RECENT TRENDS AND THE FUTURE OF ANTIMICROBIAL AGENTS

PART 2

Editors:
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Recent Trends and The Future of Antimicrobial Agents *(Part 2)*

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(Part 2)

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CONTENTS

FOREWORD

The book "Recent Trends and The Future of Antimicrobial Agents" tries to explore various alternatives of multi drug resistant bacteria which are the major causes of therapeutic failure. The book provides various approaches to the solution and each section describes and analyses the approach towards the problem. Research is going on globally on various alternatives to treatment like Plant based antimicrobials, Photodynamic therapies, enzyme based and antibody based antimicrobial approaches, chemical compounds that act as antimicrobial agents, nano-materials which act as antimicrobial agents, probiotic, prebiotic and peptides compounds or agents. The writers have taken up each scenario to make the readers understand about the macro and micro factors associated with the approach.

The book attempts to throw light on the various aspects of the pathogenic multi drug resistant bacteria and takes a wide horizon on the impact of antibiotics on them. The discovery of penicillin paved the way for the antibiotics to become popular but as the bacteria can accumulate on multiple genes making them resistant to a particular drug, similarly the resistance can also be caused by an increased expression of genes responsible for multi-drug efflux pumps forcing out a lot many drugs. Hence the need to develop an alternative strategy is very critical for therapeutic success. The book describes all these scenarios in two subsequent volumes of the title. Volume-1 includes the naturally derived antimicrobial remedies/strategies. The Volume-2 of the same title incorporates the chemical and advanced nanomaterial based strategies along with sustainable antimicrobial strategies *viz*. use of probiotics and photodynamic therapy. I would like to thank the authors for their dedicated effort and the publishers in converting that effort into a reality. I am sure that the information will be very useful for Clinicians as well as Microbiologists.

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PREFACE

Many microbial pathogens have evolved as drug resistant due to indiscriminate and injudicious use of drugs. This has compelled researchers to find novel antimicrobial agents with diverse chemical structures and novel mechanisms over the conventional antimicrobial agents rendering the pathogens with minimum scope to develop resistance. Last few decades have witnessed profound research on different areas for the development of alternative antimicrobial agents. These include novel chemically synthesized molecules, nanomaterials and probiotic/prebiotic mediated immunity boosters, *etc*. **"Recent Trends and the Future of Antimicrobial Agents"**, Part 2 is a continuation of the Part 1 of the same title that dealt with the naturally derived antimicrobial remedies/strategies. The present Part 2 of the same title deals with the chemically synthesized compounds, nanomaterials and probiotics.

The devastating pandemic caused by the severe acute respiratory syndrome-causing corona virus-2 (SARS CoV-2) virus has once again taught us that "Prevention is better than cure". The overburden of xenobiotic drugs can be drastically reduced by boosting our immune system and fighting the disease causing microbes in association with the helpful bacteria and their metabolites. Three chapters of the book uncover the probiotic/prebiotic/antibacterial peptide compounds as novel antimicrobial approaches and disorder-management therapies. All of these "-biotics" are designed to modulate the gut microbiota in a way that improves health and reduces the need to gulp antibiotics indiscriminately and thus indirectly assist in fighting potential bacterial threats. But, prevention may not always be able to protect us from infiltrating microbes. Chemical synthesis enables researchers to develop target based prospective drug molecules to fight against ever-changing microorganisms. The potent synthetic pathways are discussed in a chapter. The plant-based products have traditionally been used as natural healing systems. Although, modern scientific approaches focus on active compounds. Bioactive natural compounds and synthetic drug candidates are promising therapeutic agents for human health and disease management. Their therapeutic efficacy can be enhanced if their bioavailability is raised to the optimum level and/or delivered to the target cells/tissue involving nanocarriers. The membrane targeting bactericidal agents are also emerging as potent antimicrobials since developing resistance against them demands extensive restoration of membrane compounds, which is a conceivably formidable challenge for the bacteria. In this regard, membrane-targeting nanoscale materials, amphiphiles, and antimicrobial peptides bear special merit. Two chapters discuss the potential of cationic amphiphiles as promising antimicrobial entities and amphiphilic nanocarriers as delivery vehicles. Another chapter discusses the design, synthesis and antimicrobial applications of Metal-Organic Frameworks (MOFs). Thus, amphiphiles of this new genre have enough potential to deliver several antibacterial molecules in years to come. The emergence of nanoscience and technology in recent years offers great promise in therapeutics. Nanomaterials are emerging as a novel class of antimicrobial agents to overcome the challenges faced by conventional antimicrobials. Using nanomaterials as bactericidal agents represents a novel approach to antibacterial therapeutics. Three chapters of this book cover the recent development, antimicrobial prospects of biogenic metal or metalloid nanoparticles, bactericidal QDs and MoS_2 based antibacterial nanocomposites. A new-age approach to combat microbes, antimicrobial photodynamic therapy (aPDT), is discussed in a chapter. PDT uses a nontoxic and lightsensitive dye, a photosensitizer (PS), in combination with nontoxic visible light of the appropriate wavelength to excite the PS and oxygen that can selectively control bacterial infections by the generation of highly cytotoxic reactive oxygen species (ROS).

In the process of editing the book we have received needful assistance and inspiration from

different spheres of academy. We express our sincere gratitude to Prof. (Dr.) Dhrubajyoti Chattopadhyay, Vice Chancellor, Sister Nivedita University, Kolkata, West Bengal for his motivation throughout the project. We express our gratitude to the Vice Chancellor, University of North Bengal, Darjeeling, for all necessary facilities and support. We are thankful to Fr. (Dr.) Lalit P. Tirkey, Principal, North Bengal St. Xavier's College (NBSXC), Jalpaiguri, for his continuous encouragement. Our sincere thanks go to all authors for their hard work and professionalism in making this book a reality. Their expertise in the contributed chapters is acknowledged and appreciated. Finally, we appreciate Bentham Science Publishers for their assistance and constant support in publishing the book.

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CHAPTER 1

Probiotics as Potential Remedy for Restoration of Gut Microbiome and Mitigation of Polycystic Ovarian Syndrome

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Abstract: Polycystic ovarian syndrome (PCOS) is the most frequent endocrine disorder currently plaguing women. There are many factors associated with high androgenicity in the female body. Dysbiosis of gut microbiota may be one of the primary reasons that initiate PCOS. Emerging evidence suggests that some plastics, pesticides, synthetic fertilizers, electronic waste, food additives, and artificial hormones that release endocrine-disrupting chemicals (EDCs) cause microbial Dysbiosis. It is reported that the permeability of the gut is increased due to an increase of some Gram-negative bacteria. It helps to promote the lipopolysaccharides (LPS) from the gut lumen to enter the systemic circulation resulting in inflammation. Due to inflammation, insulin receptors' impaired activity may result in insulin resistance (IR), which could be a possible pathogenic factor in PCOS development. Good bacteria produce short-chain fatty acids (SCFAs), and these SCFAs have been reported to increase the development of Mucin-2 (MUC-2) mucin in colonic mucosal cells and prevent the passage of bacteria. Probiotic supplementation for PCOS patients enhances many biochemical pathways with beneficial effects on changing the colonic bacterial balance. This way of applying probiotics in the modulation of the gut microbiome could be a potential therapy for PCOS.

Keywords: Endocrine-disrupting chemicals, Gut microbiome, Insulin resistance, Mucin-2, PCOS, Probiotics, SCFAs, *Bifidobacteria*, *Lactobacillus*, Gut bacteria dysbiosis, hypertension, central obesity, dyslipidemia, progesterone, estrogen, luteinizing hormone, Infertility, cardiovascular disease, type 2 diabetes mellitus, visceral obesity, and endothelial dysfunction, Hyper-insulinemia, Androgens, lipopolysaccharides, reproductive abnormalities.

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a condition of hormonal imbalance that causes female reproductive abnormalities, especially in reproductive age common disorder in women, with a wide range of prevalence rate from 6 to 20% [1, 2]. The main characteristics of PCOS are polycystic ovaries, hyperandrogenism, anovulation, abnormal menstruation [3], hypertension, central obesity, and dyslipidemia [4]. Though the pathologic process of PCOS is complex and mostly unknown, the symptoms are often associated with internal secretory problems, such as decreased progesterone, estrogen, and sex hormone binding globulin (SHBG) and elevated testosterone, luteinizing hormone (LH), among other things [5]. Progesterone is one of the key hormones linked to PCOS and whose primary role is to aid in the maintenance of pregnancy [6]. PCOS patients are unable to produce a corpus luteum due to low progesterone levels and irregularities in the fertilization process [7]. Infertility, cardiovascular disease, insulin resistance (IR), type 2 diabetes mellitus (T2DM), visceral obesity, and endothelial dysfunction are all common symptoms of PCOS. As a result, this syndrome is classified as a metabolic disease that affects the quality of women's lives as well as a fertility concern [8].

While PCOS is known to cause genetic, neuroendocrine, metabolic, environmental, and lifestyle factors, the etiology of PCOS remains unclear. According to new data, the gut microbiome may have a role in the development of PCOS [9]. It is suggested that differences in gut microbiota composition are correlated with metabolic and clinical changes in PCOS patients [10, 11]. Imbalances in gut microbiology may result in Dysbiosis of gut microbiota and may cause activation of the host's immune system. The activation of the immune system causes chronic activation of inflammatory response and initiates a state of IR due to improper function of insulin receptors. It is known earlier that IR interferes with the growth of follicles for the excess production of androgen by the ovary's thecal cells [12].

An unhealthy lifestyle, consuming junk food, and various inflammatory mediators increase the risk of PCOS [13, 14]. Emerging evidence suggests interactions between endocrine-disrupting chemicals (EDCs) and the microbiome, affecting host health. EDC exposure has been shown to disrupt the microbiome, which can lead to Dysbiosis and the induction of xenobiotic-related pathways, microbiome-associated genes, enzymes and metabolite production, which can play a key role in EDCs biotransformation. This Dysbiosis of gut microbiota may be associated with the globalization of industry and the manufacture of plastics, synthetic fertilizers, pesticides, electronic trash, and additives in food that release EDCs into the environment and food chain [15]. Gut bacteria dysbiosis helps to promote

the Lipopolysaccharides (LPS) from the gut lumen to the systemic circulation. LPS causes chronic stimulation of hepatic and tissue macrophages, and insulin tolerance is increased due to impaired activity of insulin receptors. Hyper-insulinemia then increases the secretion of androgens in the ovaries and prevents normal processes of ovulation [12].

WHAT IS PCOS?

PCOS is a complex condition marked by high testosterone levels, irregular menstruation cycles, and/or small cysts on one or both ovaries [16]. Later it was redefined to establish different diagnostic criteria. It was first redefined by the National Institutes of Health (NIH) in 1990, and according to it, patients with hyperandrogenism and oligo-anovulation are diagnosed with PCOS [17]. It was further redefined by Rotterdam Consensus in 2003 that postulates patients should have at least two among the three classic features which are irregular menstrual cycle, hyperandrogenism and enlarged "polycystic" ovaries in pelvic ultrasonography [18]. In addition to the main hyperandrogenic findings, those with oligo anovulation or polycystic ovarian criteria are considered to have PCOS, according to the Androgen Excess and PCOS Society (AE-PCOS) in 2006 [19]. The three Rotterdam criteria, which are currently accepted according to the international PCOS guidelines [20], can divide the condition down into four phenotypes. These are (1) classic PCOS (chronic anovulation, hyperandrogenism, and polycystic ovaries); (2) non-polycystic ovary PCOS (hyperandrogenism, chronic anovulation, and normal ovaries); (3) ovulatory PCOS (hyperandrogenism, polycystic ovaries, and regular menstrual cycles); and (4) mild/norm androgenic PCOS (chronic anovulation, normal androgens, and polycystic ovaries) [21].

The various components of the diagnostic criteria cause changes in prevalence across the NIH criteria 1990, the Rotterdam 2003 criteria and the AE-PCOS 2006 criteria [22]. A meta-analysis was performed on all published studies which reported PCOS prevalence was 6%, 10%, and 10% according to the diagnostic criteria of NIH, Rotterdam, and AE-PCOS Society, respectively, based on at least one subset of diagnostic criteria [23]. In India, PCOS prevalence was 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria. Mild PCOS is amongst the most common phenotypes occurring in about 52.6% of women [24].

Etiopathology of PCOS

Though the main reason for PCOS is unknown, it is known to be a multifunctional disorder with genetic, endocrinological, and environmental factors having a role to play [25]. Hyperandrogenism, seen in 90 percent of women with PCOS, plays an important role in the disease etiology [26]. Androgen excess may cause

CHAPTER 2

Antibody Therapy as Alternative to Antibiotics

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Abstract: In the 1890s, Behring and Kitasato established the principle of serum therapy, which proved useful in treating infectious diseases. However, by the 1940s, serum therapy was abandoned mainly due to complications associated with the toxicity of heterologous sera and the introduction of more effective antibiotics. Although the availability of antibiotics had a tremendous impact on saving lives from infectious diseases, there was a rapid emergence of antibiotic resistance. As a result, an alternative therapy is being given due consideration. With the advent of antibody production technology, antibody therapy has gained interest as a promising treatment for emerging infectious diseases. Some monoclonal antibodies (mAbs) had already been approved for the treatment of certain infectious diseases. Many mAb candidates are currently in different phases of clinical testing for a variety of infectious pathogens. There is hope that antibody therapy may appear as a promising treatment option against infectious diseases in the near future.

Keywords: Antibacterials, Antibiotics, Antibiotic resistance, Antibody, Antibody therapy, Antifungals, B cells, Chimeric antibodies, Clinical trials, Complementarity-determining regions, Efficacy, Fragment crystallizable, Fragment for antigen binding, Humanized antibodies, Hybridoma technology, Infectious diseases, Monoclonal antibodies, Serum therapy, Toxins.

INTRODUCTION

The protection from the bacterial toxins mediated by the specific antibodies was first demonstrated by Behring and Kitasato in the 1980s [1]. This finding led to design the antibody-based therapies for different infectious diseases [2, 3]. The therapy was called ‘serum therapy’ as the antibodies were isolated from the serum of immunized animals or immune human donors. Although this form of therapy was proved effective against many infectious diseases, the use of animal serum had significant side effects, including immediate hypersensitive reactions and serum sickness, resulting in the accumulation of antigenantibody complex [1].

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

Further, serum therapy was associated with toxicity, difficulty in administration, narrow specificity, lot-to-lot variation and expense. All these complications related to early serum therapy and the rise of the antibiotic age by the 1940s led to the abandonment of passive antibody therapy against bacterial infections.

By the mid-1900s, the impact of antibiotics to combat infectious diseases was remarkably astounding. After the commercialization of antibiotics, the mortality rate of infectious diseases declined dramatically below 1% in England [4]. The impact of the antibiotics was regarded as a 'medical miracle'. The role of antibiotics is not only noteworthy in saving lives from infectious diseases but also significant in the advancement of medicine and surgery [5]. However, the rapid emergence of antibiotic resistance and slow progress in the development of novel drugs by pharmaceutical industries challenge the extraordinary health benefits of antibiotics. This altogether resulted in a global crisis [6].

During the last few decades, antibodies as therapeutics have gained priority for treating various infectious diseases because of several reasons, viz. revolutionary advancement of antibody production technology, appearance of new pathogens, existence of drug-resistant microbes and increasing numbers of immune suppressed patients [7]. Antibodies are extremely versatile antimicrobial molecules produced by the B cells in response to infection or immunization. Several effector mechanisms, such as inhibition of attachment of microbes to the host cells, promotion of opsonization for phagocytosis, neutralization of viruses and toxins, activation of the complement system and antibody-dependent cellular cytotoxicity, are mediated by the antibodies [8].

The advent of hybridoma technology in 1975 for the production of monoclonal antibodies, followed by further development of antibody engineering, leading to the creation of fully humanized antibodies, offers antibody therapy as an alternative to antibiotics for the treatment of various infections. This chapter attempts to discuss serum therapy used in pre-antibiotic era, antibiotics and antibiotic resistance, overview of antibody, advancement of monoclonal antibody (mAb) production technology, and development of antibody-based therapies against infectious diseases and limitations of antibody-based therapies.

Antibody Therapy in Pre-Antibiotic Era

Serum Therapy

In the 1890s, Emil von Behring and Shibasaburo Kitasato demonstrated that serum from rabbits immunized with tetanus toxin could prevent tetanus in rabbits,

and the same phenomenon was also shown for diphtheria toxin [9]. Emil von Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901 for his discovery of serum therapy for diphtheria [10]. In fact, the immune sera contained specific antibodies which mediated therapeutic effects by promoting opsonization, neutralizing toxins, and/or triggering complement-mediated bacterial lysis [2]. In the pre-antibiotic era, many infectious diseases, including diphtheria, tetanus, scarlet fever, pneumococcal pneumonia and meningitis caused by *Neisseria meningitis* and *Haemophilus influezae* were treated by administration of immune animal sera [2]. Several controlled trials demonstrated an approximately 50% reduction in death rate in patients with pneumococcal pneumonia after the administration of type-specific serum [11]. Although the efficacy of serum therapy was uncertain in whooping cough, anthrax, dysentery (*Shigella dysenteriae*) and gas gangrene, human convalescent serum was effective against measles, which had a mortality rate of 6-7% in some populations [3].

Shortfall of Serum Therapy

Although serum therapy was a choice of treatment for various infectious diseases in the early 20th century, this treatment had serious side effects as an immune response was induced against the animal-derived antibodies. The most severe was serum sickness, a type of hypersensitivity response characterized by fever, chills, rashes, arthritis, and occasionally glomerulonephritis. Also because of the high specificity of the antibodies, separate immune sera had to be raised for different pathogens [2]. Another disadvantage of hyperimmune sera was being a polyclonal antibody preparation with undefined concentrations of multiple specific and non-specific antibodies. Therefore, it was challenging to standardize serum quality and ensure the efficacy of the therapeutic serum. Certainly, all these complications together with the discovery of antibiotics, led to the abandonment of serum therapy by the early 1940s [12].

Antibiotics and Antibiotic Resistance Crisis

Selman Waksman introduced the term ‘antibiotic’, referring to any small molecule, produced by a microbe, with antagonistic properties on the growth of other microbes [13]. Generally, antibiotics refer to antibacterial, however, these are differentiated as antibacterial, antifungal and antiviral for the action they exert on the group of microorganisms [14]. The modern era of antibiotics started with the discovery of penicillin by Sir Alexander Fleming in 1928 from a soil-inhabiting fungus *Penicillium notatum* [15, 16]. The discovery of penicillin was reported in 1929 [17], and its first clinical trial was conducted on humans in 1940 [14]. During the 1940–1960s, most antibiotic classes used today were discovered, and this period is known as the antibiotic golden age. The rate at which antibiotics

CHAPTER 3

Cationic Amphiphiles as Antimicrobial Agents

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Abstract: Numerous antimicrobial peptides (AMP) obtained from natural sources are currently tested in clinical or preclinical settings for treating infections triggered by antimicrobial-resistant bacteria. Several experiments with cyclic, linear and diastereomeric AMPs have proved that the geometry, along with the chemical properties of an AMP, is important for the microbiological activities of these compounds. It is understood that the combination of the hydrophobic and hydrophilic nature of AMPs is crucial for the adsorption and destruction of the bacterial membrane. However, the application of AMPs in therapeutics is still limited due to their poor pharmacokinetics, low bacteriological efficacy and overall high manufacturing costs. To overcome these problems, a variety of newly synthesized cationic amphiphiles have recently appeared, which imitate not only the amphiphilic nature but also the potent antibacterial activities of the AMPs with better pharmacokinetic properties and lesser *in vitro* toxicity. Thus, amphiphiles of this new genre have enough potential to deliver several antibacterial molecules in years to come.

Keywords: Amphiphiles, Antibacterial, Antibiotic, Bacterial cell, Cationic amphiphiles, Cytotoxicity, Drug, Gram-negative bacteria, Gram-positive bacteria, Hydrophobicity, Mammalian cell, Membrane penetration, Membrane permeability, Peptide, Positively charged, Quaternary ammonium salt, Steroid, Surfactants.

INTRODUCTION

The major reasons behind the research to find a newer class of antibacterial drug molecules are the surge in antibiotic-resistant bacteria and the decreasing rate of innovation of new antibacterial drugs [1], especially in to fight against multidrug-resistant bacteria [2 - 4]. Self-healing from bacterial disease in higher order organism do not depend completely on enzymatic inhibitor, rather, higher-order organism generates wide-range antimicrobial peptides, which may target the lysis of cellular membrane leading to cell death. Disruption of membranes and cell walls is one of the most necessary steps in killing bacteria, and hence they serve

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

as suitable targets for the development of new antimicrobial agents or antibiotics. Recently, various naturally occurring as well as synthetically developed antimicrobial molecule has been reported for interrupting different stages of the formation of the bacterial cell wall. Among these new reports, there are beta-lactams and glycolipid antibiotic moenomycin A, which can permanently prevent the biosynthetic step of peptidoglycan trans peptization. There are also vancomycin-like glycopeptides that can entirely obstruct the trans-peptization step [5 - 8]. Although there are several examples of antibiotics that can target bacterial cell walls, there are only a few known for targeting bacterial membranes. Some significant advantages of developing such antibiotics are:

1. Especially for infection caused by slow-growing or dormant bacteria, bacterial membrane targeting is a better option compared to treating with the current range of clinically available antibiotics [9].

2. Bacterial membranes are hidden structures compared to the cell wall, disruption of the bacterial membrane will cause rapid killing of the bacteria, and hence it will be difficult for them to evolve against such attacks. Thus, membrane-targeting antibiotics can be used for a prolonged time without facing any resistance from the bacteria [10].

3. Although bacterial cell permeation poses a major challenge for designing antibiotics to aim intracellular targets, bacterial membrane targeting antibiotics does not need cell permeability [11].

Nevertheless, for developing an effective but safe membrane targeting antibiotics, the molecule must have the ability to differentiate between mammalian and bacterial cell membranes. The inability to elude such non-selective membrane damage could cause cytotoxicity towards eukaryotic cells and hence can be a major challenge for developing membrane-targeting antibiotics. The distinctive compositional feature of the bacterial membrane and mammalian cell membrane heightens the possibilities of developing membrane-selective antimicrobial agents. Here are some of the striking differences between the mammalian and bacterial cell membranes:

(A) In the case of Gram-positive bacterial cell membrane, teichoic acid is one of the major constituents and in the case of Gram-negative bacteria, lipopolysaccharides are one of the key components. In mammalian cell membranes, lipopolysaccharides and teichoic acids do not exist.

(B) Due to the presence of a comparatively low percentage of negatively charged lipids in the mammalian cell membrane, the negative charges on it are much weaker compared to the bacterial cell membrane [12 - 15].

(C) Neutral proteins like phosphatidylcholine and sphingomyelin are localized on the outer leaflet of the mammalian cell membrane, and the inner leaflet consists of negatively charged lipids, such as phosphatidylserine and phosphatidylinositol [16, 17]. Since the attractive force working between the positively charged amphiphilic molecules and oppositely (negative) charged membrane is an electrostatic interaction and is dependent on the distance between the opposite charges, the presence of the negative charges on the inner leaflet of the mammalian cell membrane significantly minimizes this force of attraction compared to the bacterial cell membrane where the negative charges are on the outer surface.

The above-mentioned differences in the structure and composition between the bacterial cell membrane and mammalian cell membrane help in designing several membranes, targeting cationic antimicrobial molecules.

In this chapter, we will discuss the structural aspects and working principles of some significant amphiphilic molecules and the current challenges in using these molecules as antimicrobial agents.

SYNTHETIC CATIONIC PEPTIDES AS ANTIMICROBIAL AGENTS

Antimicrobial peptides perform a major function in the human immune system and are related to diseases like Crohn's disease and Morbus Kostmann. Molecules such as AMPs, which can target cell membranes, are advantageous over the general method of drug activity as they may offer a variety of active structures while facing lesser resistance [18]. Apart from their various benefits, naturally occurring antimicrobial peptides also have a few drawbacks, which should be taken care of before applying them widely as a replacement for already well-known antibiotics. Naturally occurring antimicrobial peptides have some significant pharmacokinetic deficiencies, including low metabolic stability, poor bioavailability and formulation difficulties. These shortcomings are mainly due to several amide linkages between the constituent amino acids and their size [19]. Overcoming these shortfalls is the reason behind the recent interest in the design and development of their partially or fully synthetic analogues. In various versions of these synthetic analogues, the cationic and hydrophobic properties of the naturally occurring molecules are retained, and the cationic charges in the molecules help to increase the long-range repulsive forces and overcome the short-range hydrophobic interactions.

Amphiphilic Helices

Among various antimicrobial peptides designed, the alpha-helical peptides are one of the most heavily investigated. The secondary structure of these

CHAPTER 4

Amphiphilic Nanocarriers to Fight Against Pathogenic Bacteria

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Abstract: The emergence and expansion of antibiotic resistance in pathogenic bacteria have become a global threat to both humans and animals. Immense use, overuse and misuse of antibiotics over several decades have increased the frequencies of resistance in pathogenic bacteria and resulted in significant medical problems. To fight against the widespread drug-resistant pathogenic bacteria has become a terrific challenge for the modern healthcare system. The major challenges to fight against pathogenic bacteria involve long-term antibiotic therapy with combinations of drugs. The abundance of resistance mechanisms in pathogenic bacteria has compelled many therapeutic antibiotics to become ineffective. As a result, the elimination of drug-resistant pathogenic bacteria requires a judicious strategy. The advent of nanotechnology has unveiled a new horizon in the field of nanomedicine. Nanoparticle-based techniques have the potential to overcome the challenges faced by traditional antimicrobials. In this way, self-assembling amphiphilic molecules have emerged as a fascinating technique to fight against pathogenic bacteria because of their ability to function as nanocarriers of bactericidal agents and interact and disrupt bacterial membranes. Nanocarrier-based drug delivery systems can mitigate toxicity issues and the adverse effects of high antibiotic doses. The focus of this chapter is to discuss various amphiphilic nanocarriers and their roles and possibilities in fighting against pathogenic bacteria.

Keywords: Amphiphile, Bacteria, Copolymers, Cubosome, Dendrimer, Drug Delivery, Hydrogel, Hydrophilic, Hydrophobic, Lipidated Peptide Amphiphile, Liposome, Micelle, Multidrug Resistance, Nanocarrier, Niosome, Pathogen, Peptide Amphiphile, Polymerosome, Self-assembly, Synthetic Amphiphile.

INTRODUCTION

The emergence of bacterial-resistant strains is a global health concern [1 - 3]. Antibiotics that control bacterial infections in human and animal has been corroded continuously by the emergence of drug resistance. This consequence is

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

the outcome of the substantial changes in the microbial environment due to the widespread use of antibiotics [4]. It is assumed that if antibiotic resistance increases at the present rate, by 2050, bacterial infections will cause around 10 million deaths annually which is more than the number of deaths caused by cancer presently. Due to this reason, "The Centers for Disease Control and Prevention" has mentioned in recent times that the globe is very close to entering the "post-antibiotic era" where more people will die from infections of bacteria than cancer [3, 5]. There is a factual possibility that slight injuries and common infections can cause death in the 21st century [3].

To fight against the widespread drug-resistant pathogenic bacteria has become a terrific challenge for the modern healthcare system. The abundance of resistance mechanisms in pathogenic bacteria has compelled many therapeutic antibiotics to become ineffective. As a result, the elimination of drug-resistant pathogenic bacteria requires a judicious strategy [6]. Thus, designing and developing antibiotics that can resist pathogenic bacterial resistance is very important. But, progression in developing them has become slow. In fact, the discovery and development of antibiotics are declining while antibiotic resistance in pathogenic bacteria is rising. Unfortunately, the new classes of antibiotics introduced in the early 1960s have not yet made a major impact. The global market of antibiotics is still dominated by the previously discovered classes of antibiotics [1, 3, 7, 8].

Several classes of antibiotic-resistant pathogens have emerged as major threats [7]. In fact, six antibiotic-resistant pathogenic bacterial species, namely *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species termed ESKAPE are considered as a great threat for human health [3, 9]. Again, methicillin-resistant *Staphylococcus aureus* [MRSA], multidrug-resistant [MDR] and pandrug-resistant [PDR] Gram-negative bacteria, MDR and extensively drug-resistant [XDR] *Mycobacterium tuberculosisetc*. are also emerging as a major threat. The increasing prevalence of MRSA also increases the risk of vancomycin-resistant *Staphylococcus aureus* [VRSA] [7]. Another common example of MDR bacteria encountered presently includes *Escherichia coli* [10].

The advent of nanotechnology has unveiled a new horizon in the field of nanomedicine. The progression of nanotechnology has allowed the synthesis of nanoparticles that can be assembled into various complex nanostructures. This self-assembling property is regarded as critical for the formation of nanostructures [11, 12]. Nanoparticle-based techniques have the potential to overcome the challenges faced by traditional antimicrobials [5]. In this way, self-assembling amphiphilic molecules have emerged as a fascinating technique to fight against pathogenic bacteria because of their ability to function as nanocarriers of

bactericidal agents and also to interact and disrupt bacterial membranes [1]. Nanoparticles are likely to have an increased tendency to interact with pathogenic bacterial cells due to their larger surface area [6].

SELF-ASSEMBLY AND AMPHIPHILICITY

Self-assembly induced by the amphiphilic property is of much importance for creating functionality. In fact, one of the major driving forces for self-assembly is amphiphilicity [13]. The process of self-assembly is controlled by various factors like electrostatic interactions, hydrophobic interactions, van der Waals forces, intermolecular hydrogen bonds or intramolecular hydrogen bonds, *etc*. Altering the hydrophobic region length or the charge of the hydrophilic region also affects the self-assembling peptide morphology [14, 15]. The hydrophobic and electrostatic interactions are the main factors that help the peptide amphiphiles [PAs] to be self-assembled [16]. Amphiphilic molecules containing both polar and nonpolar elements tend to lessen unfavourable interactions with an aqueous environment through aggregation. In this process, the hydrophobic moieties of the amphiphilic molecules persist as shielded, whereas the hydrophilic domains get exposed. Various kinds of structures, from bilayer structures to micellar aggregates can be created based on the parameters like concentration, amphiphile geometry, *etc*. Examples of common amphiphiles include dialkylated molecules [*e.g*. phospholipids], single-chain surfactants [*e.g*., fatty acids] *etc*. Amphiphilic behavior is also observed in peptides and proteins. Sometimes, a direct relationship is observed between the functions and the amphiphilic property of peptides or proteins [13].

Hamley IW has reported that there are two main classes of amphiphilic peptides. The first class of amphiphilic peptides includes pure peptides consisting of amphiphilic properties with both hydrophobic and hydrophilic residues. On the other hand, the second class of amphiphilic peptides includes peptides modified by attaching hydrophobic lipid chains termed PAs. Hamley IW differentiated between amphiphilic peptides and PAs in this way, as PAs are a subset of the amphiphilic peptides but not *vice versa* [17].

PEPTIDE-BASED AMPHIPHILES

We have already mentioned that different types of peptide-based amphiphiles have been reported, like amphiphilic peptides and PAs [18]. Amphiphilic peptides contain both hydrophobic and hydrophilic regions along their lengths [12]. Amphiphilic peptides are made up of hydrophobic and hydrophilic amino acids in which a charged head is attached to a non-charged tail. On the other hand, PAs, one kind of synthetic surfactant, is made up of one or more alkyl chains coupled to a peptide moiety. In an aqueous solution, PAs can assemble into nanofibres

CHAPTER 5

Biological Importance of Some Functionalized Schiff Base-Metal Complexes

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Abstract: Schiff base ligands or compounds are useful in modern inorganic chemistry. Numerous transition metal-based catalysts have been synthesized with Schiff base scaffolds. The application of such Schiff bases is also found in biological studies. Herein, we have discussed the various synthetic procedures of diversified Schiff base compounds and their metal complexes. The biological activity of those complexes has also been delineated in this chapter with special emphasis. Various metal complexes [Co(II), Ni(II), Cu(II), Zn(II) and Fe(III)] with different Schiff base compounds displayed anti-fungal activity. Similarly, anti-viral activity was seen with Co(II) and Pd(II) metal complexes. Many Schiff base-metal complexes are found, which showed anti-cancer activity against various carcinoma cells like HpG2, MCF-7, A549, HCT116, Caco-2 and PC-3. Similarly, the transition metal complexes (generally 1st and 2nd row) of Schiff bases also exhibited good anti-bacterial activity against various bacterial strains. The ionic-liquid-tagged Schiff bases have also been found to be good anti-microbial agents.

Keywords: Anti-bacterial, Anti-microbial, Biological activity, Metal complex, Schiff Base.

INTRODUCTION

Schiff base compounds are very useful and play an important role in various fields. These compounds showed important biological activities, which are useful in many catalytic reactions when combined with metal ions [1]. The synthesis of new Schiff bases and their metal complexes played an important role in the development of co-ordination chemistry. The chemistry of Schiff base and its metal complexes attract immense attention in the field of inorganic and organometallic chemistry.

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

Schiff bases and their complexes have been synthesized by the condensation of an amino compound (aliphatic and aromatic) with carbonyl compounds under dehydrated conditions. The invention of the Schiff base by Hugo Schiff in 1864 opened a new dimension in the field of chemistry. The Schiff base complexes were widely used for industrial purposes and also showed a broad range of biological activities like anti-fungal [2], anti-bacterial [3], antimalarial, antiproliferative, anti-inflammatory, anti-viral [4] and antipyretic, and some of these also show excellent catalytic activity in various reactions [5].

ROLE OF SCHIFF BASE IN CO-ORDINATION CHEMISTRY

Co-ordination chemistry is an important part of chemistry that gives a good concept about the stability of the structure of different complexes. When dissolved in water or other solvents, co-ordination compounds showed such properties which are completely different from those of the constituents. The co-ordination complex compounds are formed by the association of one or more than one molecule or anions with a central atom or ion, usually metal cations. In the formation of a stable complex, a cation or metal to which one or more neutral molecules or ions are bonded with a central metal atom is called a ligand. Ligands can be monodentate or polydentate and have the ability to form chelate complexes. The key breakthrough occurred when Alfred Werner proposed Co(III) ion complex formation with octahedral geometry consisting of ligands in 1893.

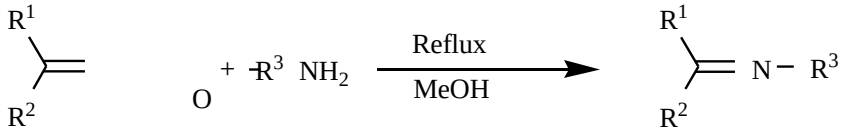
In classical co-ordination chemistry, there is an association between the ligands to central metal ions via their lone pairs of electrons residing on the main group of atoms. In co-ordination chemistry, a structure was first described by the number of sigma bonds that formed between ligands and the central metal atom is known as co-ordination number of this complex. The number of bonds depends mainly on the size, charge, electronic configuration of the central metal atom and ligand molecules or ions and the extent of interactions between s and p orbitals of ligands and d orbitals of the central metal atom or ion. In co-ordination, complex metals with small sizes lead to high co-ordination numbers, *e.g.,* $[Mo(CN)_8]^{4-}$ and small sizes of central atoms and ligands with large sizes lead to low co-ordination numbers, *e.g.,* $Pt[PC(me)_3]_2$. Further, the stability of the co-ordination complexes was vastly described by the crystal field theory (CFT) IN 1929 by Hans Bethe and by the ligand field theory (LFT) IN 1935.

There are diverse applications of co-ordination compounds in different fields, such as industrial catalysts in controlling reactivity, and they play ans essential role in biochemistry. The specific color of different metals in different complexes plays an important role in medicinal chemistry. The ligands are used in the case of treatment of problems due to the presence of some metal in toxic proportion in

plants and animals. So, excess metals like copper and iron are taken away by chelating ligands D-penicillamine and desferrioxamine via the formation of the co-ordination complexes. Some co-ordination complexes of platinum are used as an inhibitor of the growth of tumors.

WHAT IS SCHIFF BASE LIGAND?

Schiff bases are versatile compounds synthesized from the condensation of primary amino compounds with aldehydes or ketones (Scheme **1**). The high thermal stability of many Schiff bases and their complexes were useful attributes for their application as catalysts in reactions involving high temperatures. This activity of Schiff bases was usually increased by complexation therefore to understand the properties of both ligands and metal ions can lead to the synthesis of highly reactive compounds. Schiff bases are some of the most widely used organic compounds that are used as pigments and dyes, catalysts, intermediates in organic synthesis, and polymer stabilizers. Schiff bases have also exhibited a broad range of pharmacological activities such as anti-fungal, anti-bacterial, antimalarial, antitubercular, antiproliferative, anti-inflammatory, anti-viral and antipyretic properties. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities, which can be altered depending upon the type of substituent present on the aromatic rings.



R^1, R^3= Alkyl or aryl substituents
R^2= H or alkyl or aryl substituents

Scheme 1. The general methods of preparation of Schiff base compounds.

This type of Schiff base is used for the preparation of different types of co-ordination complexes through co-ordination with several numbers of transition metals. The transition metals generally serve as a bridge or transition between the two sides of the periodic table. These have diverse applications in the different fields of chemistry, not only and also biological field. They have certain characteristic properties, which result from partially filled *d* shell. These are (i) the colour of the compounds due to *d-d* transition, (ii) many oxidation states are found, (iii) paramagnetism property has been found due to the presence of unpaired electrons. Actually, such types of characteristics were shown in Schiff

CHAPTER 6

Metal-Organic Frameworks (MOFs) for the Antimicrobial Applications

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Abstract: Metal-Organic Frameworks (MOFs) are a class of porous crystalline materials made-up of transition-metal cations linked with multidentate organic ligands by the coordination bonds. The strong, flexible frameworks and the porous structure of the MOFs establish them as an effective carriers of various functional compounds, such as gases, drugs, and anti-microbial agents. The MOFs render high loading capacity and sustained release, which is the desired property in anti-microbial applications. Similar porous material for the anti-microbial application is Zeolite, however, it is more complex to synthesize than MOFs. Currently, MOFs are used mainly in catalysis, gas separation and storage, and water purification applications. In the applications as anti-microbial agents, MOFs are just emerging into the field application from the laboratory scale. Hence, this chapter discusses the properties, synthetic procedures, anti-bacterial mechanisms and various forms of MOFs for anti-microbial applications. The MOFs are often doped with metal nanoparticles, polymers, and metal-polymer complexes. Each category of MOFs has a different mechanistic approach to inhibiting microbial colony growth. In this regard, this chapter will provide sufficient information on the MOFs, which will help to understand their significance in anti-microbial applications and their scope.

Keywords: Anti-microbial, Metal-Organic Frameworks, Nanoparticles, Polymers, Porous materials.

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

INTRODUCTION

Microbial contamination negatively impacts various industries such as food, livestock, medical, and environmental management, threatening millions of lives globally [1]. Measures to eradicate these microbial contaminations through antibiotics have further raised the antibiotic resistance of the microbes targeted. World Health Organization (WHO) has urged that antibiotic abuse leading to drug resistance of the microbes has led to a greater challenge to public health around the world [2]. In 2017, WHO announced the priority list of bacteria for which new antibiotic development is urgently required [3]. According to WHO, in 2016, a lower respiratory infection caused 3 million deaths, diarrhea caused 1.4 million, and tuberculosis caused 1.3 million deaths globally [4]. Antibiotic resistance, on the other hand, is usually a natural process, but the misuse of antibiotics on humans and animals further worsens the situation. This makes it hard to treat the growing infection cases such as tuberculosis, gonorrhea and salmonellosis. Economically, antibiotic resistance casts a burden by an extended hospital stay for treatment, prolonged medication, and increased mortality states WHO [5]. In the current situation, efficient new methods or systems are urgently require combating bacterial infections due to the existence of multi-drug resistance bacteria [6]. The use of antibiotics to cure infections caused by many pathogens is becoming inefficient, and fewer antibiotics have been marketed in recent years [7]. Hence, it is an exigent need to develop novel anti-microbial agents or systems to restrict the growing issues of microbial contamination and antibiotic resistance.

Due to the rise in the number of antibiotic-resistant pathogens, the attention of various research communities was drawn to develop an efficient anti-microbial agent alternative to antibiotics. Developing new anti-microbial agents came up in three eras. The first era discovered anti-microbial molecules, such as penicillin, the second era marked the development of metallic carriers for antibiotics, and the third era developed the nontoxic metal-organic carriers for anti-microbial agents [8]. A breakthrough in the third-era discovery is the formulation of metal-organic frameworks (MOFs). The MOFs are polymeric porous crystalline metal-organic frameworks with large specific surface areas, high porosity, well-dispersed active centers and tunable functional groups with appropriate metal ions and organic linkers. A general schematic representation of MOF is elucidated in Fig. (**1**). Structural building blocks of MOFs have two major components;

i) Metal ions or metal ion clusters forming a continuous framework through coordination bonds or covalent bonds using

ii) Linkers made up of organic molecules [9, 10].

The metal ions and ligands arrange geometrically, rendering corresponding physicochemical and functional properties to MOFs, which can be altered by varying the arrangement of the framework [8]. By selecting the appropriate geometry of the framework, the composition and size of the pores can be controlled, thereby determining the porosity and specific surface area of the skeleton corresponding to various applications [11, 12].

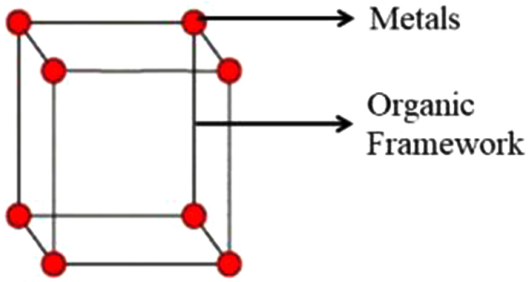

Fig. (1). General schematic representation of a MOF.

MOFs are either used to carry the anti-microbial agents with the desired porosity and crystal structure for the optimal loading and release, or they are used as antibiotics themselves, having metal ions that are lethal to microbial cells [13, 14]. This chapter discusses the synthesis methods, anti-microbial activities, and the prospects of the anti-microbial MOFs.

SYNTHESIS OF MOFs

Synthesis of MOFs is easier than other porous materials, such as zeolites, as the nucleation, crystal growth and template removal for MOFs require mild conditions [14]. The synthesis of zeolite is complex and expensive [15]. Whereas, MOFs are simple to synthesize and effective in functionality. MOFs are formed by the coordination of polymers with an open framework containing potential pores [16]. MOFs are formed by the self-assembly of polymeric linking organic ligands and metallic ions. The metals used to synthesize MOFs are copper [Cu], zinc [Zn], aluminium [Al], iron [Fe], chromium [Cr] and gadolinium [Gd]. The organic linkers used are 2,5- dihydroxyterephthalate (DOT), 2,20- bipyridine-5,50- dicarboxylate (BPYDC), N,N-diethylformamide (DEF), p-terphenyl-4,-0-dicarboxylate (TPDC), biphenyl-4,40-dicarboxylate (BPDC), 2-methylimidazolate (MIM), 2-formylimidazolate (FIM), pyrazine-2,--dicarboxylate (PZDC), 4,4'-bipyridine, 1,10-phenanthroline (phen), 4,4-[hexafluoroisopropylidene] dibenzoate (HFBBA), m-benzenedicarboxylate (m-BDC) [17]. The parameters that control the formation of MOFs during the synthesis process are temperature, reaction time, pressure, pH, and solvent

CHAPTER 7

Biogenic Metal Nanoparticles: A Sustainable Alternative to Combat Drug-Resistant Pathogens

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Abstract: The natural environment acts as the largest 'bio-laboratory" of yeast, algae, fungi, plants *etc.,* which are used as an abundant source of biomolecules. These different biomolecules play vital roles in the formation of different biogenic metals or metalloid nanoparticles. Recently, the overburden from the different microbial diseases has increased rapidly in different application sectors, viz., drug delivery, DNA analysis, cancer treatment, antimicrobial agents, water treatment and biosensor and catalysts, as a result of multipurpose work occurrence globally. The indiscriminate and arbitrary use of antibiotics in clinical practice has spurred the emergence of potentially life-threatening multidrug-resistant pathogens. In the quest for novel antimicrobial agents, the current interest is to develop potent antimicrobial agents which exhibit broad-spectrum bactericidal activity and possess a mechanism of action that does not readily favor the development of resistance. The use of nanoscale materials as bactericidal agents represents a novel paradigm in antibacterial therapeutics. Actually, eco-friendly, sustainable modern approaches, such as green syntheses of different biogenic metals or metalloid nanoparticles, are cost-effective and environment-friendly, and they are used as strong antimicrobial agents. This chapter focuses on synthesizing biogenic metal or metalloid nanoparticles with special emphasis on microbial synthesis, particularly from yeast, bacteria, algae, fungi, plants extract, etc. Finally, a detailed description of the biosynthesis mechanism using different green sources, along with their antimicrobial activity and mode of action, has been presented.

Keywords: Antibiotic, Antimicrobial agents, Biogenic metal nanoparticles, Biomolecules, Copper oxide nanoparticles, Green synthesis, Gold nanoparticles, Iron nanoparticles, Metalloid nanoparticles, Multidrug-resistant pathogens, Nanoparticles, Photo activation, Phytochemicals, Reactive oxygen species, Silver nanoparticles, Titanium dioxide nanoparticles, Zinc oxide nanoparticles.

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

INTRODUCTION

One serious global issue in modern biomedicine and healthcare regime is the emergence of multidrug-resistant bacterial strains. These pathogens have evolved mechanisms to evade the action of most commercially available antibiotics, underscoring the need for novel and potent antibacterial agents. The problem, especially the biogenic nanoparticles. The terminology 'biogenesis' was first coined by Henry Charlton Bastian, which means manufacturing a new life form from nonliving components/materials. Biogenic metal nanoparticles (NPs) technology is a hot topic in modern science, especially nanotechnology. This novel branch of nanoscience research includes materials science, physics, chemistry and biological science. Nanoparticles represent a particularly innovative regime, displaying unique properties with potentially wide-ranging therapeutic applications. Generally, nanoparticles (NPs), ≤100 nm in particle dimension, are primarily produced through bottom-up and top-down strategies. In the bottom-up approach, molecules and atoms are assembled to form molecular structures in the nanometer range, whereas, in the top-down approach, bulk raw materials are gradually broken down into nano-sized materials. Among these two methods, scientists world-wide used bottom-up-based chemical or biological approaches for nanoparticles (NPs) synthesis.

The synthesis of nanoparticles can control the shape, property and particle size of NPs. Crystalline property, among them, has been considered as prime in chemical science that could be used for vital applications viz., biosensor, bio-medical, catalyst for the bacterial biotoxin boycott and lower price electrode [1, 2]. The promising applications of NPs are nanowires, nanosheets and nanotubes, which have acquired more care in nanoscience [3, 4]. NPs function as a bridge between bulk materials and molecular or atomic structures. So, they are a very good choice for applications like electrochemistry, catalysis, biotechnology, trace materials and medical [5, 6].

Nature has provided lots of ways and insight for the synthesis of commercial nanomaterials. The natural environment act as the largest 'bio-laboratory" including yeast, bacteria, algae, fungi, plant extracts and waste materials, which are considered as eco-friendly materials for the synthesis of NPs with effective applications [7 - 10]. The biological pathway, which includes various types of microorganisms, has been used for synthesize various metallic NPs, which has benefits over chemical methods as the biological pathway is cost-effective, energy saving and greener. In addition to this, the coating of bio-molecules on the NPs surface makes them biocompatible in parallel to the NPs prepared by different chemical methods [11, 12]. The biocompatibility of bioinspired NPs offers very interesting use in biomedicine and allied fields [13]. The biogenic methods lead to

designing NPs with varied sizes and interesting morphologies [14]. For example, sulfate-reducing bacteria are used to modify the shape and size of NPs by cell-soluble protein extract method [15]. These modified shaped-NPs *via* biogenic enzymatic methods were superior to the NPs synthesized through a chemical process as biogenic enzymatic methods used minimum expensive chemicals and performed higher catalytic work. Recently, an industrially significant different type's fungus was used to synthesize uniform-sized Au NPs, easier to handle than other types bacteria and yeast [16]. In addition, several forms of algae are currently being used for NPs synthesis due to their tremendous power of bioremediation of different toxic metals. Further, they are used very decently to fabricate various metal and metal oxide NPs [17].

Apart from these, plant root, stem, leaf, latex and seed have extensively been used for NPs synthesis, and they act as strong reducing or stabilizing agents [18]. More recently, different waste materials have been used for NPs synthesis. Accordingly, this chapter is therefore primarily focused on the synthesis of biogenic metal or metalloid NPs. Additionally, this chapter will address different biosynthesis mechanisms along with different influencing factors.

CAPPING AGENTS AND THEIR DIFFERENT TYPES

The capping agents perform a very central and versatile role in the synthesis of NPs. NPs can be used as capping agents to deliver fruitful properties by monitoring their morphology and size and protecting the total surface, thereby prohibiting the total quality. Many surfactants are used for capping agents for gating, but the most difficult problem is removing the surfactants because their properties are not easy to degrade. Liu *et al*., and Gittins *et al.*reported that in their work, commercial surfactants are more hazardous for the environment [19, 20]. So, eco-friendly capping agents are more needed for industrial and laboratory-level NPs synthesis.

Biomolecules

The formulation of homogenous NPs using biomolecules has recently obtained prime interest because of its non-toxic character and not involving harsh synthetic origin. Different amino acids play a reducing role as well as capping materials to synthesize the NPs due to their unique shape and size. For instance, twenty different amino acids accept L-histidine, which reduces tetraauric acid to Au nanoparticles, but the formation of NPs is dose-dependent; the higher dose produces the smaller nanoparticle [21].

CHAPTER 8

2D Molybdenum Disulfide (MoS_2) Nanosheets: An Emerging Antibacterial Agent

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Abstract: The development of resistance against antibiotics in microorganisms has led to the search for alternatives that can effectively kill microbes and will have a lesser probability of the generation of resistance. In this regard, nanomaterials have emerged as protagonists demonstrating efficient antibacterial activities against drug-resistant strains. Amongst nanomaterials, 2D nanosheets have attracted attention as an antibacterial agent due to their sheet-like features, having sharp edges and corners which can pierce through bacterial membranes, subsequently leading to membrane damage. The present chapter discusses the antibacterial potential of one such 2D material, transition metal dichalcogenides, specifically MoS_2 nanosheets and their composites. A brief discussion about the synthesis of MoS_2 nanosheets is presented, and a detailed overview of its application as an antibacterial agent is illustrated. The mechanism of action of antibacterial activity of 2D MoS_2 nanosheets is discussed, which shows that these nanosheets can cause bacterial cell death through membrane damage and depolarization, metabolic inactivation and generation of reactive oxygen species (ROS). Further, the photothermal property and the intrinsic peroxidase-like activity in certain conditions can also show antibacterial activity, which is summarized in the chapter along with the biocompatibility evaluation.

Keywords: 2D Nanomaterials, Antibacterial, MoS_2, photothermal, Nanomaterials, Nanosheets.

INTRODUCTION

The development of widespread antibiotic-resistant bacteria has proved to be a global health burden for antibiotics currently available in the market [1]. The IDSA has classified some of the bacterial strains as the most dangerous pathogens owing to their fast growth of antibiotic resistance [2, 3] ESKAPE [4] pathogens, which include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

Enterobacter species and comprises both Gram-negative and Gram- positive pathogens. Gram-positive bacteria can successfully escape the bactericidal activity of maximum traditional antibiotics due to the presence of an extra lipopolysaccharide layer which acts as an additional barrier for antibiotic interactions or modification of the target site. Further, the presence of powerful efflux pumps in Gram-negative bacteria that easily pump out drugs from the cytoplasm (Fig. **1**) puts an additional burden on antibiotic therapy [5, 6]. Since ESKAPE pathogens may cause life-threatening infections, therefore,to overcome the problem of antibiotic resistance, it is important to create an alternative therapeutic approach. In recent years, small-molecule-based antibiotics, such as daptomycin, fidaxomicin, and retapamulin, were confirmed to have resistant bacterial species [7]. As a result, researchers are looking for novel antibacterial agents that can destroy pathogenic strains selectively and effectively while causing no negative side effects to the host [8].

Several nanomaterials have emerged as potential antibacterial agent that has shown strong antibacterial action towards ESKAPE pathogens without developing resistance andare now considered a potential therapeutic option for treating drug-resistant infections. Silver nanoparticles are by far the most investigated and used antibacterial agents in clothing and food packaging, water disinfection, wound healing, and antibacterial coatings [9 - 15]. The toxicity of silver nanoparticles to human or hosts have raised concern about their transition to antibacterial therapy [16]. Further, for photo-thermal inactivation of bacteria, the conventional gold nanoparticles with near-infrared responsive photo-thermal activity have been investigated. Besides metal nanoparticles, the class of 2-D (two-dimensional) nanomaterials have gained a lot of recognition as possible antibacterial agents in the last decade. Amongst 2D materials, graphene has been widely investigated for antibacterial applications [17]. Recently, 2D material, transition metal dichalcogenides (TMDs), has arisen as a potential candidate for antibacterial agents. TMDs are X-M-X sandwich layered materials in which chalcogen atoms are linked to metals through covalent bonds and the layers are attached by weak van der Waals forces [18]. Molybdenum disulfide (MoS_2) is an S-Mo-S sandwich layered material belonging to the TMDs family that has drawn increasing interest as a 2D layered nanomaterial due to its intriguing properties, such as excellent mechanical properties arising from the in-plane stiffness of monolayer [19, 20], having suitable band gap for light harvesting thereby exhibiting strong photo-catalytic and photo-thermal properties [21 - 24], and potential antibacterial activity against bacterial pathogens. The main mechanism behind the MoS_2 killing or inhibiting microorganisms is oxidative stress and inducing contact-mediated membrane damage. It is important to use an antimicrobial agent that possesses biocompatibility along with the efficient antimicrobial activity. In this regard,

MoS_2 has been reported to show low cytotoxicity and genotoxicity [25 - 27], making it a suitable antibacterial nanomaterial.

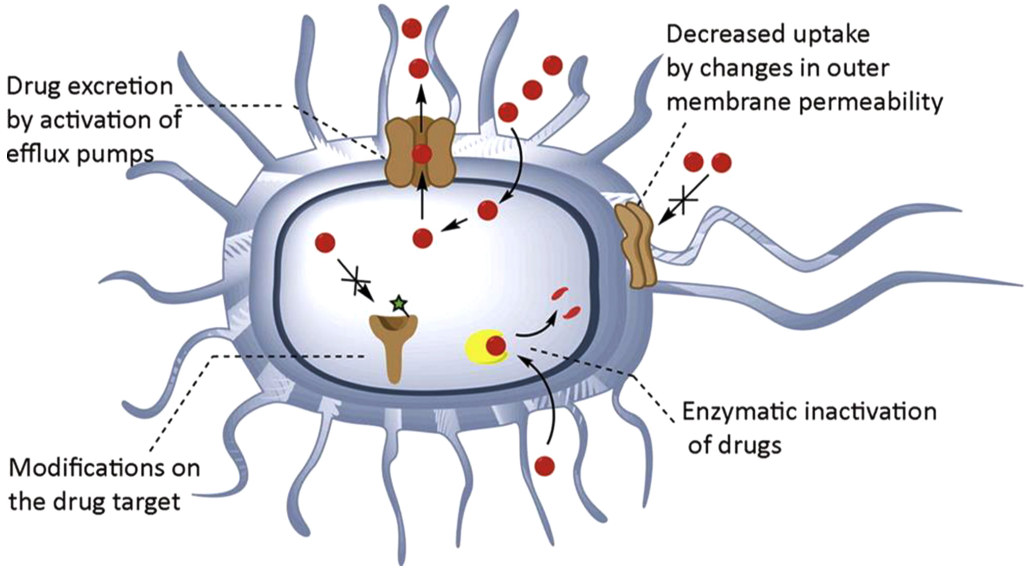

Fig. (1). Schematic illustration of the bacterial mechanisms of antibiotic resistance With permission, this image has been reproduced [28]. Copyright 2017, Elsevier.

Methods of Preparation of MoS_2 Nanomaterials

MoS_2 nanomaterial exists in various forms categorized as 0D, 1D, and 2D, and for the synthesis of these nanocomposites, a range of approaches have been developed. Bottom-up and Top-down are two widely used strategies for nanomaterial synthesis. The top-down method involves the breakdown of bulk material into its compositional components. This process involves the exfoliation of MoS_2 multi-layered bulk into mono or few layers by applying physical/mechanical force or intercalation and exfoliation by solvents and chemicals. Solvent-assisted exfoliation, mechanical exfoliation, thermal decomposition, electrochemical exfoliation and chemical-assisted exfoliation are a few examples of top-down approaches which are presently used for the synthesis of MoS_2 nanomaterials [29, 30]. Physical processes such as mechanical exfoliation and laser thinning, as shown in Figs. (**2a** & **2b**), generally use micromechanical force to synthesize MoS_2 monolayer from bulk [29]. The mechanism of electrochemical exfoliation of MoS_2 is represented in Fig. (**2c**). The first step in this process is the oxidation of water. The resulting formation of $\cdot OH$ and $\cdot O$ radicals around the bulk MoS_2 layer then lead to the expansion of the interlayers resulting in the exfoliation of MoS_2 nanosheets [31]. The bottom-up

CHAPTER 9

Metallic and Non-Metallic Quantum Dots as Potent Antibacterial Agents

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Abstract: The emergence of antibiotic-resistant bacteria poses a critical public health issue worldwide, which demands the development of novel therapeutic agents as *via*ble alternatives to antibiotics. The advent of nanoscience and technology offers the synthesis of several potential anti-microbial agents that are effective against both Gram-positive and Gram-negative bacterial strains. One such nanoscale material that fascinated researchers due to its unique optoelectronic properties is Quantum Dots (QDs). Moreover, these are found to be highly bactericidal, even against resistant bacterial infections. Thus, a significant number of researches have been going on globally to employ QDs as potent bactericidal agents alone or in combination with antibiotics. Studies demonstrated that intracellular uptakes of QDs elevate the level of reactive oxygen species (ROS) inside the cells, which turns-on cascades of intracellular events that cause damage to DNA and proteins. However, the inherent reactive nature of these metallic and semiconductor QDs raises huge concern for translational research as these are found to be cytotoxic and non-biocompatible. Moreover, the human body does not have a proper sequester mechanism to remove these metallic ions from the body, which limits its direct applications. Recent progress in this line of interest has focused on developing non-metallic quantum dots, such as carbon dots (CQDs) and Black Phosphorus quantum dots (BP QDs) which showed less toxicity and immunogenicity suitable for real-life applications. Therefore, in the present chapter, we are going to discuss the recent development of bactericidal QDs and various types of surface functionalization illustrated recently to increase biocompatibility.

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

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INTRODUCTION

Antibiotic-resistant bacterial infections are found to be one of the most alarming threats to mankind as the conventional antibiotics found to be futile against it, which have been employed as useful gold standard medicines for more than fifty years [1, 2]. All parts of the world are now reported cases of resistant bacterial infections; however, the situation is very serious in third-world countries, including India, possibly due to a lack of awareness and poor healthcare systems. The incomplete dose of antibiotics and misuse of antibiotics in humans, as well as animals, lead to the occurrence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, which are not possible to treat by conventional therapeutics. For example, multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB), vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most frequent among the reported drug-resistant cases. This causes higher medical costs for treatment, and longer hospital stays for patients of any age. Moreover, antibiotic resistance in bacterial infections also caused co-morbidity as well as increased mortality rate. This is a critical health crisis that has been going on globally because of an increasing number of cases of bacterial infections and the occurrence of drug-resistant strains. Hence, there is an urgent need to develop advanced therapeutic agents and/or strategies to address antibiotic-resistant bacterial infections.

The advent of nanotechnology offers several innovative solutions to address these contemporary issues. Nanoscale materials having the size of a few nanometers (1 nm = 10^{-9} m) provide the scope for easy penetration through the bacterial cell wall and leads to bacterial cell death [3 - 6]. In this regard, metallic nanoparticles (NPs) provide huge promises to kill different bacterial strains. Studies showed that size, shape, and surface chemistry play a vital role in bactericidal activity [5]. One of the most explored nano-scale materials is silver nanoparticles (Ag NPs) and their composites, which have been at the forefront owing to their highly bactericidal activity against a broad range of bacterial strains, more importantly, antibiotic-resistant bacterial strains [5]. Generally, Ag NPs damage bacterial cell walls after interactions with them; however, intracellular uptake leads to the elevation of reactive oxygen species (ROS) that damage various important biomacromolecules, including DNA and enzymes. Metallic NPs may also increase the concentration of intracellular metal ions, which directly affects

several cellular functions that ultimately cause bacterial cell death. Apart from the Ag NPs, other metal NPs, such as copper, gold, and platinum, NPs also showed promising outcomes [5, 6]. Additionally, there are reports of the use of metal oxide NPs, such as copper oxide, zinc oxide, titanium oxide, and iron oxide NPs, which are found to be equally potent against bacterial infections [7, 8]. However, in most cases, higher doses of metal and metal oxide NPs are cytotoxic, which limits their direct use as an antibacterial agent for real-life applications. Thus, in the last few decades, researchers all over the world proposed the use of these metal and metal oxide NPs along with conventional antibiotics for combination therapy that offered reasonable success against several resistant bacterial strains due to synergistic bactericidal effects. Moreover, the use of other antibacterial agents such as amphiphilic molecules, cationic polymer (*e.g.,* chitosan), and supramolecules, in tandem with these metal and metal oxide NPs have been explored widely that reduces the effective concentration of the metal ions.

Another nanoscale material that has drawn significant consideration from the scientific community for the last few decades is quantum dots (QDs), a new form of fluorescent nanostructures. QDs are semiconductor nanocrystals (usually 2-10 nm in diameter), which possess size-dependent optical properties. They have been proven effective in several biophotonic and biomedical implementations [3, 4]. The dimension of this nanoscale material is that it shows a "quantum confinement" effect, which causes discretization of the energy levels responsible for size-tunable luminescence. QDs have specific physical and chemical characteristics compared to conventional materials, such as narrow emission bands, stability, and high quantum yield. Therefore, QDs are generally employed in various biomedical applications such as biosensors, cell labelling, drug delivery, photodynamic therapy and bioimaging [3, 4]. In addition, QDs are gaining significant attention due to their antibacterial activity, which suggests that QDs could be used as an antibacterial agent as an alternative to conventional antibiotics [4]. Different types of metallic and semiconductor quantum dots (ZnO, TiO_2, and CdTe) have been reported as potential bactericidal agents in the last decades. However, the cytotoxicity of metallic QDs has been proved in several *in vitro* researches that have restricted their use, particularly in medical applications. Presently, the researcher focuses on developing non-metallic QDs such as carbon dots (CQDs) and phosphorus QDs that have shown less toxicity suitable for biomedical applications. In this chapter, we have demonstrated the recent progress in the synthesis of various kinds of metallic and non-metallic QDs (Fig. **1**). Emphasis has been given to illustrate the recent outcomes and the scope of non-metallic QDs as potential bactericidal agents against both Gram-positive and Gram-negative bacterial strains.

CHAPTER 10

Photodynamic Therapy: A Viable Alternative Strategy to Control Microbial Invasions

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Abstract: Antimicrobial photodynamic therapy (aPDT) is a new-age therapeutic technique that by principle, focuses on the eradication of target cells by highly cytotoxic reactive oxygen species (ROS) generated through the activation of a chemical photosensitizer (PS) molecule with visible light of appropriate wavelength. The cytotoxic species can arise *via* two main mechanisms known as Type I and Type II photoreactions: the former leads to the generation of ROS and the latter to the formation of the singlet oxygen. These highly reactive oxidants can bring about instantaneous oxidation of a great array of biological molecules, causing havoc to the target cell. This technique provides significant advantages over conventional antimicrobial therapies in practice which are now facing the burning threat of growing complete resistance against them. To combat this world-wide health concern, new treatment strategies are the need of the time while ensuring no further rise of resistance against those alternative therapies, and aPDT appears to be highly promising in this aspect by fulfilling all the demands at the same time. It appears not only equally effective at killing both antibiotic-sensitive and multi-resistant bacterial strains, but also highly selective, non-invasive and rapid in action than other antimicrobial agents, and there have been no reports of resistance till date. The success of this phototherapy relies on several factors, including the target cell type, reaction conditions, and the type, molecular structure and cytolocalization of the PS; because its potency depends on the distribution, high reactivity and short lifetime of ROS as well as the PS itself in electronically excited states.

Keywords: Alternative therapy, Antibacterial, Antibiotic-resistance, Antibiotic-sensitive, Antifungal, Antimicrobial, Antiviral, Illumination, Gram-negative, Gram-positive, Oxidative stress, Photodynamic therapy, Phototherapy, Photoreactions, Photosensitization, Photosensitizer, Reactive oxygen species.

INTRODUCTION

Antimicrobial is a general term that refers to a group of agents used to destroy or inhibit microorganisms, mainly pathogenic ones. Thereby, these antimicrobial

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Tilak Saha, Manab Deb Adhikari and Bipransh Kumar Tiwary (Eds.)

occupy the central position in therapeutic measures against microbial invasions; one of the major groups of antimicrobials is specifically antibiotics. Although different kinds of antimicrobial agents have been in use for centuries, the discovery of penicillin in 1928 by Alexander Fleming revolutionized the medical field. Since then, treatment for microbial infections has been mainly channeled through antibiotics as the most effective chemotherapeutic option, but the rapid emergence of resistant strains of bacteria has seriously limited the efficacy of many commonly used antibiotics to treat bacterial infections, leading to a desperate search for alternative therapy to combat health hazards [1].

Antibiotic resistance happens to be nothing new rather, it is basically an evolutionary mechanism for bacteria to fight against antibiotics, as all the natural antibiotics are substances secreted by a group of microorganisms to inhibit the other for gaining survival advantage. Hence, it is an inherent tendency of microorganisms, especially bacteria, to develop appropriate resistance against antibiotics in a short time just to be in the game. Many strains show a natural phenotype of low or no susceptibility to particular antibiotics, known as intrinsic resistance, whereas many susceptible ones acquire the resistance through mutations and horizontal gene transfer mechanisms mainly due to extensive and inappropriate use of antibiotics in the healthcare system [2]. Some of the antibiotic-resistant pathogens that have already emerged as major threats to public health are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* (VRE), multidrug-resistant mycobacteria, Gram-negative pathogens and fungi [3]. Not only are resistance mechanisms emerging fast and spreading globally, but it also threatens our ability to treat common infections, resulting in prolonged illness, disability, and death. The gravitas of the situation has forced the World Health Organization (WHO) to declare in their report in 2014 [4] about the global surveillance of antibiotic resistance that "antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill". Besides, antimicrobials are also essential in medical procedures such as surgery, organ transplantation, cancer chemotherapy, and diabetes management to control the probability of opportunistic infections. Therefore, antimicrobial resistance puts these procedures at very high risk, simultaneously increasing the overall cost of health care with lengthier hospital stays and more intensive care required.

The urgent need to get over the already-aggravated situation has drawn substantial research interest from all over the world into finding alternative methods of controlling microbial growth that would be clean enough to negate the threat of

resistance against antibiotics having a lower probability of developing resistances themselves. A new-age approach to achieve this goal is antimicrobial photodynamic therapy (aPDT) which uses a non-toxic and light-sensitive dye, the so-called photosensitizer (PS), in combination with harmless visible light of the correct wavelength to excite the PS and oxygen that can selectively control bacterial infections [5]. Light has long been an effective agent for decreasing the microbial population and has been used in treating several medical conditions. Given the rise in antibiotic resistance and unknown consequences of long-term use of chemotherapeutic agents, photomedicine is gaining revived interest and being considered more convenient, safe, and efficacious. Antimicrobial photodynamic therapy (aPDT) is one such alternative therapy that fits quite promisingly for all the criteria to treat microbial infections.

The antimicrobial effectivity of PDT comes from the free radicals released from the photosensitizing agents upon stimulation with light. This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light-mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen and can safely be used as a non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses [6]. Photosensitizes are commonly aromatic molecules with a central chromophore with variable auxochrome groups that are mainly responsible for further electron delocalization of the molecule, thereby changing its absorption spectrum [7]. Though originally an age-old practice, this therapy has primarily come around in recent years mostly as a cancer therapy, finally reaching out as a potential antimicrobial therapy due to exhibiting features favorable for the treatment of microbial infections, such as a broad spectrum of action, efficient inactivation of multi-antibiotic-resistant strains, low mutagenic potential, and the lack of selection of photo-resistant microbial cells [7].

BRIEF HISTORY

The inception of using electromagnetic radiation, especially ultraviolet radiation or visible light, for therapeutic purposes dates back to ancient times, practiced efficiently in ancient Greece, Egypt and India. But with time, it majorly lost into oblivion until it resurfaced in the Westerly world at the onset of the 20th century by a Danish physicist, Niels Finsen, who successfully demonstrated PDT by utilizing heat-filtered light from a carbon-arc lamp (The Finsen Lamp) treating a tubercular condition of the skin, called Lupus Vulgaris and consequently he won the Nobel Prize in Physiology or Medicine in 1903 [8]. In 1913, Meyer-Betz injected himself with hematoporphyrin (Hp, a photosensitizer), which led to general skin sensitivity when exposed to sunlight, and this is still a major issue with many photosensitizers [8].

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

K

L

M

O

P

R

S

T

U

V

W

X

Z

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