically modified microorganisms (GMs) can be spread in nature and how they should act to inhibit the development of target parasites in mosquitoes have already been envisaged. This is illustrated in Figure 3, which presents the paratransgenesis process as a multifaceted approach to combating mosquito-borne diseases using GM microorganisms.

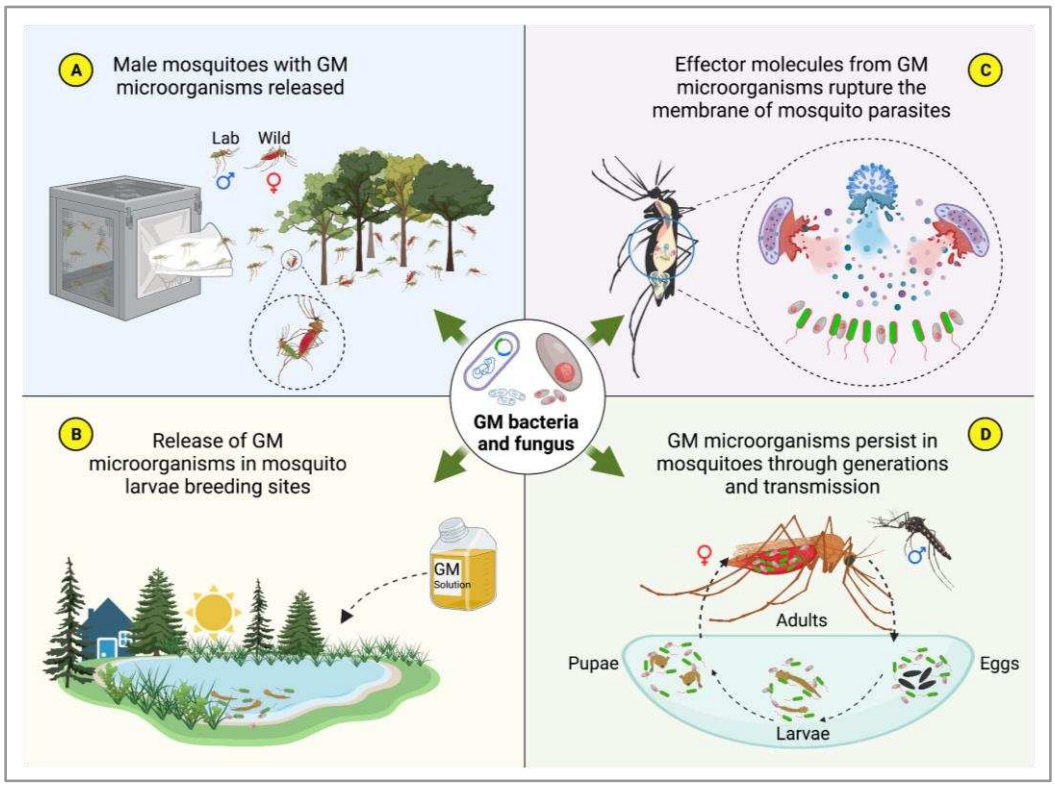

Figure 3. Paratransgenesis: A multifaceted approach to combating mosquito-borne diseases using GM microorganisms. **A**, in the laboratory, male mosquitoes are fed a sucrose solution containing GM microorganisms and then released into the wild to mate with wild females. This enables the

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transmission of the GM microorganisms forward, allowing them to spread throughout the population of wild mosquitoes and helping to reduce the transmission of vector-borne diseases. **B**, release of GM microorganisms in natural larval breeding sites. GM microorganisms are ingested by larvae and remain associated until the adult phase. If the mosquitoes become infected with any virus or parasite, the GM microorganisms will interfere with the development of the pathogen, thus preventing their transmission. This would result in a reduction in the burden of diseases in the region. **C**, GM microorganisms can express effector molecules that act directly on the membrane of target parasites in the gut of adult female mosquitoes. These molecules can cause the parasite membrane to rupture, leading to their death or inability to develop. **D**, persistence of GM microorganisms in mosquitoes for generations through vertical and horizontal transmission. Vertical transmission occurs from parents to their offspring, while horizontal transmission occurs between mosquitoes during mating or sharing of breeding sites. The presence of GM microorganisms can continue to affect mosquito populations for a prolonged period. While it is important to carefully evaluate and monitor the release of GM microorganisms, it is also important to highlight their potential for controlling vector-borne diseases. Created with BioRender.com.

5. Roadmap for the development of microbe-based products for controlling mosquito borne diseases

In this review article, we explored the biotechnological potential of microorganisms for mosquito population control and reduction of vector competence. We list many microbial agents with mosquito larvicidal activity and provide information on their active metabolites and mechanisms of action. However, most of these mosquitocidal microorganisms and their metabolites have not been developed into new products and marketed as tools and innovations that can be applied to public health interventions. The explanation for the few biolarvicides available on the market is complex and is determined by technical, regulatory, social, and economic factors.

For example, the Organization for Economic Co-operation and Development (OECD) provided a document with Data Requirements and Approaches to Biological Pesticide Registration (https://www.oecd.org/env/ehs/pesticides-biocides/data-for-biopesticide-registration.htm) including Guidance for Registration Requirements for Microbial Pesticides (https://one.oecd.org/document/env/jm/mono(2003)5/en/pdf). Accordingly, the Regulation of European Commission (EC) No. 1107/2009 regarding criteria for the approval of microbial pesticides emphasizes the importance of assessing the active substances or the microorganisms themselves for effects on the environment or harmful effects on human or animal health [272]. These directives require collaborative research efforts which may take years to complete. In the United States, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires similar assessments, and the U.S. Environmental Protection Agency (EPA) evaluates biopesticides to assure they do not pose unreasonable risks of harm to human health and the environment.

In Brazil [273], the registration of new pesticides, including biolarvicides, requires evaluation by three federal government agencies that assess them independently and in a specific manner. The Ministry of Agriculture and Livestock (Ministério da Agricultura e Pecuária -MAP) evaluates efficiency and potential for use in pest control; the Brazilian Institute of the Environment and Renewable Natural Resources (Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis-IBAMA) provides an environmental report; and the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária-ANVISA) conducts the toxicological dossier, assessing the product's toxicity for the population and the restrictions and requirements for pesticide use. Like in Europe, the USA, and Brazil, regulatory agencies around the world regulate the registration and application of biopesticides, monitoring efficacy and safety.

The main stages for discovering and developing new larvicides, based on the requirements set forth by the government entities mentioned above, have previously been reviewed [274–276]. In summary, the process consists of 1) Discover larvicidal microorganisms; 2) Identify the mechanisms

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of action of larvicidal microorganisms (live microbial fractions versus metabolites fractions); 3) Evaluating human toxicity and pathogenicity of microorganisms and evaluating their effects on nontarget organisms and the environment; 4) Determine the stability of the candidate larvicide product under field conditions and its shelf life considering its applications in tropical/subtropical, hot and humid environments; 5) Compare the activity of the candidate product with currently available larvicides; and 6) Cost analysis (production, storage, transportation, and field application costs) and research of market viability.

Similar considerations will be necessary for the applications designed for reducing disease transmission, such deployment of microorganisms with antiparasitic activity, including paratransgenesis discussed above.

We hope that this review will encourage additional research and investment in the development of new biopesticides, highlighting the need to follow the requirements established by regulatory agencies for the approval and registration of products that will assist in the control of mosquitoes and the diseases they transmit.

6. Final considerations

Biotechnological approaches using microorganisms have a significant potential to control mosquito populations and reduce their vector competence, making them alternatives to synthetic insecticides. The ongoing research has been crucial in identifying new products and approaches that can be used effectively to control disease transmission. However, the successful implementation of these newly proposed approaches requires a thorough understanding of the multipronged microorganism-mosquito-pathogen-environment interactions. The release of mosquitoes or microorganisms, genetically modified or not, into the environment requires an assessment of the associated risks and benefits. Therefore, environmental and ethical implications of these proposed releases are active areas of debate [277,278].

Although much has been done in discovering new entomopathogenic microorganisms, antipathogen compounds, and their mechanisms of action, reviewed above, only a few have been turned into viable products for mosquito control such as the Bti and Lbs. There is a discrepancy between the number of microorganisms with potential for the development of new products and the actual available products, highlighting the need for investments in the intersection of research and biotechnology to improve the transition of basic into applied research.

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