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Innovative Approaches to Mosquito Control: A Comprehensive Review on Beneficial Bacteria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Mosquito bites spread many deadly diseases like dengue, chikungunya, zika virus, malaria etc. The spread of these diseases can be controlled by checking the mosquito population. Bacterial control is an effective way to kill mosquitoes without harming non-target organisms. The review discusses the role of bacteria in mosquito control. Several useful bacteria involved in mosquito control such as *E. coli, Streptococcus, Pseudomonas, Bacillus* and *Enterococcus* that effectively kill the mosquitoes by producing insecticidal proteins such as endotoxins, Bin and Mtx proteins that specifically bind only with targeted mosquito species and kill them. Bacteria belongs to genus *Bacillus* found most effective against mosquito larvae such as *Bacillus thuringiensis israelensis* and *Bacillus sphaericus*, which produces endotoxins, selectively target mosquito larvae. When these toxins are consumed by

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larvae, these endotoxins disrupt the cells of midgut of larvae, which kills them before they can develop into adult mosquitoes. This selective and ecologically benign strategy minimizes damage to creatures that are not its intended targets. The environmental safety and specificity of bacterial control methods make them more sustainable and effective as compared to chemical control of mosquitoes population. This approach is more selective and more sustainable since it minimizes the impact on the environment and reduces the likelihood that resistance would develop. In this review we are presenting about the bacterial world and their interactions with mosquitoes, parasites, nematodes etc. and how they prevent disease transmission.

Keywords: Bacterial control; biological control; larvicidal activity; mosquito control.

1. INTRODUCTION

Many diseases are spread by mosquito vectors and harm human population worldwide. It is important to control mosquito in order to prevent disease transmission. Mosquito can be controlled at larval, pupal or adult stage by chemical or biological methods. Chemical compounds such as Bordeaux mixture, copper acetoarsenite (Paris green) and phenol are traditional insecticides used for decades [1,2]. DDT is the synthetic insecticide used to control mosquito populations [3]. Whereas, chemical control may develop resistance in mosquito as well as kill non- targeted organisms [4]. Therefore, chemical insecticides need to be replaced by bio insecticides to control the mosquito population [5,6] with the help of some biological agents such as bacteria, fungi, larvivorous fishes, nematodes etc. [7]. In this review we will discuss the mosquito borne diseases, role of bacteria in controlling these diseases and the economic importance of bacteria. Soil bacteria such as *Bacillus sphaericus* and *Bacillus thuringiensis* able to control the mosquito population at larval stages. These bacteria produced a variety of endotoxins which paralyzed the targeted mosquitoes and ultimately kill them. Before going into details it is important to know about the diseases transmitted by the mosquitoes and their specific methods of controlling mosquitoes.

2. TRANSMISSION OF DISEASE VIA MOSQUITOESAND CONTROLLING THE MOSQUITO POPULATION

Female mosquitoes act as vector for many harmful diseases which is responsible for health risks of human, birds and other animals and their death. It required blood meal for the nourishment to their eggs. Female mosquito bites the human being and if they carry the parasite of a particular disease, then they can transfer the parasite present in their saliva to the human. Female *Anopheles* acts as vector for malaria [8]. Other mosquito borne diseases includes dengue fever, yellow fever, West Nile fever, chikungunya, zika virus and eastern equine encephalitis that are transmitted by *Aedes*mosquito [9]. *Culex* also acts as vector for many harmful diseases such as Saint Louis encephalitis, Japanese encephalitis [10], avian malaria, and West Nile virus infection [11]. The disease spread can be controlled by checking the mosquito population. Regardless of types of mosquitoes, they can be controlled by chemical insecticides or biological agents. There are many chemical compounds such as copper acetoarsenite (Paris green), naphthalene, phenols, cresols, mercuric chloride, nicotine sulphate, calcium arsenate, Bordeaux mixture and fish oil soap used as chemical insecticides [2]. Chemical insecticides can apply by using IRS (Indoor residual spraying), LMs (Long lasting insecticidal Material), and ITNs (insecticide treated nets) [12]. The DDT comes in existence in the beginning of 20th century. DDT (Dichlorodiphenyltrichloroethane) was the first synthetic organic insecticide used for vector control. It is very toxic chemical and also responsible for biomagnifications, therefore it is prohibited by Environmental Protection Agency (EPA) in 1972 [1]. The Convention of Stockholm listed DDT as POPs (Persistent organic pollutants) in 2001 [1] and banned its uses. Therefore it is important to find an alternative way of chemical control [4,6].

Biological control is an alternate to the chemical control in which mosquitoes are killed by the help of some biological agents without harming our environment [13]. Biological control is the most recent, inexpensive and effective way to control the mosquito population without harming the non targeted organisms [14]. The use of bacterial approach for the control of vector-borne diseases is gaining importance due to its economic and ecological properties. It is, found almost everywhere in nature and easy to grow the desirable bacteria in large quantity inside the laboratory and they can be utilized for larvicidal and mosquitocidal activity. *Bacillus*, *Pseudomonas* and *Clostridium* are some commonly used bacteria against various mosquito vectors. This way the bacteria can reduces the environmental pollution by replacing the toxic chemical insecticides.

2.1 Different Types of Bacteria Involve in Controlling the Mosquitoes and their Larvae

There are many bacterial species associated with larvicidal or adulticidal activity against mosquitoes. Some of soil bacteria identified with larvicidal activity are *Bacillus, Staphylococcus, Pseudomonas, Enterobacter, Acinetobacteria* species [15]. *Bacillus thuringiensis* (Bt), *Bacillus sphaericus*(Bs)and *Bacillus subtilis,* Acetic acid bacteria, wMelPop strain of *Wolbachia* are some most important mosquito controlling bacteria [7,16,17,18,19,20]. It is reported that the larvae of *Anopheles gambiae* affected most by *Bacillus thuringiensis* (Bt) and *Bacillus sphaericus* (Bs) infections while the larvae of *Aedes, Anopheles arabiensis, Culex quinquefasciatus*are comparatively less sensitive to these bacterial infections. Even the low dosage of *Bacillus thuringiensis* (Bt) infections are able to kill the late instars and early pupae of *Anopheles* mosquito. A research was conducted to observe the efficacy of toxin produced by *Bacillus thuringiensis* and *Bacillus sphaericus* in the Democratic Republic of Congo, revealed that the Bt infected larvae start recovering after 5-7 days of infection. Bs was found more effective as compared to Bt. Bs infected larvae retains residual larvicidal activity of Bs strain. Residual persistence of larvicidal activity of bacterial strains is associated with different factors such as method of application of bacterial insecticide, specific larval species, density and type of bacterial formulation used [21]. It is reported when the high density larvae are added at regular intervals; they show long lasting residual persistence of Bs.

2.1.1 *Bacillus thuringiensis*

Bacillus thuringiensis is a gram positive soil bacterium that kills the *Anopheles*, *Aedes* and *Culex* mosquito*.* The bacterium produces toxic protein in the form of crystals i.e. endotoxin. It is safe for humans and specifically acts on their target. *Bacillus thuringiensis* var. *israelensis* (Bti) kills the larval stage of mosquitoes. Two mosquito species i.e. *Aedes* and *Psorophora* was found more sensitive to Bti. *Culex* and *Anopheles* larvae required comparatively high amount of Bti [22]. The toxin is not harmful for non targeted organisms. The bacteria produce protein crystals known as δ- endotoxins or Cry protein. The greater toxicity of Bti is contributed to the synergetic interaction between Cyt1A protein and different types of cry [23]. The protein crystals are not the contact poison so, the bacteria are required to be ingested by the targeted insect. After ingestion when the bacteria reach to the midgut of mosquito larvae, the endotoxins get activated due high pH and enzymatic activity. The Inactive protein solubilizes in insect digestive fluid and converted to active toxin core [24]. Bti toxin induces histopathological changes of gut epithelium of *Aedes aegypti*. These activated endotoxins bind to the receptors present on the apical cell membrane of mid- gut wall of larvae. These specific receptors are actually cadherins which are GPI anchored to cell membrane. After the cry protein binds with its receptors, it either leads to activation of oncotic death pathway or formation of toxin oligomere. Toxic oligomere binds with cadherin receptor mainly at lipid rafts. As the amount of accumulation of toxin oligomere increases it creates pores [25] in gut membrane and results in osmotic shock. Toxin causes paralysis in insect larvae and all the content of gut comes to the body cavity and the larva stop feeding which ultimately causes death of larvae. The use of BT in controlling mosquito larvae is schematically presented in Fig. 1.

Sometimes resistance is developed for Bti toxin in mosquitoes such as resistance developed for cry protein. Cyt1A protein decreases resistance for cry proteins in the mosquitoes. It was found that resistance is developed against Cry11A protein in *Culex quinquefasciatus.* To overcome the Cry11A resistance the protein is combined with Cyt1A. The ratio of Cry11A to Cyt1A is 3: 1 [26].

2.1.2 *Bacillus sphaericus (Bs)*

Bacillus sphaericus (Bs) is found very effective against *Culex* mosquito. The bacterium is divided into two groups based on their mosquitocidal activity. One group consist of highly active strains with high toxicity and the another group consisting of less active strains [27]. Highly active group contains the bacterial strains: IAB 59, 2297, 2362 and 1593. Active strains of bacteria produces binary toxin i.e. Bin. Bin is a crystal protein that is composed of two subunits: Bin A (42kDa protein) and Bin B (51kDa protein). Bin B is non toxic protein that have role in effective binding with receptor (α- glucosidase) present on microvilli of midgut in *Culex pipiens* larvae [28]. Equimolar amount of these two Bin proteins yields the greatest toxicity [29]. Research revealed that radiolabelled Bin toxin binds with specific receptors present in midgut apical cell membrane of *Culex pipiens* mosquito. Similar experiment was also performed in *Anopheles aegypti* (naturally resistant) without any specific receptors. However, *Anopheles gambiae* and *Anopheles stephensi* larvae have specific receptors for Bin toxin [30]. Affinity of Bin toxin is more for the receptors present in *Culex pipiens* as compared to *Anopheles gambiae.* Similarly efficiency of toxin is greater for *Anopheles gambiae* as compared to *Anopheles stephensi.* It is revealed by experiments on *Culex pipiens* that Bin B toxin binds with receptors with high affinity, while Bin A toxin has low affinity for binding with receptors [31]. Later the receptors were also identified as a protein of 60kDa. It was found that the receptors are attached to the cell-membrane by GPI anchoring [31]. Research reveals that sometimes resistance is also developed for Bin toxin of *Bacillus sphaericus* 2362 strain [30] due to absence of the receptors for Bin toxin on the apical membrane of midgut of *Culex quinquefasciatus* mosquito [32]. The mosquito can be make sensitive to Bin protein by creating lesions in cells of apical membrane of midgut epithelium. Through these lesions, Bin toxin enters to the cells and shows their toxic effect [33].

Another group of *Bacillus sphaericus* includes low activity strains. These bacterial strains do not produce Bin proteins but their mosquitocidal activity is due to Mtx (Mosquitocidal toxin) proteins. Mtx proteins have less proteolytic activity during sporulation [34]. There are different mosquitocidal toxins as Mtx 1, Mtx 2 and Mtx 3. Genes encoding these toxins shows high level of similarities [35]. Mtx shows high level of toxicity to *Aedes aegypti*, where in contrast Bin protein shows almost zero toxicity level to that mosquito species. Mtx1 is a 100 kDa protein undergoes proteolytic cleavage when goes to midgut of mosquito larva. A trypsin like protease is present in midgut which cleaves the Mtx 1 into a fragment with ADP- ribosyl transferase activity (27 kDa) and a receptor binding domain of 70 kDa [36]. Several formulations of Bti and Bs available [37] in several forms such as: Water dispersible powder (WDP), Wettable powder (WP), Flowable concentrate (FC), Emulsified concentrate (EC) and dust, granules.

2.1.3 *Bacillus subtilis*

Bacillus subtilis is a ubiquitous but mostly found in soil and non- pathogenic in nature [38]. The bacterium is tolerant to extreme conditions of desiccation and heat due to endospore formation. A strain of bacterium isolated from mangrove forest of Andaman and Nicobar Island, India is *Bacillus subtilis* subsp. *subtilis* [39] found effective against larval and pupal stages of mosquito [40]. The mosquitocidal activity is due to production of secondary metabolite i.e. cycliclipopeptide (CLP) surfactin, which is responsible for the mortality of *Anopheles culicifacies* (Prime vector of malaria in India) larva [41]. The first microbial adulticide of mosquito is bio- surfactant surfactin, produced by VCRC B471 strain of *Bacillus subtilis* subspecies *subtilis*. It is potent bioadulticide for ultra-low volume spray. It was found effective against *Anopheles stephensi* mosquito [42]. *Pseudomonas stutzeri* NA3 and *Bacillus subtilis* A1 strain have insecticidal properties against malaria mosquito [43].

2.1.4 *Bacillus cereus*

Bacillus cereus is rod shaped soil bacterium. It is a gram negative, spore forming bacteria effective against mosquitoes [44]. It colonizes the gut of mosquito larvae and kills the mosquito. It is effective against larvae of *Aedes aegypti* [45]. A large scale destruction of larvae of *Anopheles subpictus grassi* was observed by using *Bacillus cereus* (facultative pathogen) in natural environment [44], *Bacillus brevis* [45], *Bacillus circulans* [46], *Bacillus alvei* are some other bacterial strains that found effective against mosquitoes. A new bacterial strain of *Bacillus nealsonii* show very high toxicity [47] in comparison of other bacterial strains against *Aedes albopictus* (Table 1).

2.1.5 *Brevibacillus laterosporous*

Brevibacillus laterosporous bacterium forms lamellar bodies and act as bio control agentto check mosquito population [49] Two strains of this bacterium identified later were- LAT006 and 16- 92. These strains were found highly toxic to mosquitoes [50]. *Aedes aegypti* and *Anopheles stephensi* are most sensitive to these two strains of bacteria as compared to *Culex pipiens.* These bacterial strains form crystalline inclusions which are toxic in nature [51].

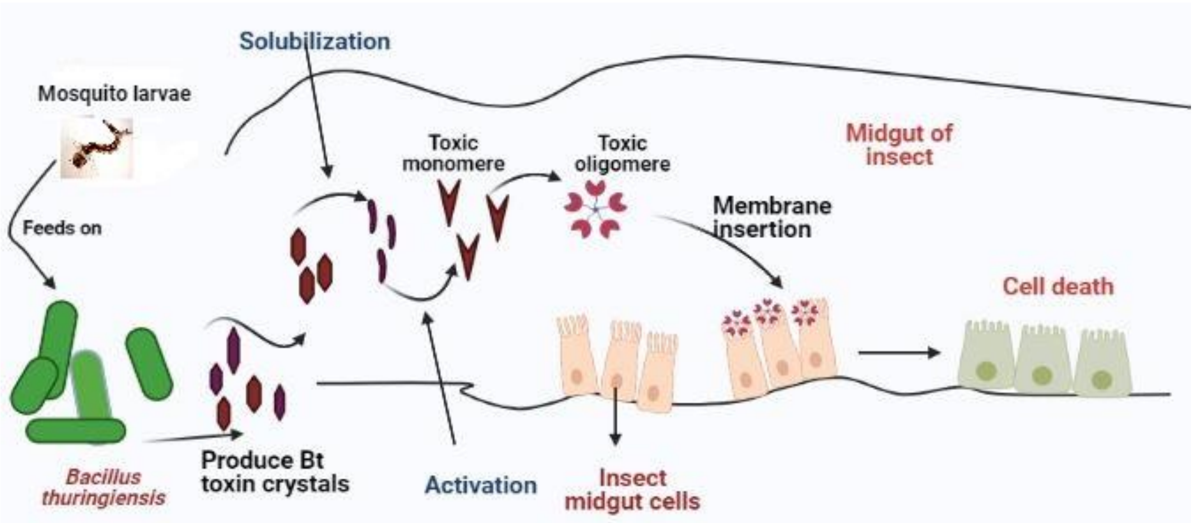

Fig. 1. Schematic diagram of the activation of *Bt* toxin causes disturbance of larval midgut and causes cell death

Table 1. Different bacterial strains and their toxicity level against *Aedes albopictus*

Mosquito	Bacterial strain	Mortality rate	Result	References
Aedes albopictus	*Bacillus nealsonii Sen* 132	70%	Highly toxic, More larvicidal activity	[48]
Aedes albopictus	*Streptomyces sp. Sen* 86	41%	Moderately toxic	[48]
Aedes albopictus	*Streptomyces sp. Sen* 39	36%	Less toxic	[48]
Aedes albopictus	*Streptomyces sp. Sen* 154	31%	Less toxic	[48]

2.1.6 *Clostridium bifermentans*- CH18

Clostridium bifermentans- CH18 was first anaerobic isolate with high mosquitocidal activity, isolated from mangrove swamp soil of Malaysia. It is identified as *Clostridium bifermentans* serovar *Malaysia* i.e. Cbm [52]. Experiments were performed to see the insecticidal activity of *Clostridium bifermentans.* Treatment of Cbm with protease is responsible for the inactivation of its mosquitocidal activity [53]. Later on in 1997, another strain of the bacteria was identified i.e. *Clostridium bifermentans* serovar *Paraiba* i.e. Cpb. Both strains of bacteria effectively kill *Anopheles* mosquito. Larvae of *Aedes* and *Culex* mosquitoes also show high susceptibility to Cbm and Cpb strains.

2.1.7 *Pseudomonas sp.*

Pseudomonas sp. isolated from soil, producing secondary metabolites that effectively kill larvae of mosquitoes. Two strains *Pseudomonas fluorescens* and *Pseudomonas caryophily* produce endotoxins. Studies revealed that δ-endotoxin gene of *Bacillus thuringiensis* inside the *Pseudomonas fluorescens* shows four times more toxic effect. So, it more effectively kills the insect larvae [54]. The research conducted in lab by taking bacterial strains of *Pseudomonas fluorescens* (NCIM- 2631) and *Pseudomonas caryophily* (NCIM- 5094) inoculated separately in different glucose peptone salt medium broth. Then the larvae of *Aedes aegypti* were grown in bacterial broth. The result shows that the endotoxin produced by these two bacterial strains show larvicidal activity [55]. *Pseudomonas fluorescens* was found more toxic than *Pseudomonas caryophily* against the *Aedes aegypti* (Table 2).

Pseudomonas fluorescens produces a large number of secondary metabolites such as Phenazine [57]. Pyoluteorin and Rhizoxin [57], 2, 4-Diacetylphloroglucinol i.e. DAPG [58], Pyoluteorin [59]. Other 2º metabolites are HCN and Pyrrolnitrin- chlorinated molecule (antifungal compound) [60]. The bacterium produces phenazine-1-carboxylic acid i.e. Yellow phenazine which shows antitumor, antimicrobial, antimalarial and antiparasitic activity andfound non- toxic to mammals. Some other strains of bacteria showing insecticidal activities are *P. pseudomallei* and *P. aeruginosa* [61].

Table 2. Mortality rate of *Aedes aegypti* when infected with different strains of *Pseudomonas*

Mosquito	Bacterial strain	Mortality rate	Result	References
Aedes aegypti	*Pseudomonas fluorescens*	40%	More toxic; More Larvicidal activity	[56]
Aedes aegypti	*Pseudomonas caryophily*	20%	Less toxic; Less Larvicidal activity	[56]

2.1.8 Actinomycetes

Actinomycetes are gram positive microorganisms. It is not true bacteria but it is much closer to fungi. Two strains of soil actinomycetes are H11809 and FH025 having potent anti- malaria activities. *Plasmodium falciparum* have PfGSK 3 kinase (Ser/ Thr), similar to eukaryotic kinase (GSK- 3β) is essential for growth of *Plasmodium*. So, in order to prepare drug for the *Plasmodium*, PfGSK 3 acts as anti- malarial drug target [62]. The kinase is capable of phosphorylation of proteins and thus inactivating glycogen synthase. GSK- 3β is responsible for the response of host against fungal, viral and parasitic infections as malaria. Inhibitors of mammalian GSK- 3β are also responsible for inhibiting the PfGSK [63]. This inhibition contributes to anti- malarial activity. Lithium chloride potentially inhibits PfGSK in *Plasmodium berghei* infected mice [64]. Previous evidences shows that the bacteria can influence the susceptibility of mosquitoes to human pathogens and can also influence the capacity of mosquitoes to transmit the diseases [65]. Microbiota of mosquito can also prevent the disease spread by affecting the growth and development of *Plasmodium* either by producing anti- malarial compounds or by basal immunity [66]. A bacterium i.e. Enterobacter, isolated from the mosquito population in Zambia found to show co- feeding activity with *Plasmodium* gametocytes [67].

2.1.9 *Leptothrix buccalis*

Leptothrix buccalis or *Leptothrichia buccalis* is the gram positive, filamentous bacterium obtained from polluted or fresh water. The bacterium shows larvicidal activity and effectively kills the larvae of *Anopheles maculipennis* mosquito [15].

Not only soil bacteria but the bacteria present inside the reproductive organ of mosquito, bacteria present in symbiotic association with soil nematode and even the bacteria present on the human skin are effective in controlling mosquito population. Some details of these bacteria and their mode of controlling mosquitopopulation as discussed below.

2.2 Human Skin Bacteria Affecting Mosquito Biting

It is well reported that human skin contains different types of bacteria and these different bacterial compositions are responsible for producing a particular type of body odor. By using 16SrRNA sequencing and plating of bacteria, the diversity and number of bacteria can be observed and it was reported that the person having large number of bacteria but with low diversity is found to be more attractive to *Anopheles gambiae* [68]. Female mosquito attracts towards the host by chemical or physical signals. Physical signals involve heat, moisture and visual signals. Warm and humid conditions are favorable for mosquitoes. Chemical signals involve the volatile compounds produced by skin bacteria that are responsible for body odor and also found attractive to mosquitoes by guiding them for orientation and landing. They attract towards humans due to emanations released by their skins. *Staphylococcus*bacteria found attractive to *Anopheles gambiae,* while some bacterial species are ineffective in attracting mosquitoes as *Corynobacteria*, *Micrococcus* and *Propionibacteria* [69]. Consequently by changing the bacterial composition and reducing the number of bacteria attractive to mosquito, the transmission of various diseases can be prevented.

2.3 Prevention of Mosquito Borne Diseases by the Soil Bacteria Present in Association with Nematode

The recent studies revealed that the soil bacterium *Xenorhabdus budapestensis* (Xbu) is present in symbiotic association with entomopathogenic nematode *Heterorhabditis megidis,* producing a potent mosquito feeding deterrent i.e. Xbu compounds (secondary metabolites) with activity comparable to mosquito repellant piacardin and DEET (N, N- diethyl- 3-methylbenzamide) against *Aedes aegypti* and also decreases the rate of feeding in *Anopheles* gambiae and *Culex pipiens* to a considerable extent. These secondary metabolites exhibit antibiotic, insecticidal and antifungal activities [70,71,72]. The genome of *Xenorhabdus budapestensis* and *Xenorhabdus szentirmaii* bacteria contains a gene cluster that produce chemical compound Fabclaviens with antibiotic and insecticidal activities [73].

2.4 Control of Mosquito by Using Infectious Bacteria of Animal Fauna

One of the infectious bacteria of human is Streptococcus that is also found with insecticidal activity as described below.

2.4.1 *Streptococcus*

Streptococcus is a gram positive bacterium that causes rheumatic fever, acute glomerulonephritis [74]. It is pathogen of animal and human fauna [75]. The bacteria attached to the larvae in very large number and penetrate the integuments of the insects which slowly cause internal damage to the larva (L3 and L4 stages). It is responsible for mortality of mosquito larva to a great extent [76].

2.5 Effect of Bacteria Present Inside the Mosquito in Control of Diseases Transmission

Various bacterial species are present inside the mosquitoes that are present in symbiotic association with mosquitoes and produce the chemical substances important for the immunity, development and the reproduction of mosquitoes. We are discussing here about these bacteria and their effect on mosquitoes and parasite.

2.5.1 *Enterococcus durans*

Enterococcus durans is a gram positive bacterium. It was investigated by the experiment that when the bacteria isolated from the intestine of dead mosquito, introduced to the third instar larvae of *Culex quinquefasciatus* show about 20% to 60% larvicidal activity [77].

2.5.2 *Enterobacter cloacal* and *Serratia marescens*

Enterobacter cloacal and *Serratia marescens* bacteria are present in the midgut of mosquitoes. *Enterobacter cloacal* secretes haemolytic enzymes that help the mosquito in digestion of sucked blood. It was found that when these two bacteria isolated from the mosquito when introduced separately into the *Anopheles gambiae* reduces the survival rate of mosquito [78]. Another experiment revealed that *Enterobacter* Esp_Z strain which is isolated from the mosquito when reintroduced to *Anopheles* reduces the growth of *Plasmodium* due to production of reactive oxygen species, without harming the mosquito species [79].

2.5.3 Acetic acid bacteria

Acetic acid bacteria (genus- Asaia) present in different tissues of *Anopheles stephensi* as symbiont. It is present in salivary gland, reproductive and various other organs of mosquito. Rifampicin is an antibiotic effective against Asaia. When larvae of *Anopheles stephensi* treated with Rifampicin, the growth and development of larvae delayed [17]. It causes asynchrony in late instars. However, if larvae provided with mutant strain of Asaia (Rifampicin resistant) then the larval growth is not much more affected.

2.5.4 *Wolbachia*

Wolbachia is endosymbiotic bacteria present in gut of nearly 60% of arthropods. It is gram negative bacteria that interfere with reproduction of mosquitoes [80], hence effective in controlling vector mosquito population. Most commonly it is present in *Aedes albopictus* and *Culex pipiens* while naturally absent in *Aedes aegypti* and *Anopheles*. wMelPop strain present inside *Aedes albopictus* and drosophila. The strain is isolated and experimentally introduced into *Anopheles* and *Aedes aegypti* to reduce the development of virus (as dengue, chikungunya virus) inside the mosquitoes [81,82]. Another strain of *Wolbachia* is wAlB. When both the strains wAlB and wMelPop injected to *Anopheles stephensi*, the bacterium induced mosquito pertinaciousness towards *Plasmodium falciparum*- the malaria causing parasite [83]. Male and female *Aedes aegypti* infected with *Wolbachia,* released into virus infected area. It was found that *Wolbachia* infected mosquitoes when bread with the wild mosquito population, the bacterium transfer to their progeny too. Over the time most of the wild population will carry the bacterium. When the infected male mosquito (carrying *Wolbachia*) mated with uninfected female that will results into sterilization the eggs. So, there is complete loss of reproduction. However, if the female is already infected with bacteria and mated with infected male, mosquito become resistant to sterilization (Fig. 2).

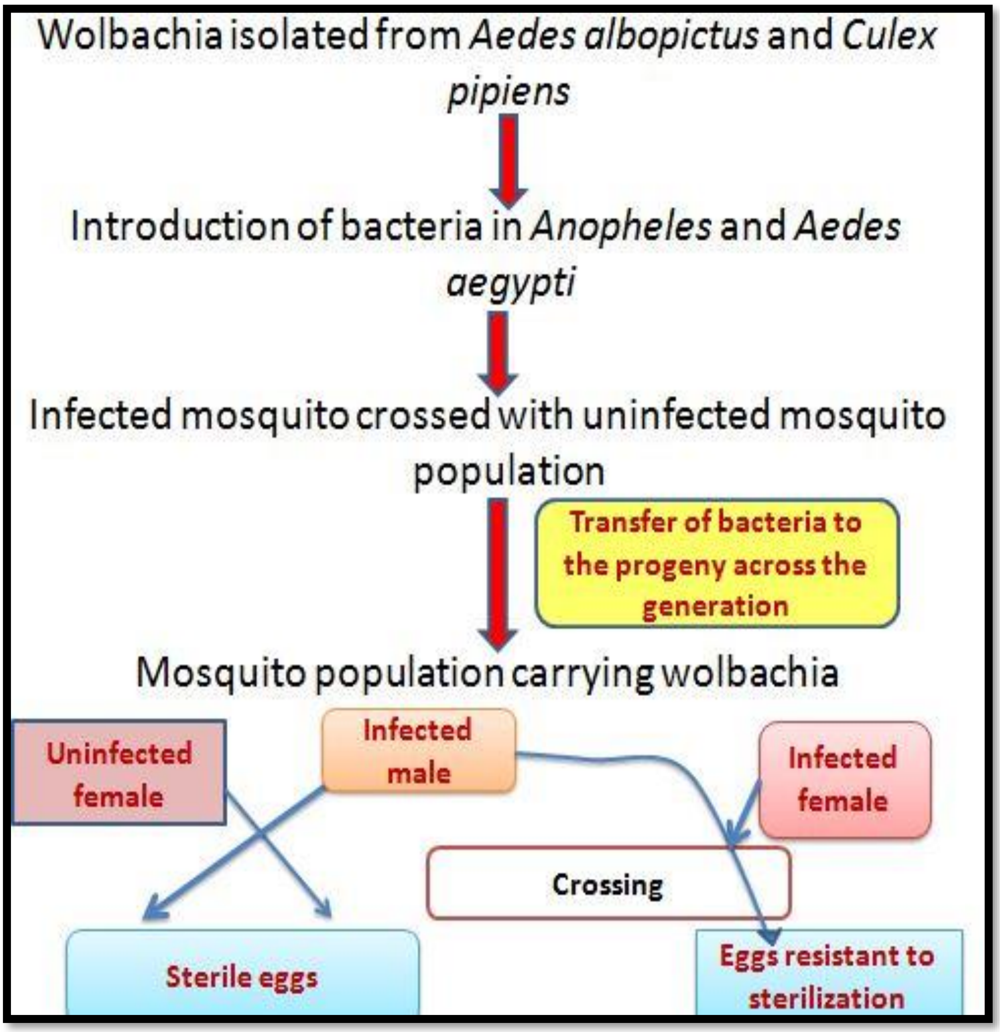

Fig. 2. Impact of *Wolbachia* infection on male and female mosquitoes sterlity

Sometimes the bacteria may increase the susceptibility of mosquito towards parasite. Experiment found that when wAlB strain of bacteria introduced into *Anopheles gambiae*, results into increased susceptibility of mosquitoes towards *Plasmodium berghei*- the parasite of rodent [84]. *Wolbachia pipientis* i.e. wPip strain of bacteria is naturally present in *Culex quinquefasciatus*, *Aedes albopictus*, *Anopheles gambiae* and *Anopheles coluzzi* [85,86], but absent in *Anopheles aegypti*. wPip strain of *Wolbachia*, when` introduced into *Culex pipiens* the susceptibility of mosquito towards avian parasite *Plasmodium relictum* increases [87]. The reason behind this differential impact is supposed due to differential immune response to different bacterial strains, different composition of mosquito gut microbiota and environment inside their gut [87]. *Wolbachia* also alter the lipid metabolism of *Aedes* and *Anopheles* mosquito, so that the *Plasmodium* becomes unable to develop inside the host [88].

3. MODIFICATION OF BACTERIAL STRAIN AND THEIR MOSQUITOCIDAL ACTIVITY

In this age of science, genetic engineering is the most powerful tool in the hands of scientists. With the help of genetic engineering we can manipulate the genetic content of all the living organisms including bacteria, plants and animals. Thus, we can add desire genes of interest in any organism. Genetic engineering is also useful in controlling mosquito population. With the help of rDNA technology genes encoding endotoxins of Bti and Bs can be manipulated. Subsequently, generating the new recombinant bacteria, which are more effective than the original strains. These recombinants developed by scientists show about ten times more larvicidal activity as compared to either Bs (*Bacillus sphaericus*) or Bti (*Bacillus thuringiensis* subsp. i*sraelensis*) strain [89]. When two bacterial strains i.e. Bs and Bti combine, the new recombinant strain of bacteria with all desirable genes including Cyt1A, Cry11A, Cry4A, Cry4B and genes for Bin toxin will produce [90]. It was found that when Cry toxin combined with Cyt1A gene, it develops least resistance to Cry toxin and also help to overcome Bs resistance. It shows great mosquitocidal activity against *Anopheles gambiae, Culex* and *Aedes aegypti* [85]. Some bacterial strains with the genes of another mosquitocidal protein were also cloned such as the Mtx protein genes [91] and few peptides (such as Trypsin modulating oostatic factor) [92] was expressed in new recombinant bacteria. These bacteria developed with increased insecticidal activity [89].

3.1 Formation of Recombinant of Bti and Bs Bacterial Strains

A short stretch of gene that encodes Cry11A and Cry1A genes were isolated from *Bacillus thuringiensis* subsp. *Israelensis* and cloned into a vector pPL603E. It results into the production of recombinants and these recombinant vectors were introduced into Bs 2362 [93]. So, new strain of bacteria is produced with more potent larvicidal genes. It was observed that recombinant bacteria were about ten times more lethal to *Aedes aegypti* in comparison to original Bs 2362 strain. Different types of effective bacterial recombinant can be produced by introduction of various endotoxin genes in different strains of bacteria by protoplast transformation. It was found that endotoxin gene producing Cry4B protein increases toxicity to *Aedes aegypti* hundreds of fold [94]. These recombinant proteins create pores in gut of *Anopheles* mosquito due to increased toxic effect. It eventually leads to death of vector mosquito of malaria. An alternative strategy is also developing in order to increase the efficacy of bacterium against mosquitoes. Symbiotic bacteria from midgut of *Anopheles* mosquito were isolated and genetically engineered to produce interfering proteins [95]. This bacterium lives inside the same compartment where the parasite of malaria grows [96]. As the mosquito feeds on the human blood, there is about thousand fold increases in the number of symbiotic bacteria [97]. The genetically engineered bacteria produce anti plasmodium molecules i.e. Paratransgenesis. It shows the promising effect to control *Anopheles* mosquitoes.

3.2 Mosquito management using field applications of bacterial control methods Water Treatment

Bacterial formulations such as *Bacillus thuringiensis israelensis* (Bti) are injected into standing water bodies (such as ponds, marshes, and irrigation ditches) in both urban and rural regions. These sprays safely target other species while effectively lowering mosquito populations by targeting their larvae [98].

IPM or Integrated Pest Management: Using bacteria as a biological control agent is a common practice in agricultural contexts when pest management measures are implemented. In order to reduce their dependency on chemical pesticides and manage mosquito populations, farmers might, for example, apply Bti to rice fields [99]. This promotes sustainable agricultural practices.

Restoration Projects: In wetland restoration efforts, bacterial control agents can be employed to manage mosquito larvae in newly established habitats. By utilizing these biological controls, project managers can maintain ecological balance without resorting to chemical treatments that may harm native flora and fauna [100].

Public Health Initiatives: Bacterial control agents have been included into mosquito management tactics by a number of public health efforts worldwide. For instance, Bti has been used to aid in prevent disease transmission by reducing mosquito populations in areas where mosquito-borne illnesses like malaria and dengue fever are common [101].

Larvicidal Treatments: Bacterial larvicides are sprayed to sources of stagnant water, such as flower pots, bird baths, and septic tanks, in limited habitats, such residential areas, to stop mosquito larvae from growing into adults [102].

These uses highlight the adaptability and potency of bacterial control techniques in controlling mosquito populations and reducing any negative environmental effects.

4. CONCLUSION AND FUTURE PROSPECTIVE

Mosquito control is important as it act as vector for several diseases responsible for the death of the millions of people every year all over the world. Therefore it is important to check the mosquito and their larvae. Bacterial mediated disease control is an effective and inexpensive way to control the vector mosquitoes without contaminating the environment unlike the chemical control. Bacterial control of mosquito is gaining importance due to its economic and ecological benefits. It is well studied that the bacteria present in different environment actively involves in mosquito control such as soil bacteria, bacteria present inside the gut, intestine and reproductive organ of mosquitoes or present in symbiotic association with nematodes. These bacteria produce mosquitocidal proteins such as Mtx, Cry and Bin protein crystals or secondary metabolite products that act either as mosquito repellants or bio insecticides. Even the reintroduction of bacteria (isolated from some other mosquito) into the mosquito interferes with tripartite (mosquito- bacteria-parasite) interaction. It either show larvicidal and mosquitocidal activity (eg. *Enterobacter cloacal*, *Serratia marescens*) or inhibits the parasite development inside the mosquito (eg. *Wolbachia*, *Enterobacter* Esp_ Z). Knowledge of bacteria and their mode of action would be of great help in increasing the toxicity level of larvicidal proteins to create even more potent bacterial strains that would make mosquito control more effective and thus control many diseases transmitted by mosquitoes. Sometimes resistance can develop in mosquitoes due to prolonged use of bacterial insecticides and to overcome this resistance, recombinant bacteria with desired insecticidal genes are developed with a manifold The bacterial control of mosquito becomes more effective in future with the help of genetic engineering.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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