eISBN: 978-1-68108-479-4
ISBN: 978-1-68108-480-0

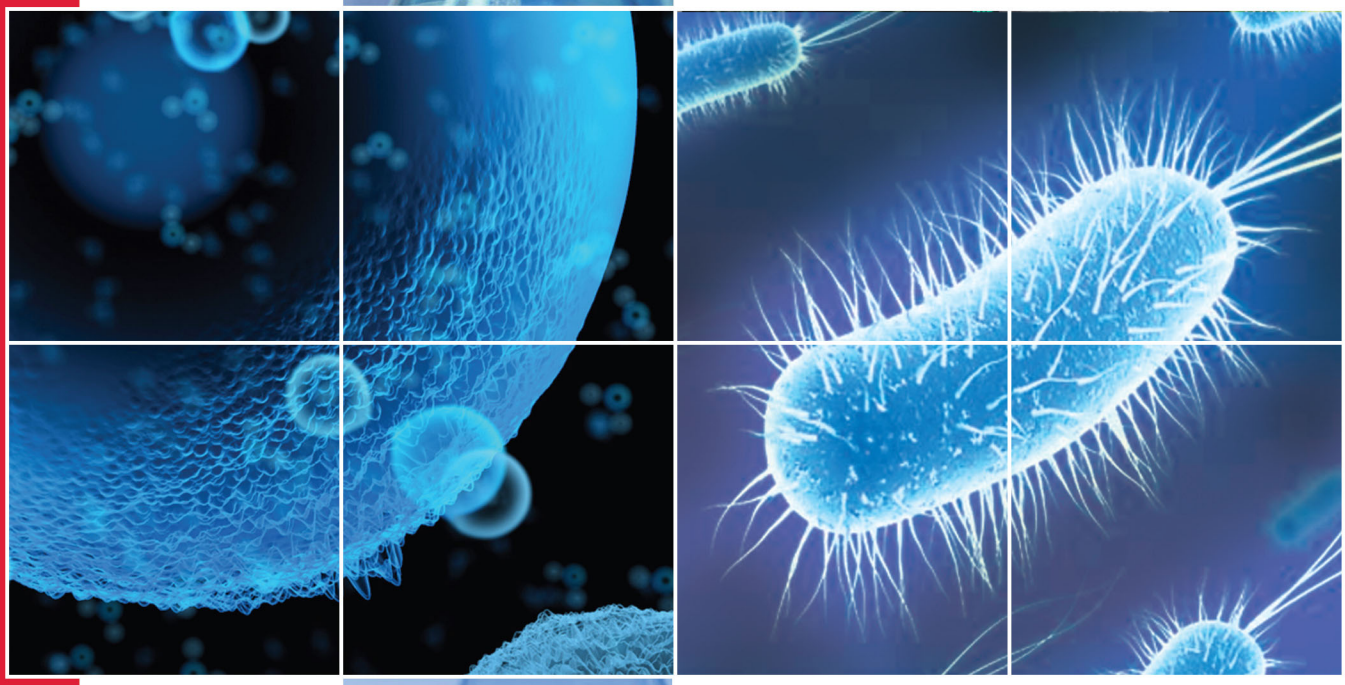
eISSN: 1879-663X
ISSN: 2451-9162

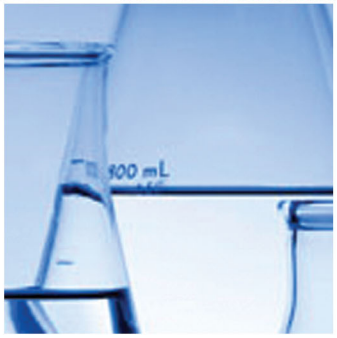
Frontiers in Anti-Infective Drug Discovery

Volume 6

Editors:

Atta-ur-Rahman, *FRS*
M. Iqbal Choudhary





Bentham Books

Frontiers in Anti-Infective Drug Discovery

(Volume 6)

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Frontiers in Anti-Infective Drug Discovery

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ISSN (Online): 1879-663X

ISSN (Print): 2451-9162

ISBN (Online): 978-1-68108-479-4

ISBN (Print): 978-1-68108-480-0

First published in 2017.

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PREFACE

Infections kill more people than all other diseases combined. Despite the tremendous development in this field, infections are increasingly difficult to treat today because of the development of organisms resistant to antibiotics. Human sufferings because of bacterial, fungal, parasitic, and viral infections are therefore likely to increase many fold in the new future. Emerging antibiotic resistance in all infection-causing microorganisms is making many believe that the era of antibiotics is coming to an end. Recent reports establish that the chances of dying from hospital-acquired pneumonia or septicaemia are much higher from drug-resistant infections. In this context, extensive research, both in academia and in pharmaceutical industries, has begun, covering various aspects of this complex topic, such as infection biology, genomics of resistance, new drug target identification, and search for new antibiotics. It is often difficult, even for a prolific reader, to keep pace with these exciting developments. Thus, the need of a comprehensive book review series is greatly felt. The present series of volumes, partly addresses this need.

The last five volumes of the ebook series "*Frontiers in Anti-Infective Drug Discovery*" have attracted great scientific interest, as a welcome addition to the global literature in this active area of research. The present volume of this internationally recognized books series comprises of six carefully selected reviews on various aspects of infection, etiology, and treatment, contributed by leading experts in this field. Each review is focused on important aspects of anti-infection drug discovery and development, based on various innovative approaches, including relationship between infections and neurological disorders, identification of new molecular targets, outcomes of pre-clinical and clinical studies on new and novel classes of antimicrobial and antiviral drugs, combination therapies, and strategies to overcome emerging antibiotic resistance.

Pantazaki *et al*., have reviewed some of the most striking recent reports on the relationship of infectious and inflammatory etiology with the on-set of Alzheimer's diseases (AD). Recent research has shown that many microorganisms, such as bacteria (*Helicobacter pylori*), viruses (*Herpes simplex virus*, *influenza*, CMV, *etc*.) and fungi can cause AD. It has been reported that these microorganisms and viruses can cross the blood brain membrane and cause mild to severe infections in the brain. Persistent or acute neuronal and peripheral inflammatory response against these infectious agents lead to accumulation of amyloid protein aggregates which are the major cause of AD. It has also been reported that an alternation in normal gut microbiota can cause the accumulation of functional amyloid proteins which are then transported to the Central Nervous System (CNS) causing neurologic and psychiatric disorders, such as schizophrenia, anxiety, and AD. The review provides an interesting description of the effects of chronic inflammatory responses against immune-reactive proteins as risk factors for nervous system disorders. The authors have also recommended the consumption of natural products and natural diets, such as Mediterranean and Asian diets, which are capable of preventing AD or reducing the risk of AD, and strengthening the body's ability to confront infections. In brief, this review is a comprehensive commentary based on recent literature on the possible relationship between the infection, microbiota and the on-set of Alzheimer's diseases. The authors thus support the use of chemotherapeutic and dietary approaches for the prevention of AD.

The review contributed by Dwivedi *et al*., focuses on the conventional and current treatments of malaria comprising of natural substances and synthetic analogues. The choice of therapeutic agents against malaria depends on the species of parasite, the pattern of resistance, and the seriousness of the infection. Despite major developments in the understanding of the

aetiology of malaria at the molecular level, and the introduction of new drugs, the disease is causing considerable morbidity and mortality in Asia, South America, and Sub-Saharan Africa. According the WHO, malaria kills more people world-wide than all other parasitic diseases taken together. The emergence and spread of multidrug resistant strains of malarial parasites have further limited the choice of antimalarial chemotherapeutics. This highlights the urgent need of efficient research for developing newer and broad spectrum antimalarial drugs. The development of an effective malaria vaccines has remained a major challenge for scientists, with only limited success achieved so far. This review highlights the importance of the development of new drug delivery systems which maximize the *on-site effect* and minimize the adverse effects of existing antimalarial drugs. Recent development of nanoparticles as careers for malaria chemotherapy which can minimize the side effects and improve bioavailability and selectivity of the drugs has also been discussed in this review. The authors have emphasized the need for continuous search for antimalarial drugs, giving the example of arteether (ART) and bulaquin. The review provides a comprehensive account of challenges and opportunities in malarial chemotherapy, and proposes several directions for future research in this important field.

Zehra Küçükbay and Hasan Küçükbay have contributed a chapter on recent developments in the field of novel antibiotics and antimicrobial agents. Their review presents merits and demerits of various classes of antibiotics, such as b-lactams, macrolides, fluoroquinolones, tetracyclines, and aminoglycosides, in the context of emerging resistance against them. The authors have focused on natural products as possible antimalarial agents which can circumvent the emerging resistance issues while having limited side-effects. By providing examples of fascinating natural products used against infections such as aspirin (willow plant), opioids (opium poppy), atropine (*Atropa belladonna*), and quinine (cinchona), the authors have advocated the need for searching natural chemical diversity as a source of new antimicrobial and resistance-reversal agents against increasingly resistant infections. This review thus provides an in-depth look at the most significant developments in antimalarial drug development and prospects of natural products as sources of new antimalarial drugs.

Tuberculosis or TB is among the most serious infectious diseases that can affect almost any tissue of the body, especially the lungs. Once considered to be a disease of the developing world, TB has recently emerged in the developed world as a co-infection along with HIV, since people with a compromised immune system develop TB very quickly. Many strains of *Mycobacterium* have now developed resistance against the arsenal of available drugs, making the treatment increasingly difficult. TB patients are now required to take several types of medications for long durations to eradicate the infection, prevent relapse, and avoid the development of antibiotic resistance. Recently two drugs, Bedaquiline and Delamanid, have received conditional approvals for the treatment of MDR-TB, for patients where other treatments fail. Jawed Ahsan has reviewed the recent developments in the TB chemotherapy, including new and repurposed antitubercular drugs in advanced phases of clinical trials. He has also commented on various vaccine candidates which are in clinical development. The review also discusses the need of new diagnostics, and anti-TB drugs as well as TB vaccines to control the spread of TB pandemic in the developing and the developed world.

Naseem Ahmed has contributed a review on widespread hepatitis viral infectious disease and its treatment. Hepatitis is wide spread, particularly in the poor regions of the world. Various forms of the hepatitis virus (hepatitis A- E) are wreaking havoc to many the health care systems of the developing world. Among the various forms, hepatitis A, B, C, D, and E are the most common. Over a billion people are estimated to be either patients or carrier of hepatitis. Cases of non-viral, and autoimmune hepatitis are widely reported due to alcohol consumption, use of medications against chronic disorders, and spread of autoimmune

diseases. Current treatment options are often expensive, and beyond the reach of poor patients. However recent developments in this field have been very promising. Interferons alone or pegylated interferons have been used with 35-40% success, and numerous side effects. New medicines which target NS3/4A protease, NS5B polymerase, and NS5A enzymes have been developed with phenomenal success of 70-90%. Several other inhibitors of NS5B and NS5A polymerase targets are in various stages of development. The chapter provides an excellent review of the recent literature on new antiviral drug development, identification of new targets, investigational and novel therapies and most importantly merits and demerits of existing anti-hepatitis medicines.

Finally, the review by Shukla *et al*., is focused on the discovery and development of various classes of natural and synthetic peptides and polypeptides as novel anti-infective agents as well as structure -function relationships. The emergence of resistance has led to the development of non-classical antibiotics, including peptide antibiotics, especially cationic peptides. Several thousands of such peptides have been isolated from natural sources (plants, animals, microbial, *etc*), and many more have been synthesized. However only a few have entered into clinical trials. As antimicrobial peptides (AMPs) kill bacteria quickly by the physical disruption of cell membranes, the emergence of resistance against them is less likely. The authors have also discussed various aspects of uses of AMPs, including their possible use as delivery vectors to transport the cell impermeable drugs to the cell interior. Their diverse and broad spectrum antimicrobial activity has been described in literature. These peptides offer a potentially rich source of novel antimicrobial agents. The authors have presented numerous examples of AMPs along with reports of modifications in the existing peptides, isolation of novel peptides from nature, the introduction of non-natural amino acids in their structures, and their mechanisms of action.

We are pleased to express our gratitude to all the authors of the above cited reviews for their excellent scholarly contributions to the 6th volume of this ebook series. We also appreciate the efforts of the brilliant publication team of Bentham Science Publishers for the efficient processing of the treatise. The skills and efforts of Ms. Fariya Zulfiqar (Assistant Manager Publications) & Mr. Shehzad Naqvi (Manager Publications), and excellent management of Mr. Mahmood Alam (Director Publications) are greatly appreciated. We also hope that like the previous volumes of this internationally recognized book series, the current volume will also receive a wide readership from scientists and research students.

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CHAPTER 1

Alternative Anti-Infective/Anti-Inflammatory Therapeutic Options for Fighting Alzheimer's Disease

Magda N. Tsolaki[1], Euphrosyni S. Koutsouraki[2], Georgios K. Katsipis[3], Pavlos Gr. Myserlis[1], Marilia A. Chatzithoma[1] and **Anastasia A. Pantazaki[3,*]**

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Abstract: Neurodegenerative diseases (NDs) have a serious impact on global health with no effective treatments yet available. Alzheimer's disease (AD) is an incurable, progressive neurodegenerative disorder, considered to be the most common cause of dementia. There is increasing evidence for the infectious/inflammatory etiology of AD. Although brain is assumed to be an immunologically isolated organ, many bacteria (*Helicobacter pylori*), viruses (*Herpes simplex virus*, *influenza*, CMV *etc*.), fungi, toxoplasma, are associated with AD. The presence of immune-related antigens around amyloid plaques, activated complement factors, cytokines and a wide range of related receptors in the brain of AD patients, led to the concept of "neuro-inflammation". Persistent or acute neuronal and peripheral inflammatory response to infectious agents is gradually gaining more attention, as a risk factor for someone to develop sporadic AD. The human microbiome (HM) has a pivotal role in nutrition, health and disease. About 100 trillion bacteria from up to 1000 bacterial species inhabit the gastrointestinal (GI) tract, contributing, at least in part, to what is known as the "human-biochemical" or "genetic-individuality" and resistance to disease. Several pathologies, including AD and inflammatory bowel disease, are associated with alterations in gut microbiome. Microbes of the gut microbiota or of extracorporeal origin possess the ability of producing functional amyloid proteins. These amyloids, *via* lymphatic and systemic transport to the Central Nervous System (CNS), seem to have an important role in the expression of neurologic and psychiatric disorders, such as schizophrenia, anxiety and AD. Cross-seeding of the neurodegenerative disorder proteins may be induced by these amyloids. Moreover, chronic inflammatory response to these immune-reactive proteins can also be an important risk factor for CNS well-being. Therapeutic/preventive options for halting CNS disorders' onset, could include: (a) Anti-inflammatory,

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anti-amyloid drugs (β-sheet breakers and other inhibitors of amyloid fibrillization), monoclonal antibodies, nanoparticles, which target pathological components of AD, or other medical interventions to remove infectious agents or to ameliorate their biochemical influence on GI-CNS tract, (b) Prebiotics to enhance the growth of desired organisms and reduce oxidative stress - a cause that has been implicated with AD, (c) Probiotics to provide both the desired bacteria, which increase the competitive effects with pathogens, and essential metabolic products, and to modulate the host immune system to resist in infection (d) The consumption of natural products, and the dedication to the Mediterranean (MeDi) and Asian (AsDi) Diets, abundant in bioactive compounds, are capable to prevent AD or reduce danger of AD, and strengthen the host's ability to confront infections. The significance of diet diversity leading to the microbiota diversity is a new clinically important concept. Finally, and (e) preventive medical and/or other therapies to alter the amyloids produced by bacteria, to decrease their production or stimulate their removal. This chapter is addressed to, and urges the excellent cooperation between experts of neurology/psychiatry, microbiology, biochemistry, dietary and nutritional sciences, in order to confront AD.

Keywords: Alzheimer's disease, Infection, Inflammation, Dietary interventions, Natural products, Mediterranean Diet (MeDi), Asian Diet (AsDi), Anti-amyloid treatment, Monoclonal antibodies, AD diagnosis, AD treatment.

1. ALZHEIMER'S DISEASE (AD)

1.1. Epidemiology

AD is a progressive neurodegenerative disorder affecting millions of people worldwide.

Due to an increasingly aging population, AD represents a crucial issue for the healthcare system because of its widespread prevalence and the burden of its care needs. It is one of the most devastating diseases for the older population, and has become a major healthcare burden in the increasingly aging society worldwide. Currently, there are still only symptomatic treatments available, just to manage the symptoms and slow down disease progression. It is a progressive brain disorder that minimizes memory ability and other cognitive functions associated with intellectual and social skills. It has become a colossal medical and socio-economic challenge in the growing elderly population. As the most common dementia known, AD affects 5.4 million Americans, 10 million Europeans and nearly 47 million people worldwide [1]. The number of dementia cases is anticipated to triple by 2050 [2]. Two forms of AD are known: sporadic and familial AD. Sporadic AD affects people mostly after age 60 and makes up about 97% of all cases. Familial AD occurs at an earlier age between 30-50 and results when one parent passes a mutated gene associated with this dementia to their offspring. Each child of an individual with familial AD has a 50% chance of

inheriting the mutated gene and developing this dementia. There is an amyloid precursor protein (APP) mutation [alanine-673-->valine-673 (A673V)] that causes disease only in the homozygous state, whereas heterozygous carriers were unaffected, consistent with a recessive Mendelian trait of inheritance. The A673V mutation affected APP processing, resulting in enhanced beta-amyloid (Aβ) production and formation of amyloid fibrils *in vitro* [3].

It is a considerable and galloping public health anxiety, with significant augmentation reflected in the future, especially in low-to-middle income countries [4]. Moreover, there is at present unanimity that a considerable analogy of cases are potentially preventable [5]. Preventing or delaying the clinical onset of dementia would have a substantial effect on disease numbers [6]. It has been suggested that approximately a third of AD cases could be attributed to seven potentially modifiable risk factors: diabetes, midlife hypertension, obesity, smoking, depression, cognitive inactivity, and low educational attainment [7].

1.2. Pathogenesis

Several hypotheses have been proposed for the pathogenesis of AD, but none of them is satisfactory enough to elucidate its full spectrum. Most possibly this is why the current therapeutic strategies have shown limited – if any – effectiveness [8]. In the last two decades, more evidence has supported a role for neuro-inflammation and immune system dys-regulation in AD [9 - 11]. It remains unclear whether astrocytes, microglia and immune cells influence disease onset, progression or both. Aβ peptides that aggregate extra-cellularly in the typical neuritic plaques generate a constant inflammatory environment. This engenders a protracted activation of microglial and astroglial cells that excite neuronal injury and provoke the alteration of the blood brain barrier (BBB), damaging the permeability of blood vessels. Recent data support the role of the BBB as a link between neuro-inflammation, the immune system and AD [12 - 14]. Hence, a thorough investigation of the neuro-inflammatory and immune system routes that affect neurodegeneration and unusual enthralling findings like microglia-originated micro-vesicles, particulate as inflammasomes and signalosomes will ultimately contribute to the elucidation of the pathological process. Finally, we should advance with attention in order to define whether the role of neuro-inflammation in AD is "causal or sequential", but rather focalize on the identification of its precise pathological participation [15].

Two basic discoveries spurred research into inflammation as a driving force in the pathogenesis of AD. The first was the identification of activated microglia in association with the lesions [16]. The second was the discovery that patients with rheumatoid arthritis, who regularly consume anti-inflammatory agents, were

CHAPTER 2

The Menace of Malaria: An Overview

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Abstract: Malaria remains one of the most dreadful diseases affecting millions of people across the world. It is an infectious disease spread through the (female anopheles) mosquito caused by the parasitic protozoans belonging to genus Plasmodium. The most lethal species is *Plasmodium falciparum* which if left untreated, may cause organ failures (severe malaria) or may accumulate in brain (cerebral malaria) causing coma and finally leading to the death. The disease is mostly prevalent in Sub-Saharan Africa. Children under the age of 5 years, pregnant women and travellers to the malaria prone area are particularly at higher risk of getting malaria. It is typically diagnosed by microscopic examination of blood using blood film or antigen-based rapid diagnostic tests. The treatment of malaria comprises various synthetic, natural analogues administered orally or parenterally. The choice of therapeutic agents depends on the species of parasite, pattern of resistance and the seriousness of the infection.

Emergence and spread of the multidrug resistant strains of the causative organisms has extremely limited the choice of antimalarial chemotherapeutics. Only limited treatment options are currently available due to the resistant species highlighting the need of efficient research for developing newer broad spectrum antimalarial drugs. The discovery of potent vaccine against malaria still remains a major challenge amongst scientific community, with only limited success achieved till now.

The choice of the delivery system plays a vital role in determining fate of the drug as it's not only important for delivering the right drug at the right site, but also it can minimize the untoward effects of drugs. Nano-carriers or nanosystems are useful tools that are particularly gaining distinctive attention in malaria chemotherapy because of their ability to minimize the side effects, improve bioavailability and the selectivity of the drugs by altering the biopharmaceutics and pharmacokinetic property of the drug molecules.

Discovery of potent drugs like Arteether (ART) and Bulaquin have been some major breakthroughs in antimalarial research. However; the major challenge in management

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of malaria in the current scenario is to combat drug resistance and to develop new potent drugs in order to completely irradiate this fatal disease. This chapter is intended to highlight on some basic aspects of malaria, challenges in current chemotherapy, current investigations towards malaria chemotherapy and vaccine, and the use of nanotechnology as a promising strategy for malaria treatment.

Keywords: Malaria, *P. falciparum*, *P. vivax*, Artemisinin, Cinchona, Drug-resistance, Malaria vaccine, Nanotechnology, Parasite.

INTRODUCTION

Malaria is one of the most predominant ubiquitous parasitic diseases throughout the globe. The cause of the disease is an apicomplexan protozoan of *Plasmodium (P.)* genus. *P. falciparum* and *P. vivax*, are the major causative organisms. Malarial infection can be found all over the world but it is more common in tropical countries. In 2013, malaria was prevalent in more than 100 countries [1] over hundred million episodes of malaria have been estimated in 2012; in which more than 80% of these cases were reported in Africa, resulting over millions of deaths [2]. This is the statistics, when there was a drop of 50% or more malaria burden in 11 African and 32 of 56 malaria endemic countries outside Africa [3]. In 2015, the number of people infected from malaria have witnessed 21% decline with approximately 212 million malaria cases compared to 2010 because of the increased access to the disease-cutting tools to the needed populations. Approximately 4,29,000 death occurred in 2015 of which 92% deaths occurred in WHO African Region [4]. Among the cases occurring outside Africa, majority of cases were reported in Asian countries including India [1, 4]. The recent figures although show positive trends, there is a lot more to achieve for getting malaria free world.

Among several deaths which occur due to malaria every year, the majority are of children below 5 years of age. The occurrence of malarial infection is so high that most of the children without having acquired adequate immunity went through this infection in the initial years of their lifespan [1, 2, 5, 6]. WHO (World Health Organization) has started several programs to overcome these mortal malarial infections throughout the world, but still there is a lot of need for research and development as the current status of research in not considered being sufficient and there is a need for new therapies and vaccines.

Available malaria chemotherapy has been helpful but not in a significant manner, as these are associated with recurring failures [7]. The unique nature of the disease in relation to its transmission conditions, becomes a significant factor as it is more complex to manage its transmission throughout tropical areas [8]. The complex life cycle of the parasite and development of resistance to the drug are attributed

as the principal challenging factors in new drug discovery [9] and causing higher mortality. An alarmingly high incidence of immune-compromised patients suffering from co-infections of malaria and HIV happens to be another crucial factor in new drug discovery [10, 11]. These infections together; account for more than millions of life per year. Moreover, the complex recommended regimen based on combination therapy increases the cost of treatment and brings down patient compliance, due to the associated side effects [7]. Tools and methodologies adopted to detain the prevalent dissemination of malaria include effective disease prevention by abolition of mosquitoes by means of insecticidal spray and providing treatment based on artemisinin combination therapy. The sporadic prophylactic treatment with antimalarial drugs has been used as a last option in case of pregnancy, to lower and reduce the deleterious effects of malaria infection on the fetus. Treatment protocols and regimens for malaria directly correlate to resistance developed by the parasite for the drug, as well as governed by government approach for prevention and control of mortality rate [12]. Taking into consideration the fact that fewer numbers of new antimalarials have been approved since 1990, the search for novel efficient and less toxic antimalarials accomplished with nano-delivery systems assumes significance

The present chapter is aimed to take the brief account of important aspects of malaria including its biology, current malaria chemotherapeutics and the associated problems with them, the current research in the field of antimalarial drug discovery with special focus on nanotechnology. The chapter also covers the role of Central Drug Research Institute (CSIR-CDRI) in the discovery and development of antimalarial drugs.

Methods

The authors made use of search engines and databases such as ScieFinder and Pub-Med and relevant guidelines from World Health Organization, (WHO) for data collection. Data was collected on current global status, statistics, biology and the detailed pathophysiology of malaria. Details about the risk factors, preventive measures, treatment regimens, and the problems associated with the malaria chemotherapy were collected. Detailed information about currents antimalarial leads (from both synthetic and natural sources), research on malaria vaccine, role of CSIR-CDRI in antimalarial research, and the role of nano-formulations in malaria treatment was obtained. The detailed information regarding each topic was collected by narrowing the search by using 2 or more key words. The assimilated data was studied and interpreted, compiled and arranged under different headings covered in this chapter to create a comprehensive insight into the topic and to produce a detailed overview.

CHAPTER 3

Chemical Structures and Classification of Anti-microbial Drugs

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Abstract: This chapter aims to review the literature on anti-infective (also known as antimicrobial) drugs among the anti-infections drugs, and to highlight recent developments relating to novel antibiotics and their classification. Antibiotic classification is determined according to their structure and mechanism of action; the main groups include β-lactams, macrolides, fluoroquinolones, tetracyclines, and aminoglycosides. Despite significant progress in anti-infective therapies, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to the rapid development of resistance to existing drugs. This resistance increasingly limits the effectiveness of current anti-infective drugs. To overcome this problem, scientists are searching for novel therapeutic agents that are efficacious against microorganisms and cause limited side-effects. Naturally occuring compounds in plants have previously been used successfully to treat many types of infection and illness. For this reason, it is quite important to understand the chemical composition of natural products and their mechanisms of action, in order to synthesize semi-synthetic or synthetic anti-infective drugs. Indeed, many chemically synthesized drugs originated from natural sources, *e.g.* aspirin (willow plant), opioids such as morphine (opium poppy), atropine (*Atropa belladonna*), and quinine (cinchona). Therefore, nature is a very fruitful source for pharmacy, medicine, biology and chemistry students.

Keywords: Anti-bacterial drugs, Aminoglycosides, Anti-fungal drugs, Anti-infective agents, Antibiotic, Cephalosporins, Chloramphenicol, Classification of antibiotics, Drug research, Drug resistance, Fluoroquinolones, Infectious diseases, Macrolides, Microorganisms, Natural products, Penicillin, Penicillium species, Synthesis, Tetracyclines, β-lactams.

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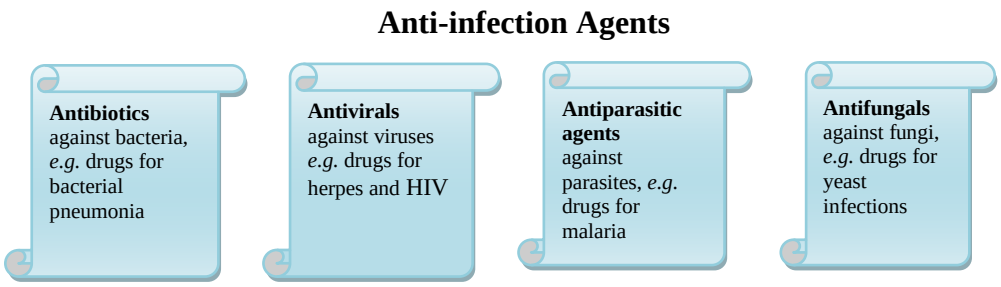
INTRODUCTION

Infectious diseases are responsible for more deaths worldwide than any other single cause. Their pathology is attributed to microorganisms such as bacteria, viruses, fungi, or parasites that are virulent and can spread between individuals.



Antibiotics are an important subset of antimicrobial chemotherapeutics. An antibiotic is any therapeutic agent that kills or prevents the reproduction of bacteria in the body. An antimicrobial is a substance composed of natural, semi-synthetic, or synthetic, a broad term for compounds that kill or inhibit the growth of microorganisms but cause little or no damage to the host. Antibiotics are a subset of antimicrobials that specifically treat bacterial infections.

Microorganisms are ubiquitous; they can be found in the air, water, soil, and rocks; many microorganisms also live inside and on the surface of our bodies [1].

Most of the microbes living in our bodies are symbiotic and assist normal bodily function. Many of the drugs available today are derived from compounds first found in microorganisms. However, under certain conditions, some micro-organisms become virulent and cause harmful infections in humans, animals, and plants. Infectious microorganisms can be passed directly between people or indirectly from an infected person to the environment (for example door handles, bedding, toilets, *etc*.) and then to another person who comes in contact with the contaminated source. Some are transmitted by bites from insects or animals, while others are acquired by consuming contaminated food or water. The symptoms and

signs of infection vary depending on which part of the body and which type of organism is involved. The first signs of infection are often inflammatory symptoms (fever, pain, swelling, redness, and purulence). Mild infections may respond to rest and home remedies, while life-threatening infections may require hospitalization. The main form of treatment is usually antimicrobial medication. There are several types of anti-infective drugs, depending on the type of organism targeted (such as antibiotics for bacterial infections, antiviral drugs for a limited number of viruses, antifungal medications for fungal infections, and antihelmintic drugs for worms) [2]. The treatment of bacterial infections with antibiotics is one of the most important developments of the twentieth century. Penicillin, a β-lactam antibiotic developed in the 1940s, has been at the forefront of antibacterial drug treatment [3]. Since then, several new antibiotics have been developed, either semi-synthetically or synthetically by chemical modifications (Fig. **1**) [4].

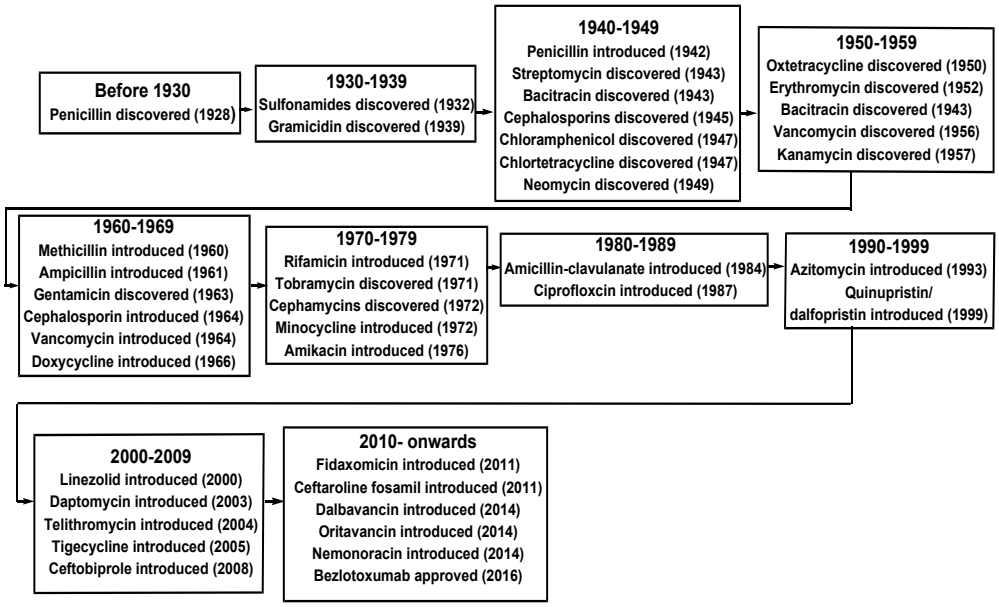


Fig. (1). A timeline of important historical antibiotic discoveries [4].

There was no effective treatment method for infections such as pneumonia, gonorrhea, or rheumatic fever before penicillin. However, the use of antimicrobial agents is known to have been a common practice for at least two millennia. Many ancient Egyptians and Greeks used various molds and plant extracts to fight bacterial infections [5]. Furthermore, ancient Egyptians applied moldy bread to infected wounds for its antibiotic effects. Much later, it was determined that the ssscharacteristic blue-green discoloration seen on moldy bread was the useful antibiotic-producing *Penicillium chrysogenum* mold. In 1928, the active

CHAPTER 4

Antitubercular Agents and Tubercular Vaccines in Clinical Trials

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Abstract: In 2015, an estimated 10.4 million people were infected with and 1.8 million people were killed by tuberculosis (TB). Multi-drug resistant (MDR) and extensively drug resistant (XRD) TB were other reported complications in the treatment of TB. Almost 3.3% of new TB cases and 20% of previously treated cases have multi-drug resistance (MDR) TB while 9.7% of people with MDR-TB have XDR-TB. Recently, two chemical entities, namely bedaquiline and delamanid were granted conditional approval for the treatment of MDR-TB, and are recommended only to those patients for whom other treatments fail to cure. The diagnostic platform, including GeneXpert Omni® and Xpert Ultra® is in development. There are seven new compounds and eight approved or repurposed antitubercular drugs in advanced phases of clinical trials, while thirteen vaccine candidates are in clinical trials. New diagnostics, anti-tubercular drugs and tubercular vaccines will be needed to achieve the targets set in the End TB strategy. This chapter explores the medicinal chemistry of anti-tubercular agents in various phases of clinical trials. The present chapter also deals with various diagnostic technologies for early detection of tuberculosis, as well as the tubercular vaccines in various phases of clinical trials.

Keywords: Anti-tubercular agents, Delamanid, Diagnostics, TMC207, Tubercular, Tuberculosis vaccines.

INTRODUCTION

Tuberculosis, (TB) a dreadful disease, mainly caused by *Mycobacterium tuberculosis*, (MTB), is one of the major health problems worldwide. It primarily affects the lungs (pulmonary TB) and can also affect other sites as well (extra pulmonary TB). In 2015, there were an estimated 10.4 million new cases of TB and 1.8 million people died from TB, including almost 1.4 million deaths among HIV-negative individuals and 0.4 million among HIV-positive individuals.

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Globally, there were an estimated 580,000 people who have developed the multidrug resistant tuberculosis (MDR-TB) in 2015. An estimated 49 million lives have been saved through TB diagnostic and treatment between 2000 and 2015 [1]. Nearly 10 percent of infected people usually develop active TB in their lifetime [2]. A research led by the scientists at Stanford University revealed that the MTB can persist in the hostile intracellular microenvironment, evading immune cells and drug treatment. They isolated MTB from bone marrow, derived CD271+/CD45-mesenchymal stem cells [3]. Tubercular bacteria are spread through the air by active TB patients and most commonly affect the lungs. The directly observed treatment short-course (DOTS), and a multidrug therapy program developed by WHO, is one of the most efficient artilleries against the global plague with success rate of 85% among all new TB cases and 87% among new cases of sputum smear-positive pulmonary TB in 2010. Unfortunately, the first-line treatments can fail due to poor compliance and lead to the emergence of multi-drug resistant (MDR) strains of TB. The drug resistant TB is classified into two categories, such as multi drug resistant tuberculosis (MDR-TB) that is resistant to isoniazid and rifampicin, and extensively drug resistant tuberculosis (XDR-TB) that is resistant to isoniazid and rifampicin, plus the fluoroquinolones and any one of the three injectable second line drugs (kanamycin, capreomycin, or amikacin). In 2016, US$ 6.6 billion were available for TB care and prevention in low and medium-income countries [1].

Today we have comparatively sufficient number of antitubercular agents in preclinical, as well as, clinical stages of development. In this chapter, we emphasize the chemical entities currently in the clinical trials, the new tubercular vaccines in the developmental pipeline, and the new diagnostic tests either endorsed by WHO, or commercialized. After four decades since the discovery of rifampicin, two new chemical entities bedaquiline (Sirturo) and delamanid (Deltyba) were granted approval for the treatment of MDR-TB. However, both of the drugs induce arrhythmia, and are recommended only in patients for whom other treatments fail [4 - 7].

CURRENT THERAPY

Antitubercular agents are drugs used in the treatment of TB. WHO has recommended Directly Observed Treatment Short-course (DOTS) for the treatment of TB. DOTS, for the treatment of TB is nothing, but a combination of antitubercular drugs including isoniazid (INH), rifampin RIF, ethambutol (EB) and pyrazinamide (PZA) for a 6 months therapy. WHO has also recommended the use of second-line drugs, which include aminoglycosides (kanamycin, amikacin), capreomycin, cycloserin, *p*-aminosalicylic acid, thioamides (ethionamide (ETH), prothionamide), and fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin,

etc.) for the treatment of MDR-TB. Bedaquiline (Sirturo) and delamanid (Deltyba) were also included in the treatment of MDR-TB. Both of the drugs induce arrhythmia and are recommended only when other treatments fail to cure the patients.

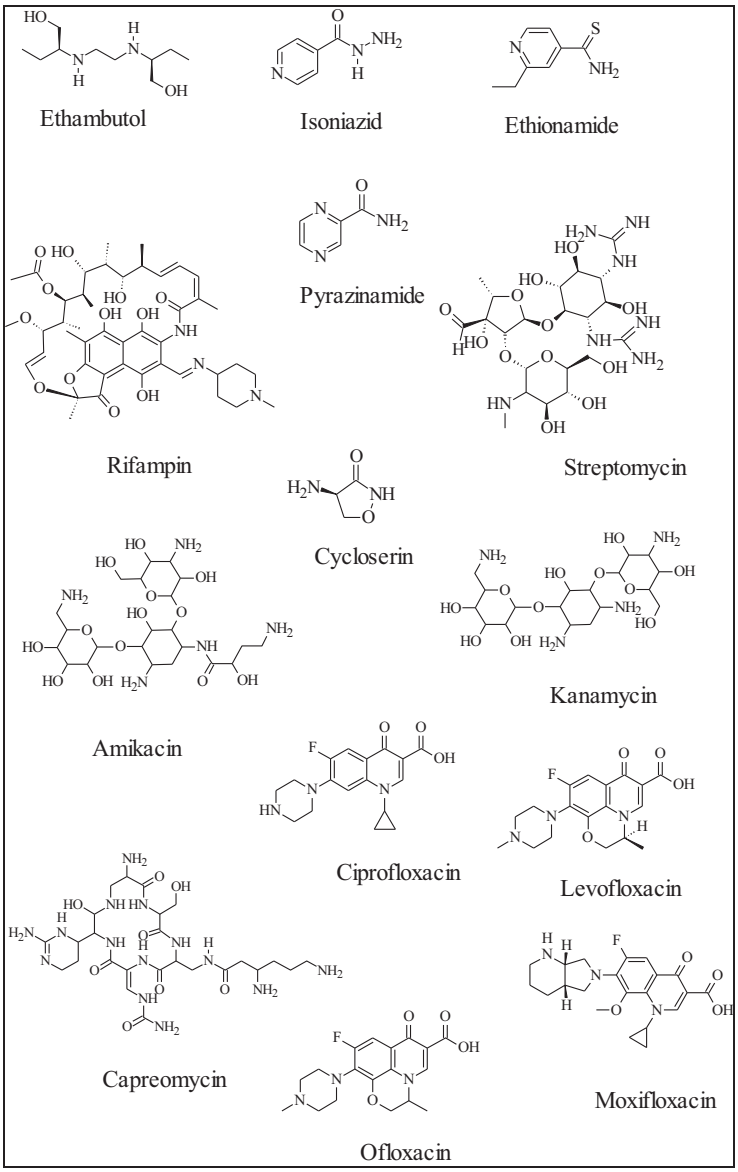

Fig. (1). Some of the anti-tubercular drugs in current therapy.

CHAPTER 5

Recent Advances in Molecular Scaffolds towards the Identification of Novel Receptors in the Treatment of Hepatitis Diseases

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Abstract: Widespread outbreak of numerous infectious diseases across the globe has created awareness in chemists for the novel design and synthesis of lead molecules. Like hepatitis is one of the viral infectious disease, damages the liver function and therefore causes major complications, even leads to death in many cases. More than one third population of the world is affected by hepatitis. Different viral hepatitis are Hepatitis A (HAV), B(HBV), C(HCV), D(HDV) and E(HEV), depending upon the infecting virus type. Hepatitis A and E viruses are usually contacted after eating and drinking contaminated food and water. While, HBV, HCV and HDV are transmitted through contaminated blood. Hepatitis B and C are typically chronic, but HDV may be acute or chronic in nature. Non-viral hepatitis are also reported either due to alcohol consumption or metabolic disorder medications, which causes the liver stress or inflammation.

The treatment options of hepatitis vary depending upon what form you have and what caused the infection. Until recently, the treatment of hepatitis B has been reported with interferons alone or pegylated interferons while hepatitis C with interferons only or pegylated interferon (PEG-IFN) and ribavirin in combination, both are less successful (35-40%) and have side effects. Thus, a virus-specific, efficient and drug resistant free, anti-HBV and anti-HCV therapeutics are needed. Since 2011, the use of new drugs in targeting NS3/4A protease, NS5B polymerase and NS5A enzymes have enhanced treatment rates (70-90%) but still showed some side effects. Furthermore, inhibitors are at diverse stages of clinical development for NS5B and NS5A polymerase targets. Future design and synthesis of novel drugs must address genetic difference in HBV and HCV with least drug resistance. Also, for the genetic over-expression in HCV, a number of investigational techniques have developed which led to the comprehensive analysis of different aspects of viral life-cycle and interactions between virus and host (human). Thus, a rising list of targets for therapeutic involvement has been revealed. The directly acting anti-virals (DAAs) is another therapy method which helps in exploring novel and highly developed combinations of drugs.

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In this chapter, we discuss the synthetic advances of receptor based anti-viral scaffolds in hepatitis, which afforded significant numbers of agents such as drugs or drug leads, their mechanisms of action (MOAs), structure-activity relationships (SARs) and future structural perspectives as drug candidates.

Keywords: Antiviral agents, Combination therapy, Direct acting anti-virals (DAAs), Drug resistance, Hepatitis, Receptor inhibitors, Structure-activity relationships (SARs).

1. GENERAL INTRODUCTION

More than one third of the world's population is affected by hepatitis diseases. It damages the liver and causes major complications, even leading to death in many cases. The viral hepatitis has been sub-divided into Hepatitis A (HAV), B(HBV), C(HCV), D(HDV) and E(HEV), depending upon the infecting virus. HAV and HEV are usually transmitted after eating and drinking contaminated food and water. While, HBV, HCV and HDV are transmitted through contaminated blood. Hepatitis B and C are chronic in nature, but HDV may be acute or chronic in nature. The non-viral hepatitis has also been reported either due to alcohol consumption or metabolic disorder medications that causes the liver stress or inflammation [1].

A number of anti-viral hepatitis inhibitors are obtained from plants or prepared by synthetic and semi-synthetic methods. Many of them have the drug-resistance because of different reasons and are used in combinations. In future, the design and the development of new molecules need greater attentions. This chapter reports research, recent development of drugs and directional trends in the past, present and near future for the hepatitis infections [2].

2. HEPATITIS A

Annually, about 1.4 million hepatitis A (HAV) infection arises worldwide either periodically or epidemically. In the developing and tropical countries, the virus is generally spread *via* the fecal-oral route due to low hygienic conditions [3] and in the industrialized countries may be due to travel to countries endemic of HAV infection or linked to frozen berries or imported pomegranate arils [4]. The infection is restricted to humans only which shows initial symptoms fever, vomiting, nausea, anorexia, weakness, abdominal discomfort and right upper quadrant pain. In advance stages, patients develop jaundice, darkened urine and uncolored stool and approximately 8% cases are associated with acute kidney injury [5].

This virus belongs to the hepadnavirus genus of *Picornaviridae* family. Genetically, HAV resembles typical picornavirus and insect picorna-like viruses which have a 27 nm long single-stranded, non-enveloped and icosahedral RNA, shown by immune electron microscopy in 1973. A rodent origin HAV is also suggested based on more than 200 small mammal species screening for hepatoviruses [6]. The host cell exosome membranes are used by virus as an envelope to protect itself from antibody mediated effects and facilitates detection of HAV by plasma cytoid dendritic cells for type-I interferon in infection [7]. Out of seven pathogenic HAV genotypes, four are able to infect humans. A limited type I interferon response is found in acute hepatitis A cases due to break down of vital adaptor proteins by HAV protease and polymerase precursor. The CD4+T cells play a major role in terminating HAV infection, has been shown in HAV-infected chimpanzees. Similarly, HAV-specific CD8+T cells have been reported a potential contributor to the infection in humans [8]. Anti-HAV IgM antibodies and/or HAV RNA is detected in acute HAV infection after vaccination and IgM antibodies persisting for at least 2-3 decades [9]. For the treatment of hepatitis A, drugs are not available. Recently, it was found that cyclosporine A and silibinin products inhibit HAV replication *in vitro* [10].

3. HEPATITIS B

3.1. Introduction

About 350-400 million people are surfacing HBV antigen (HBsAg) carriers and around one million people die annually due to HBV infections. The high mortality rate is found in HBsAg-positive patients due to chronic liver disease, non-Hodgkin lymphoma and hepatocellular carcinoma [11]. Since the discovery of HBV in 1965 by Blumberg, much development has been made in the vaccines and the advancement of potent anti-viral agents. However, the global burden of disease is still substantial. In chronic HBV therapy, the aim is either to inhibit the viral replication or to enhance immunological responses against virus or both. R-Interferon (R-IFN, Intron A) has been used effectively in 30-40% cases of chronic HBV infections. Thymosin-R1 (Zadaxin), interleukin-12 and therapeutic vaccines have been also used as immunotherapy regimens with limited success. Interferon-α and pegylated interferon-α-2a are used as immunomodulatory agents with poor response and adverse side effects [12].

Many Ape and African old world monkey species have been detected with HBV infection in the polymerase chain reaction (PCR) and pattern recognition receptors (PRR) screening [13]. Genetically, it is a lipid enveloped DNA virus with icosahedral core called Dane particles (the organizing framework of the virion) [14]. The lipid envelope is studded with surface protein (HBsAg) and

CHAPTER 6

Antimicrobial Peptides against Microbial Biofilms: their Structures and Modes of Action

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Abstract: The formation of biofilms contributes significantly to bacterial resistance to antibiotics, innate host defences and in persistent infections. In this era of multidrug-resistant bacterial infections, the discovery of novel antibacterial agents is required to treat infections that kill these organisms *via* novel mechanisms of action. Antimicrobial peptides, also known as host-defence peptides are short polypeptides (<40 amino acids) and are an integral part of the innate immune system that protects a host from bacterial infection. This chapter discusses the potential of anti-microbial peptides as an anti-infective agent, its advantages, disadvantages, their structures and mechanisms of action. A perception of the bacteriostatic and bactericidal mechanism of antimicrobial peptides is required to facilitate the rational design of novel antimicrobial agents. Thus a deeper understanding of the mechanism of natural AMPs will also aid in developing new antibacterial agents. Furthermore, the chapter also considers the possibility of the use of synthetic antimicrobial peptides containing both natural and unnatural amino acids as anti-infective agents. Apart from the antibacterial property, AMPs are also being used as drug delivery vectors to transport the cell impermeable drugs to the cell interior. The diversity and broad spectrum antimicrobial activity of AMPs along with its multidimensional properties could be exploited as a potential and promising drug candidate.

Keywords: Antimicrobial peptides, Human β-defensin, Indolicidin, Synthetic peptide, biofilms, host defences, host-defence peptides, unnatural amino acids, β-peptides.

BIOFILMS AND ANTIBIOTICS RESISTANCE

The breakthrough in antibiotics production is one of the paramount achievements in the history of medicine. Antibiotics are used in the treatment of small to life-threatening infections, in organ transplantation, in oncology to give higher doses

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of chemotherapy for cancer treatment. However, the emergence of antibiotic resistant bacteria is alarming, which are undoing all the earlier advances and forcing a return to the pre-antibiotic era [1]. In the recent years, antibiotic-resistant bacteria have emerged as a biggest challenge for the medical community. The major reason behind enhanced antibiotic resistance was the persistent biofilm formation, which was previously neglected during the development phase of new antibiotics. Bio-molecular matrix enclosed microbial biomasses that stick on to biological or non-biological surfaces are called biofilms. Microbial biofilms protect the bacterial communities present inside antagonistic environment [2]. The production of biofilms and enhanced antibiotic resistance are linked each other. Most of the antibiotics are tested against the bacterial community growing in planktonic growth. Microbial communities growing inside biofilms need 1000 times higher dose of antibiotics to kill them. This demonstrates the striking difference in nature of planktonic life and biofilm-associated bacteria [3]. Bacterial communities residing in biofilm matrix are highly complex to treat with conventional antibiotics [4]. In hospitals, major antibiotic-resistant bacteria develop due to poor practice of handling antimicrobial drugs and the emerging resistant bacteria [5]. The problem of antibiotic resistance can be minimized by preventing unnecessary usages of antibiotics, which is the major reason behind the development of antibiotic resistance among bacteria [6]. The phenomenon of "persistence "also affects antibiotics action against bacterial communities. Persister cells are a small sub-population of microbes that survive the lethal effects of a drug and after the effect of the drug is minimized, they start growing again. The phenomenon of survival of persistent cells against antibiotics is illustrated in Fig. (**1**). When the antibiotic treatment is applied it kills a majority of cells but fails to eradicate a small subset of the population known as persister cells. When the presence of antibiotic is removed, persister cells resume growth and cause the recurrent infection. The persister cells are slightly different from resistant cells. Antibiotic resistant cells can grow even in the presence of antibiotics, but persister cells cannot. The persister cells can survive and grow after the release of antibiotics pressure. Unlike resistance, persistence is not an inherited phenotype, which is shown by the fact that once the organisms resume normal growth they remain drug sensitive similar to the initial population. In this context, persistent *Mycobacterium* infection is well studied and the results showed that such infections need a longer course of treatment, which is comprised of various antibiotics combinations. Infections with these are real challenges in medical science [7]. In the present scenario, there is a need to find out a new alternative antimicrobial drug which can work equally against bacterial community residing inside and outside the biofilm matrix.

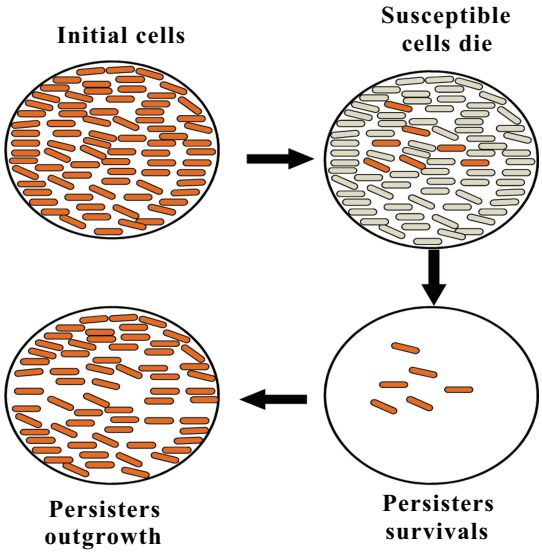

Fig. (1). Illustration showing the survival of persistent cells against antibiotics.

In the past 30 years, no new class of antibiotics had come in the market and a major reason is the increase in resistivity. In 1994, the WHO Scientific Group dealing with antibiotic resistance and surveillance stated that resistance to antibacterial agents is already a serious public health problem [8].Therefore, the current interest is antimicrobial peptides [9] which is mainly due to their ability to kill bacteria quickly by compromising the cell membrane integrity, hence they do not face the problem of resistance development against AMPs. AMPs are an intrinsic factor of the host's innate immune system in higher organisms [9]. AMPs are produced in response to various bacterial infections. AMPs are showing promising action to deal with antibiotic resistant bacteria in the present scenario [10]. AMPs which are distributed plentifully in nature can be a potential substitute to current anti-microbial drugs. The effectiveness of AMPs is broad-spectrum as they can act on a variety of bacteria, fungi, viruses, and parasites, and even cancerous cells [11]. Due to their ability to exert direct and/or indirect antimicrobial action, they are also termed as host-defence peptides [12].

BIOLOGICAL ROLES OF AMPS

Antimicrobial peptides belong to a diverse group with multi-dimensional properties and functional roles, that can't be denied. Apart from having antimicrobial activity, AMPs are also involved in the various intracellular processes such as angiogenesis, wound-healing, inflammatory response, and cell signalling. Different AMPs can perform differently as signalling molecules,

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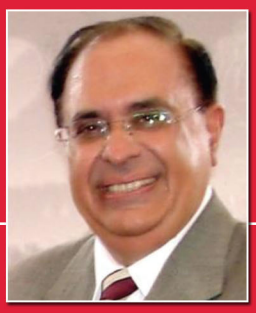

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Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.

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