Microbial Control of Vector-Borne Diseases

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Contents

SECTION V Microbial Control of Flea Vector

Foreword

Vector control is the primary intervention for most of vector-borne diseases, including malaria, dengue, and Zika, due to lack of effective drug and vaccine. For a long history, we had heavily relied on chemical insecticides to suppress the vector populations in hopes of reducing them below epidemiological thresholds that are required for disease transmission. Now, we learn that this has to be changed after seeing the rapid development of strong resistance to insecticides in vectors and the significant negative impact of chemical sprays on environment and nontarget species. We also realize the urgency to make such change because some old vector-borne diseases like dengue become more serious than before, new diseases like Zika emerge as global threats, and progress made in control of other diseases like malaria has now stalled and even reversed. There is a consensus that we need to better understand pathogen-vector interactions that determine the ability of vectors to transmit diseases and utilize those knowledge for developing novel tools and strategies with the potential to lead to sustainable disease control. One of the most promising areas is microbial control of vector-borne diseasesas addressed by this book.

Like vertebrate hosts, insect vectors have close contacts with microbes in nature. Some microbes form intimate relationships with vectors and play essential roles for vector survival, reproduction, or development; some just stay together with vectors as guests; and others infect vectors as pathogens, reduce insect fitness, and even kill them. All of the abovementioned three types of microbe-vector relationship can be utilized for vector control reduce insect fitness as introduced in different chapters of this book. The most straightforward approach to develop microbial control of vector-borne disease is to kill directly the vectors or their offspring to reduce the quantity of pests. Alternatively, efforts can be developed to reduce the quality of an insect to serve as a vector for human pathogens. It is worthy to note that those human pathogens transmitted by vectors are not harmful to vectors in most situations. After encountering vectors and becoming their guests, they complete replication, development, or both, inside the body of the insect, to prepare for their next journey in humans. In order for an insect to be able to transmit a specific human pathogen, its physiological environment and behavior have to match perfectly to the pathogen's requirements. This provides an opportunity for the other microbes to perturb or finely adjust to this environment, either naturally or artificially, such that insects are no long hospitable for pathogens or incapable for moving pathogens to human. To a certain degree, such modification of the insect's physiological microenvironment to break the linkage between vectors and pathogens is similar to the traditional environmental management for vector-borne disease control by preventing contact between vectors and human. Thus, microbial control of vector-borne disease can be accomplished by either reducing vector density or the ability of vectors in transmitting human pathogens.

While many novel microbe-based approaches have been demonstrated in the laboratory, exciting progresses have recently been made to provide proof of concept through field trial. One good example is the maternally transmitted endosymbiotic bacteria *Wolbachia*, which are estimated to be present in 65% of millions of insect species in nature. As selfish microbes, *Wolbachia* manipulate insect reproduction for their own benefit such that they can invade and spread into populations. Different insects may carry different *Wolbachia* strains, indicating that indicating that millions of *Wolbachia* strains may be present in nature. With the ability established to manually introduce a *Wolbachia* strain into an insect host to build a novel symbiosis in laboratory, we can make a naturally uninfected mosquito to carry *Wolbachia*, displace the existing *Wolbachia* with a novel strain, or add novel *Wolbachia* to create multiple strain combination. Importantly, some of those novel *Wolbachia* strains in mosquito can act like a vaccine to protect the mosquito from human pathogens. Recent field trials show that releasing *Wolbachia*-infected *Aedes aegypti* can result in invasion of *Wolbachia* in mosquito population and reduce its potential in transmitting dengue and Zika. This approach is attractive due to its low cost and sustainability in disease control because once a local mosquito population is modified to become pathogen resistant, disease transmission in this area will be reduced or blocked even given the migration of infected people from another endemic region into this control region. In a different trial, millions of *Wolbachia*-infected *Aedes albopictus* male mosquitoes are produced in a mosquito factory and released in the field every week to induce sterile matings with the wild type of mosquitoes, resulting in suppressing and even eliminating local populations. Due to these important progresses, the World Health Organization encourages endemic countries to continue developing *Wolbachia* as a practical tool for vector-borne disease control, resulting in ongoing field trials in ~20 countries or regions and the first success in registration of *Wolbachia* as a microbial pesticide in United States Environmental Protection Agency in 2017.

Due to its environment-friendly sustainability, and compatibility with the traditional approaches like vaccine and drug, microbial control of vector-borne disease is expected to play more important role in disease control and prevention in the near future. New microbes will be discovered in laboratories and gone through research and development and field trials, while specific microbes will be used to target each individual species of dominant disease vectors without negative impacts on nontarget species. Advances in biotechnology, artificial intelligence, automation, and real-time monitoring through web-based mapping service will facilitate the deployment of these approaches in field setting to accelerate the efforts for disease eradication.

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Preface

Vector-borne diseases such as malaria, dengue, chikungunya, schistosomiasis, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, onchocerciasis, Zika virus, and several different types of encephalitides including Japanese encephalitis are a major cause of human morbidity and mortality globally. More than 1 billion cases and over 1 million deaths are reported annually. These diseases, mostly rampant in tropical and subtropical regions of the world, account for over 17% of all infectious diseases. Distribution of these diseases is determined by a complex interrelationship among pathogen, vector, and human being, anchored by environmental and social factors, as well as global travel and trade, unplanned urbanization, and environmental challenges such as climate change and global warming. Some diseases, such as dengue, chikungunya, West Nile virus, and Zika virus, are emerging in countries where they were previously unknown. The recent spread of Zika virus, a mosquito-borne viral disease, across Americas, Europe, and parts of Asia, is a towering example of how rapidly some vector-borne diseases might disseminate over larger areas in a relatively short time period. Vector-borne diseases are spread mainly by the bite of insects and other arthropod vectors, such as mosquitoes, ticks, mites, triatomine bugs, tsetse flies, sandflies, and black flies, imposing heavy health and economic burdens, in addition to unmeasurable human misery and hardship, as many people who survive infection are left permanently debilitated, disfigured, maimed, or blind. Vectors of these diseases thrive under conditions where housing is poor, water is unsafe, and environments are contaminated with filth. Measures that control the vectors, the agents of diseases, provide an excellent but underutilized opportunity to help these people catch up.

For the past nearly 100 years, the vectors of these diseases were chemically controlled only to show resistance against the various chemicals that proved inhibitive in the long run and also because of their toxicity to both human and nontarget organisms as well as the environment. Subsequently, biological and environmental control methods were used in controlling these vectors but proved to no avail in emergencies of disease epidemics. Alternatively, following stringent research during the past four decades, microbial agents and tools have recently shown great promise, and the best example is *Bacillus thuringiensis* var. *israelensis* to control a wide range of vector and pest mosquitoes. Microbial control, defined simply as the use of microorganisms or their by-products by humans to suppress insect pest populations, implies that microorganisms like bacteria, actinobacteria, cyanobacteria, fungi, algae, and protozoa can bring about reduction in vector population by a variety of pathways without causing serious human health and environment concerns. Some of these are ready for field use, whereas others have already proven effective in reducing vector populations. In a similar way, many microorganisms interfere with the development of the disease causing pathogens in the vector and results in its depletion or reduction, bringing about a control of the disease before it breaks out.

This book presents a detailed overview of microbial biomolecules in meeting the challenges to control and prevent vector borne-diseases; autodissemination of current

and future potential in the application of entomopathogens against mosquito-borne diseases; and bioprospecting of bacterial, actinobacterial, cyanobacterial, fungal metabolites, gut microbiota, and *Wolbachia* for mosquito control. Finally, genetically altered microbes and viruses are also used in the control of mosquito-borne diseases. Moreover, this book also provides a comprehensive account on microbial control of leishmaniasis, aquatic snail-borne diseases, blackfly-targeted onchocerciasis, and flea-borne Rickettsial diseases. This book will be eventually beneficial to future research programmers, planners, administrators, scientists, academicians, and researchers as well as the governments of various nations who are interested in fortifying and expanding their knowledge about microbial control of vectors in the fields of microbiology, biotechnology, entomology, biomedical science, public health, and environmental science.

The book is comprised of 21 chapters from multiple contributors around the world including the United States, Mexico, China, Turkey, Thailand, India, and the Kingdom of Saudi Arabia. We are grateful to all the contributors and leading experts for the submission of their stimulating and inclusive chapters in the preparation of this unique volume on microbial control of vector-borne diseases. The book content is divided into five sections, namely, microbial control of mosquitoes and mosquito-borne diseases, leishmanias, schistosomes, blackflies, and fleas.

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1 Microbial Biomolecules
Challenges to Control and Prevent Vector-Borne Diseases

Madangchanok Imchen, Jamseel Moopantakath, Eswara Rao, and Ranjith Kumavath

CONTENTS

ABSTRACT

Vector-borne diseases (VBDs) are caused majorly by arthropods which effects millions of people worldwide. Malaria alone is a dreadful disease in developing countries. However, the emergence of new VBDs and their resistance to standard drugs have posed a serious threat to the world. Hence, a new source of drugs to treat the dreadful VBDs is the need of the hour. It is surprising that one of the most ancestral innate immunities in every class of life is known as host

defense peptides or antimicrobial peptides (AMPs) and have not been much in focus majorly due to lack of revenue generation. AMPs have shown to have promising anti-infective activates on a wide range of microbes including viral and cancer cells. In this chapter, we have compiled some of the research on microbial biomolecules targeting the vector and the pathogens along with the possible mode of action.

The later part of the chapter focuses on prevention of VBDs through mathematical models, regulatory measures, and community-level participation. Vectors are highly dependent on the environmental condition for its maturation and life cycles. Therefore, in order to make the best usage of various environmental data, models pertaining to the VBD outbreaks or the abundance of vectors can be built using environmental data and NASA's satellite-based Moderate Resolution Imaging Spectroradiometer in order to predict the most likely possibility of prevention using powerful algorithms. We have also discussed the importance and the problems faced in imparting knowledge through a public awareness program regarding various VBDs and the importance of community-level participation along with personal prophylaxis measures.

1.1 INTRODUCTION

1.1.1 Brief Introduction to Vector-Borne Diseases (VBDs)

Vector-borne diseases (VBDs) are those that are transmitted from an infected vector source to humans, plants, or animals. Biologically, vectors can be defined as organisms that carry disease-causing agents. Vectors are considered to be invertebrates, most commonly arthropods, since a majority of VBDs are caused by arthropods. However, vertebrates such as foxes, rats, certain bats, and a species of aquatic snail can also act as vectors. The disease-causing pathogen thrives within the vector, which is then transmitted to another biological body mostly through bites and stings or infestation of tissues. Since most vectors are arthropods ectothermic (cold blooded), they are highly influenced by the landscape and climatic conditions for their proliferation. Trade and commerce between countries has also led to the transmission of vectors to places previously unknown (World Health Organization [WHO] 2016).

1.1.2 Effects of VBDs on the Public

Vector-borne disease causes more than 1 million deaths annually, accounting for more than 17% of the overall infectious diseases. Emerging VBDs such as dengue have the potential of contracting to over 2.5 billion people. Malaria alone kills over 400,000 individuals mostly under the age of 5 (WHO 2016). Rural schools can be a breeding ground for malarial vector such as female *Aedes aegypti* and *Culex quinquefasciatus* (Olano et al. 2015). Besides the dreadful effects of VBDs in humans, the economic growth of a country could be hindered by vector-borne plant and animal diseases through reduced agricultural productivity and socioeconomic status. Tropical and subtropical areas experience the highest rate of VBD infections (Institute of Medicine 2008).

In order to control the emergence of VBDs, usage of insecticides to keep the vector under control can be followed. Malaria, dengue, and filariasis (WHO 2006) can be prevented by wise usage of insecticides where breeding of mosquitoes is most likely to occur. However, insects, as compared to microbes, can also gain resistance to insecticides (WHO 1998). This resistance could be due to changes in metabolic processes of the vector (Hemingway et al. 1998) through increased production of enzymes such as carboxylesterases, glutathione-S-transferases, and cytochrome P450-dependent monooxygenases, which are involved in sequestering, metabolism, and detoxification (Rivero et al. 2010). However, it should be noted that increased resistance of insects against insecticides does not always lead to increased transmission of VBDs. Insecticide-resistant *Culex quinquefasciatus* mosquitoes have been shown to exhibit reduced ability to transmit the filarial parasite *Wuchereria bancrofti* as compared to the wild type (Vontas et al. 2005).

1.2 MICROBIAL BIOMOLECULES AGAINST VECTOR-BORNE DISEASES

1.2.1 Introduction to Antimicrobial Peptides

The resistance of pathogens to various drugs is a serious threat. Pathogens gain resistance through different mechanisms such as plasmid encoding resistance genes or by overexpression of efflux pumps, which extrude drugs from the cells (Nikaido 2009). Antimicrobial peptides (AMPs), also known as host defense peptides (DHPs), are innate immune responses part of every class of life. AMPs are peptides that generally range from 15 to 50 amino acids and exhibit a broad range of action against pathogenic microbes. Some AMPs also act as anticancer peptides. Generally AMPs exhibit their activity due to the major difference between eukaryotic and prokaryotic cells. There are over 2400 AMPs, however, they do not show any correlation between amino acid residuals and their biological activity (Zhang et al. 2014). More than 90% of AMPs are positively charged. On the basis of amino acid residual composition, they are broadly classified into linear, cysteine rich, and specific amino acid rich AMPs. Classification based on secondary structure includes helical, sheet, mixed, and random coiled AMPs (Zhang et al. 2014). AMPs belonging to the magainin class cause osmotic lysis in various protozoa, leading to swelling of the cell until it bursts (Wu et al. 2015). This class of peptides is effective against several protozoa including *Trypanosoma cruzi*. The skin of amphibians is constantly exposed to environments that harbor an immense amount of microbes. Hence, they produce AMPs as a protective measure. One such AMP derived from *Rana temporaria*, a European frog, is temporin A and B peptides, which are composed of 13 amino acids. These peptides have anti-leishmania activity, leaving the healthy human erythrocytes intact (Mangoni 2006). AMPs also show inhibitory activity against various viruses through a range of mechanisms such as neutralization of virus by integrating with the host cell membrane or directly onto the viral envelope (Narayana and Chen 2015). They also inhibit a major viral protein, VP16, which is required by the virus for integration into the host nucleus.

1.2.2 Malaria

Malaria is caused by the protozoan *Plasmodia*. It starts with the female *Anopheles* mosquito infected with the infective form of *plasmodia* called sporozoites. When such an infected mosquito bites a mammal, the sporozoites are transmitted through its saliva into the mammal. The sporozoites then migrate to the liver cells called hepatocytes. In the liver cells, the sporozoites mature to the next phase of the life cycle and are called merozoites, followed by the rupture of hepatocytes, and finally release into the bloodstream (Vale et al. 2014). The asexual lifecycle of the plasmodia starts within the red blood cell (RBC). The merozoites develop into the ring stage followed by trophozoites that are metabolically active. The final stage is the development into schizonts that are responsible for infection of other healthy RBCs by realizing merozoites. The ring-form stage can also be developed into female and male gametocytes that can infect a healthy *Anopheles* mosquito during a blood meal. In the infected *Anopheles*, the gametocytes develop into ookinetes, oocysts, and finally sporozoites, which migrate to the salivary gland of the mosquito ready to infect a susceptible mammal in the next blood meal (Vale et al. 2014).

AMPs with broad-spectrum activity from various sources, including *Anopheles* mosquitoes, have been shown to exhibit antimalarial activates (Bell 2011). AMPs act against negatively charged prokaryotic cells. However, the antimalarial activity via inhibition of infected eukaryotic (mammalian) RBCs can sound contradicting. The selective antimalarial activity of AMPs could be linked to the changes brought about to the membrane of infected RBCs. Infection of RBCs by *Plasmodium falciparum* increases the contents of phosphatidylinositol and phosphatidic acid in the membrane and decreases sphingomyelin (Hsiao et al. 1991). Thus cationic AMPs have the potential and promising scope in the treatment of malaria as a new class of antimalarial drugs (Vale et al. 2014). Antimicrobial peptides can form channels (Krishna et al. 1990) through the formation of transbilayer bundles (Snook et al. 1998) or through dissipation of mitochondrial membrane potential or plasma membrane (Nagaraj et al. 2001). Fungal peptides efrapeptins, zervamicins, and antiamoebin inhibited the growth of *P. falciparum* in micromolar concentration. Efrapeptins inhibits mitochondrial F_0F_1 ATPase (Nagaraj et al. 2001).

Surfactants are compounds that weaken the surface tension of a given liquid. An example of a commonly used household surfactant would be soap and detergent. Surfactants have been found to be suitable candidature as an antimalarial. Rhamnolipids are produced by *Pseudomonas aeruginosa* that exhibit a low surface tension between 31.4 and 38.7 mN/m (millinewtons per meter) (Silva et al. 2015). It is biodegradable and shows low toxicity. The larvae of *Aedes aegypti* maintain balance on the water surface through air pockets in the trachea and hydrophobic region of the siphon (Christophers 1960). This hydrophobic balance is disturbed by rhamnolipids leading to difficulty of the larvae to stay on the water surface and expend more energy for active swimming to the surface (Silva et al. 2015).

Recent works by Li (2016) targeting fibrinogen-related protein 1 (*FREP1*) showed promising results as a antimicrobial. FREP1, which is produced in the midgut of mosquitoes after a blood meal, can attach to gametocytes and ookinetes. This can enable the parasite to penetrate the peritrophic matrix and epithelium. Thus, targeting

the FREP1 using a nontoxin bioactive natural product *P*-orlandin from *Aspergillus niger* showed 92% inhibition of interaction between FREP1 and *Plasmodium falciparum*-infected cells. This disruption of interaction reduces the infection of mosquitoes by *Plasmodium*.

1.2.3 Chagas Disease (American Trypanosomiasis)

Chagas disease is named in honor of Brazilian physician Carlos Chagas. It is spread through the bite of triatomine bugs (kissing bugs) infected with protozoan *Trypanosoma cruzi*, and through blood or organ transfusion from an infected source. The disease is divided into three stages: The acute stage, which is characterized by malaise and fever lasting from 4 to 8 weeks. It is followed by the indeterminate phase, which can last up to 2 decades. Active replication of the protozoan takes places during this stage; however, the clinical symptoms are minimum. This can lead to the chronic stage of Chagas disease that leads to irreversible damage to the autonomous nervous and peripheral nervous system (Maguire 1987). This stage of Chagas disease is incurable. The hallmark of Chagas disease is progressive heart disease (Bestetti and Muccillo 1997; Hurwitz et al. 2011). *Trypanosoma cruzi* strains display a high rate of polymorphism (Martínez-Díaz et al. 2001) and thus it is difficult for a simple accurate detection method. Fungal entophytes thrive inside a plant host. Such entophytic fungus has been screened in large amounts by Higginbotham et al. (2013). Entophytic fungus (104 out of 2698 fungal entophytes, 3.9%) isolated from various plants in national parks throughout Panama showed high activity against *Trypanosoma cruzi*. The same research group isolated fungal cultures from sloth hair (a mammal generally found in the tropical forests of South and Central America). Interestingly, organic crude extracts from 8 out of 62 (12.9%) cultures were highly active against *Trypanosoma cruzi* (Higginbotham et al. 2014). Five anti-trypanosomal metabolites, actinoallolides A–E, were also isolated from *Actinoallomurus fulvus* MK10-036 (Inahashi et al. 2015).

Anti-*Trypanosoma cruzi* peptides have been tested in the past such as Dermaseptin 01 from the skin of the *Phyllomedusa hypochondrialis* frog (Brand et al. 2006) as well as fungal peptides such as efrapeptins (Cataldi de Flombaum and Stoppani 1981) and antiamoebin (Kumar et al. 1991). Efrapeptins and antiamoebin act by inhibition of ATPase of the protozoan. Extracts from *Aspergillus fumigatus* exhibited lysis of trypomastigote as high as 95% while leaving the healthy red blood cells intact (Furtado et al. 2005). Since the production of microbial bioactive molecules and compounds pose the limitation of limited quantity, artificial neural networks could contribute for optimization of optimum production of trypanocidal metabolites (Furtado et al. 2005).

1.2.4 Leishmaniasis

Leishmaniasis is transmitted by the bite of female phlebotomine sand flies through the transmission of intramacrophage protozoan of the genus *Leishmania*. Annually more than 200,000 new cases of visceral leishmaniasis are reported (WHO 2016).

However, most of these cases are concentrated in poor countries, such as Bangladesh, Nepal, India, and Brazil (Murray 2004). Hence, it is also known as the diseases of the poor that is most prevalent in Southeast Asia and Latin America (WHO 2014). There are three main types of leishmaniases: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and muco-cutaneous leishmaniasis (ML) (Herwaldt 1999). The most severe among all the types of leishmaniases is the visceral leishmaniasis (VL), which is caused by *Leishmania donovani* (Davis et al. 2004). The pathogenesis of leishmaniasis is initiated by the breakdown of cell surface with the help of protease enzyme present on the surface of *Leishmania* species thus leading inside the host cell. Metalloprotease is present on the *Leishmania* promastigotes cell surface as a major surface protease (MSP), which helps in attachment of the protozoan to the sand fly gut (Sundar 2001). MSP also binds to the CR3 receptor on the macrophage, which aids in internalization of the promastigote. Treatments for leishmaniasis include Amphotericin-B and its lipid formulations, stibogluconate (pentostam) and meglumine antimoniate (glucantime). However, they are known to have severe side effects to the patients in addition to the high treatment costs, which is unaffordable to most in poor countries. Sodium antimony gluconate (SAG), which was an effective drug with antileishmanial effects, have been stopped in most countries due to the resistance developed by the pathogen (Sundar 2001).

Kojic acid (KA) is a water-soluble fungal metabolite produced by the *Aspergillus* species. Kojic acid has been shown to exhibit antiamastigote activity (Rodrigues et al. 2014). Macrophage infected with *L. amazonensis* is deprived of reactive oxygen species (ROS) and NO production (Olivier et al. 2005; Mukbel et al. 2007). However, treatment with Kojic acid reverses these inhibitory effects, which leads to production of O_2^- leading to killing of the pathogen (Rodrigues et al. 2014).

1.2.5 Dengue and Japanese Encephalitis

Flavivirus is the causative agent of Japanese encephalitis and dengue. Flavivirus is an ssRNA virus carrying a genome of 10.6 to 11 kb that encodes for capsid, premembrane, and envelope protein, and other functions such as replication of RNA genome (Green and Rothman 2006). More than 70 variants of flavivirus strains cause various diseases. Some of the most dreadful viruses of the *Flavivirus* genus are dengue virus (DENV), yellow fever virus (YFV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (TBEV) (Rohde et al. 2008; Bollati et al. 2010). Morbidity and mortality rates of Japanese encephalitis and dengue are highest in southern and eastern Asia. Although both VBDs are caused by flavivirus, the vectors differ for dengue and Japanese encephalitis. The fresh water inhabitant *Aedes Aegypti* vectors the virus that causes dengue, whereas Japanese encephalitis is caused by *Culex* (*Culex tritaeniorhynchus, Culex vishnui*, and *Culex pseudovishnui*) often found in polluted water bodies. Symptoms are similar for both organisms, including severe headache, fever and vomiting, encephalitis (brain inflammation), meningitis, weakness, and movement disorders, which can develop over a number of days and may lead to coma and paralysis (El-Kafrawy et al. 2016; Kumar and Sharma 2016).

Various drugs to treat dengue have failed due to its adverse side effects to the patients. Drugs against dengue and Japanese encephalitis from microbial sources are in the infant stage. The various microbial products that exhibit dengue antiviral activity include bafilomycins, mycophenolic acid, and other fungal metabolites that work through a range of mechanisms such as inhibition of NS2B, ATPase, inosine 5′-monophosphate dehydrogenase (IMPDH), or through inhibition of endosome acidification to prevent the entry of the virus into the endosome. A number of *Streptomyces* sp. shows promising inhibition action against Japanese encephalitis causative virus (Ratnakomala et al. 2011). Its mode of action targets the ATPase enzyme, which inhibits the RNA helicase activity.

Chitins are an essential compound for mosquitoes and act as a protective layer in their body coverings and are required during the different growth stages of mosquitoes, especially during the transformation from larvae to pupae. Chitinase enzymes from *Streptomyces cacaoi* subsp. *cacaoi*-M20 targeting the chitin required for the larvae have shown to have insecticide activity against *Aedes* mosquitoes (Janaki et al. 2016). Metabolites of *Streptomyces* PO-02, PO-08, and PO-11 showed marked larvicidal efficacy via inhibitory activity on lipase. At concentration 500 μg/ml, inhibition of enzyme ranged between 12% and 58.50% (Prashith et al. 2012). Ethyl acetate extracts from various microbes such as *Py. sanguineus*, *Pe. virgulata*, *Streptomyces* sp. VITJS4 (Naine and Devi 2014), *Bacillus*, and *Pseudomonas* sp. (Nabar and Lokegaonkar 2015) have shown to exhibit *Aedes aegypti* larvicidal activity ranging from 98% to 100% at 550 ppm. Fungal mosquito pathogens such as *Lagenidium, Coelomomyces*, and *Culicinomyces* are also a promising tool to fight against the vector (Scholte et al. 2004). Besides the natural microbial products, synthesis of nanoparticles through the aid of microbes could pave a new dimension in the fight against VBDs. Nanoparticles are generally more effective than bulk compounds. Cerium oxide nanoparticle synthesis using *Aspergillus niger* showed activity against *Aedes aegypti* 0.250 mg/L (Gopinath et al. 2015).

1.2.6 West Nile Fever

West Nile fever is caused by ssRNA West Nile virus (WNV) belonging to the *Flavivirus* genus (Petersen and Marfin 2002). *Culex* mosquitoes mainly transmit it. The West Nile virus life cycle is maintained in a bird–mosquito–bird pattern, with birds being the main reservoir and arthropod vectors. WNV is mainly observed in high temperate regions. Chimeric protein from WNV is mainly responsible for humoral and cell-mediated immunity that can be used against the WNV itself. Fusion of *Salmonella typhimurium* fljB flagellin with EIII domain of the WNV envelope protein stimulates high immune response and activation of Toll-like receptor (TLR) (Huleatt et al. 2007). Such an approach could be used for the development of vaccine against WNV. Ethyl acetate extracts from Salinispora sp. SA6E, Salinispora sp. SA22E, and Rhodococcus sp. SA12E showed inhibition of West Nile protease NS3 inhibition 84%, 79%, and 93%, respectively (Abdelmohsen et al. 2014) (Table 1.1).

TABLE 1.1
Various Microbial Products and Their Source along with Their Mode of Action

Source	Compound	Against	Action	Reference
S. gougerotii GT	4S,10R-dihydroxy-11-methyl-dodec-2-en-1,4-olide	Dengue	Inhibits the expression of NS2B protease	Lin et al. 2016
M. variabilis C-03	Cyclo-(4-trans-6-dihydroxy-proline-L-leucine)			
Streptomyces sp. YIM56209	Bafilomycins		Inhibits endosome acidification	Bowman et al. 1988; Yu et al. 2011
Penicillium brevicompactum	Mycophenolic acid		Inhibits inosine 5′-monophosphate dehydrogenase (IMPDH), which affect DNA synthesis in virus	Bartman et al. 1981; Kang et al. 2014
Beauveria bassiana	Fungal biomass		Activates toll and JAK-STAT pathway-controlled effector genes and anti-dengue activity in *Aedes aegypti*	Dong et al. 2012
Streptomyces sp., *Actinoplanes philippinensis, Kribbella flavida*	Secondary metabolites	Japanese encephalitis	ATPase inhibitor of RNA Helicase (40%–45%)	Ratnakomala et al. 2011
Streptomyces sp.			95%–100% inhibition of Virus NS3 at 0.05 mg and 0.1 mg/20 ml	Hatsu et al. 2002
Emericellopsis poonensis	Antiamoebin I	*P. falciparum*	Efrapeptins inhibit mitochondrial F_0F_1 ATPase	Nagaraj et al. 2001
Tolypocladium niveum	Efrapeptin C–G			
Emericellopsis salmosynnemata	Zervamicin IIA			
	Zervamicin IIB			
Pseudomonas aeruginosa	Rhamnolipids	Larvae of *A. aegypti*	Distribution of hydrophobic balance	Silva et al. 2015

(*Continued*)

TABLE 1.1 (CONTINUED)
Various Microbial Products and Their Source along with Their Mode of Action

Source	Compound	Against	Action	Reference
P-orlandin	*Aspergillus niger*	*P. falciparum*	Inhibits the interaction between fibrinogen-related protein 1 (FREP1) and *P. falciparum* infected cells	Li 2016
Fungal extracts	Fungal entophytes	*T. cruzi*		Higginbotham et al. 2013
	Fungal cultures from sloth hair			Higginbotham et al. 2014
Actinoallolides A–E	*Actinoallomurus fulvus* MK10-036	*Trypanosoma cruzi*		Inahashi et al. 2015
Crude extract	*Aspergillus fumigatua*	*Trypanosoma cruzi*	Lysis of trypomastigote	Furtado et al. 2005
Ethyl acetate extracts	Salinispora sp. SA6E, Salinispora sp. SA22E, Rhodococcus sp. SA12E	West Nile virus	Inhibits West Nile protease NS3	Abdelmohsen et al. 2014
Kojic acid (KA)	*Aspergillus species*	*L. amazonensis*	Reverses inhibitory effects that lead to production of O_2^- and to killing of the pathogen	Rodrigues et al. 2014

1.3 VECTOR-BORNE DISEASE CONTROL AND PREVENTION

1.3.1 Development of Model for the Control and Prevention of VBDs

The survival and maturation of vectors require suitable environments. Thus, the spread of VBDs is directly related to environmental factors and the socioeconomic status of the society. For instance, malarial transmission is dependent on air temperature where the development and maturation cycle of the parasite decreases with an increase in air temperature (Alto and Juliano 2001). Similarly, correlations were seen between cutaneous leishmaniasis and air temperature (Chaves and Pascual 2006). The level of rainfall and the abundance of malarial vector are also well correlated (Yé et al. 2009). Such information based on rainfall and weather prediction can be used as an early warning sign (Chabot-Couture et al. 2014). Other environmental factors include humidity, water bodies, and latitude and longitude.