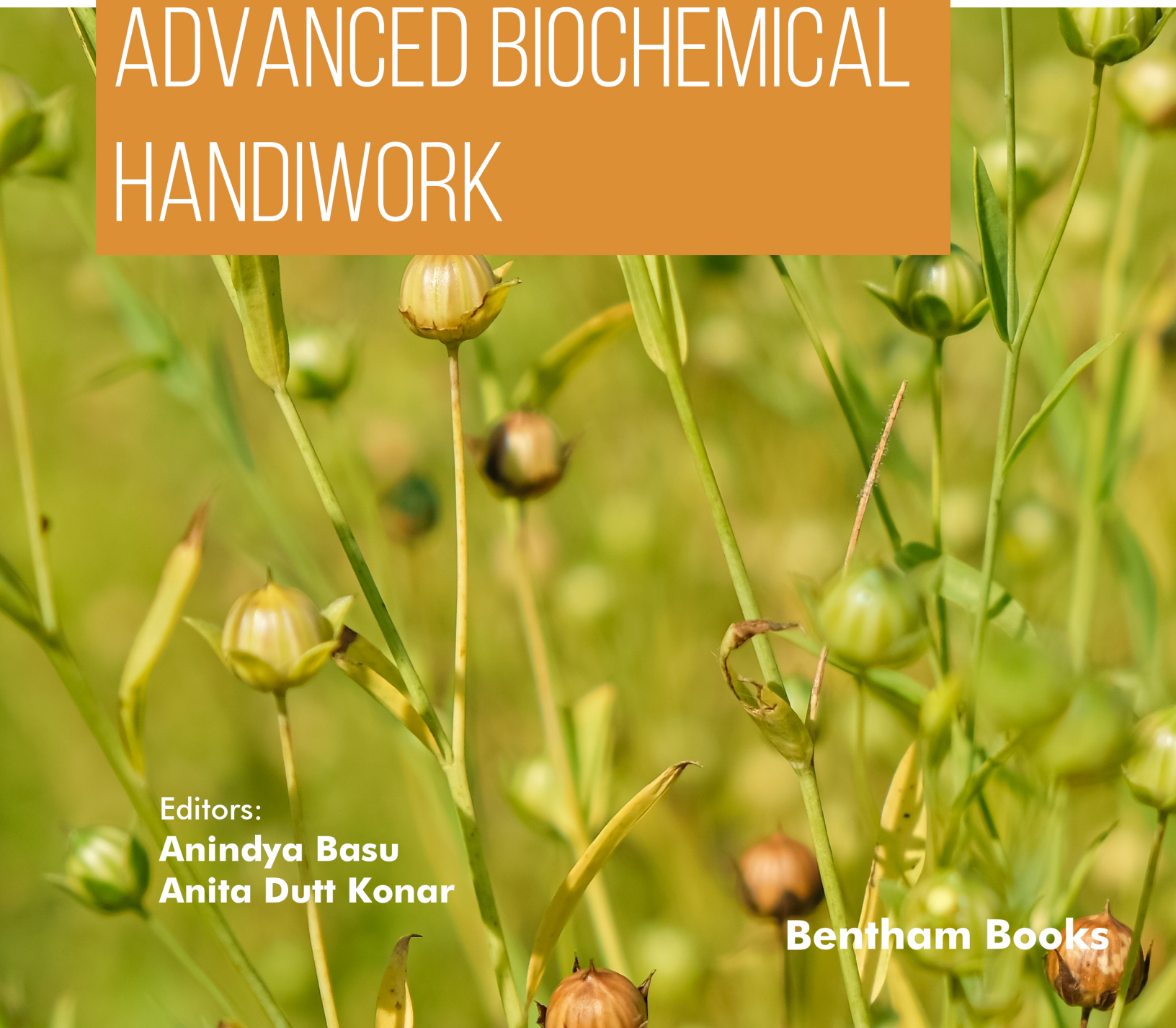
BIODERIVED MATERIALS:

HARNESSING NATURE FOR ADVANCED BIOCHEMICAL HANDIWORK



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Bioderived Materials: Harnessing Nature for Advanced Biochemical Handiwork

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FOREWORD

Biomaterials hold critical solutions to the myriad of problems modern societies face. Consequently, over the past several decades, biomaterials research has undergone a sea-change, attracting scientists and engineers from almost all conceivable backgrounds to investigate them from their perspectives. A biomaterial scientist today thus needs to be equipped with a multi-disciplinary understanding of the different aspects of any material under question and must have a general awareness of the various modifications being tried out on different types of materials. This edited book attempts to provide awareness to the students and researchers in this field of the fundamental concepts associated with the design and development of such building blocks and, subsequently, how such ideas can be used to manipulate different biomaterials to achieve the desired goals. The book chapters, contributed by the researchers, are arranged in order of complexity, starting with the fundamental concepts associated with the design and development of organic and inorganic materials, different polymers used as scaffolds for tissue engineering and complex systems like cell membranes and even whole organisms. I hope this edited book will be an asset for any student or researcher engaged in biomaterials research.

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PREFACE

Naturally-derived biomaterials (Materials derived from different organisms including animals, plants and microorganisms) invite immense interest from diverse segments of science including chemistry, physics, materials sciences, bioengineering, chemical engineering, *etc.* Although the last few decades have witnessed a thriving effort towards understanding the ongoing research with biomaterials as synthons, yet biomaterial research never fails to create surprises.

This book was conceived with the idea to summarize the modern knowledge of this field as well as lay the foundation principles for researchers and engineers from different backgrounds interested in exploring new research avenues within biomaterial sciences. For instance, the first chapter helps to lay the foundations of peptide chemistry and presents the toolsets that can be used to address / overcome the challenges associated with the design and development of peptides and peptidomimetics with desired functionalities. Chapter 2 sheds light on how these toolsets can be utilized for designing natural enzyme mimetic bioinorganic catalysts with a specific focus on redox active enzymes. Subsequently, in Chapter 3, the authors thoroughly discuss the guiding principles for tailoring bioinspired scaffolds that promote hydrogel formation through the self-assembly of peptides/peptide-based amphiphiles. They present a conceptual demonstration of the different approaches that can be considered for the tailoring of task-specific designer hydrogels for diverse therapeutic applications. Alongside, such scaffolds are now being widely used in applications related to tissue engineering and regenerative medicine which is the topic covered in Chapter 4. Here the authors present strategies for employing different moieties to build human-relevant disease models for a few highly fatal non-communicable diseases like cardiomyopathy, cancer, neuropathy and others. Further progressing with such biomaterials, in Chapter-5 the authors discuss another class of biopolymer namely Bacterial cellulose (BC) which finds widespread applications in healthcare and other industries. Here they have summarized the additives and techniques used to modify BC to form nanocomposites for applications in different industrial sectors.

Moving further from simple to more complex systems, in Chapter 6, the authors present the architecture of the cell membranes, drawing attention to how nature uses its self-designed nano-composite materials to enable execution of desired reactions under given environmental conditions. From the complex cellular membrane system, an even more complicated system is discussed in Chapter 7, wherein the authors have presented strategies to use whole cellular microorganisms for designing novel drug delivery systems. It is expected that the microbe-based drug delivery systems would possess reduced toxicities or side effects and can surely serve as a futuristic advanced drug carrier to improve patients' health.

In summary, this book focuses on bringing together diversified materials with versatile applications, derived from different sources, commencing from plant derivatives to microorganisms in partial or whole as synthons, under one roof such that readers from various disciplines end up having reasonable content.

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CHAPTER 1

Peptidomimetics a Versatile Synthon for Biomaterials: Design Principles and Solutions

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Abstract: Bioorganic chemistry, an interdisciplinary scientific branch of chemistry and biology, has grabbed considerable impetus in the last few decades, owing to its important insights into the functioning of biological systems at the molecular level. Primarily it is a discipline of science that involves the study of biological processes mainly proteins and peptides at transcriptional, translational, or posttranslational levels. Yet, at the molecular level, our basic knowledge and understanding of the structure-activity relationship (SAR) of peptides/proteins remain in their infancy. Indeed, the dissection of multidomain proteins into small and simpler fragments, shed light on the design of scaffolds that seems to mimic the function of natural proteins in an efficient way, thereby giving rise to the birth of PEPTIDOMIMETICS. At times, the mimetics of critical functional protein domains, are advantageous over normal proteins/peptides in terms of specificity and therapeutic benefits. Henceforth the latter are considered to be expensive models for the investigation of molecular recognition. In this book chapter, our effort lies in modulating the basics of principles of peptide chemistry, challenges encountered, and some very efficient examples of how Peptidomimetics serves as a road map to resolve various stumbling blocks for PROTEOLYSIS and others.

Keywords: Amino acids, Helix, Ramachandran map, Sheets, Turns.

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1. INTRODUCTION

1.1. What are Peptides?

Peptides are condensed products/polymers of two or more amino acids that are interlinked together through amidation forming an amide bond also known as a peptide bond [1, 2]. The latter possesses a partial double bond character with a nearly trans configuration that restricts the rotation around this bond, thereby making it resistant to hydrolysis (Fig. **1.1**) [1, 2]. Now in a peptide sequence, if the number of amino acid residues exceeds more than 50, it is coined as PROTEINS and if less, it is considered to be PEPTIDES.

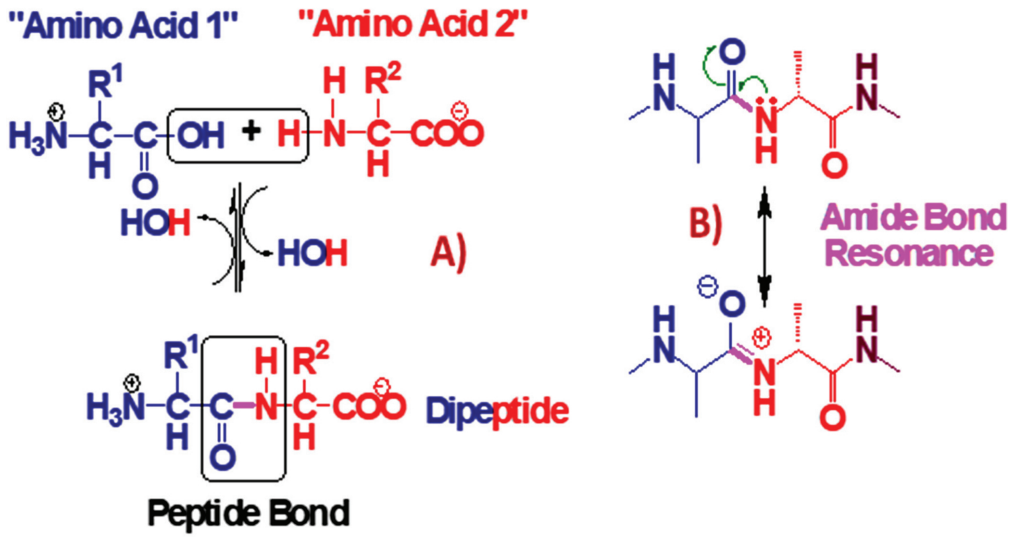

Fig. (1.1). In peptides **A**) Principle of amide bond formation; **B**) Double bond character.

1.2. A Brief Overview of Different Amino Acids

Amino Acids are bricks of proteins that possess an amine and a carboxylate functionality. Most importantly it contains an R group (side chain) appended to the same carbon, commonly referred to as the α-carbon (Fig. **1.2**). There are twenty different natural amino acids, which vary in the nature of R [1, 2]. The sidechains are classified on the basis of their nature into hydrophobic and hydrophilic residues as described below (Figs. **1.3**-**1.5**). These synthons perform important roles not only in catalytic function but also in different processes of cell metabolism. The basic stereochemistry of L-amino acids has been presented in Fig. (**1.6**).

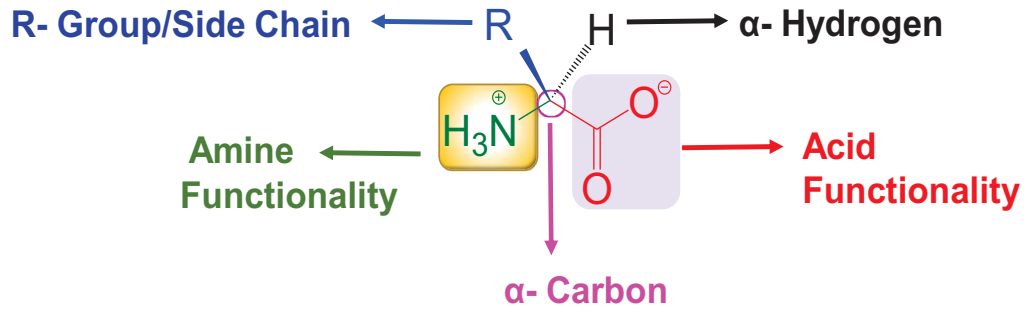

Fig. (1.2). Architectural representation of an amino acid.

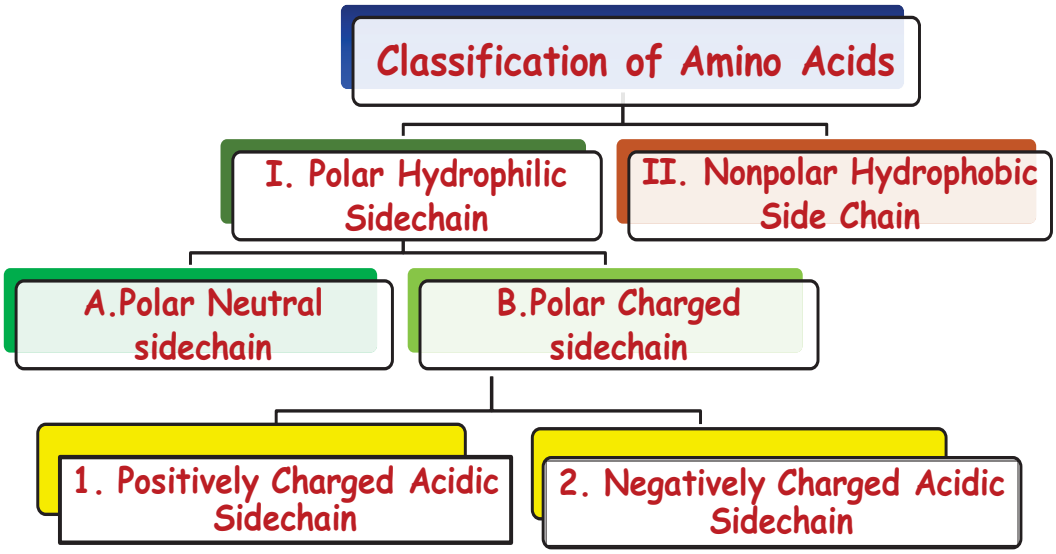

Fig. (1.3). The categories in which the amino acids are classified.

2. BASIC PRINCIPLES OF PEPTIDE SYNTHESIS

2.1. Need for Protecting Groups

If in a substrate there is more than one reacting centre, the synthesis strategy of the target molecule (TM) becomes complicated, if the reagent reacts with equal efficiency to the other reacting sites. In such chemical reactions, the reactivity of other centers should be MASKED, with the assistance of simple groups whose introduction and removal are easy and user-friendly (Figs. **1.7**, **1.8**). Henceforth originates the necessity of PROTECTING GROUPS (PG) [3].

CHAPTER 2

Bioinspired Catalysis with Biomimetic Clusters

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Abstract: Biomimetic clusters dubbed inorganic complexes are the foci of many enzymes that are frequently earmarked for biochemical pathways. Specifically, the biomimetic clusters are made up of transition metal(s) chelated with organic ligands. This book chapter details redox active enzymes for the most fundamental biochemical processes. Bio-inorganic chemists have been synthesizing numerous biomimetic clusters that have the ability not only to mimic the active site structural features but also to mimic their functions. In a similar vein, the fixation of nitrogen into ammonia is akin to the fundamental biological process and thus can be considered a biomimetic biological process. Therefore, novel materials, including electrides, nitrides, hydrides, and basic oxides, have created a niche in facilitating biochemical reaction products. Insights into biomimetic clusters, especially inorganic catalysts' mimics, new materials facilitating biological chemistries, and their mechanisms will uncover new avenues for small molecule activation, with different catalytic mechanisms yet to be elucidated.

Keywords: Biomimetic, Bio-inorganic complexes, β-Lactamase, Heterogenous catalysis, Nitrogenase, N_2 activation, Phosphatase.

1. INTRODUCTION

Inorganic complexes form the core of many enzymes involved in vital biochemical processes, which are essential for several biological processes. Notably, the bioinorganic cores are composed of transition metal clusters chelated with amino acids side chain groups. The crux of these bioinorganic complexes stems from the fact that these can readily undergo redox reactions, with concomitant increases and decreases in their coordination sphere. These redox active enzymes are therefore, involved in some of the most fundamental bioche-

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mical processes, including activation of less active species, *i.e.* dihydrogen, dinitrogen, dioxygen and carbon-bonds from hydrocarbons and carbohydrates, wherein substrates are seamlessly oxidized or reduced from their more benign forms to useful compounds.

The simple organo-catalysts, such as proline amino acid, without necessitating the presence of other functional groups, have inspired chemists to develop biomimetic catalysts. Furthermore, the tremendous rate accelerations coupled with control of the reactivity of naturally occurring enzymes have provided guiding principles to develop biomimetic catalysts. Taking inspiration from such naturally occurring enzymatic complexes, scientists have synthesized numerous biomimetic clusters that resemble or mimic the active site of these bioinorganic enzymes in terms of structures and attempting towards mimicking their functions. Biomimetic catalysts thus represent a unique platform to harness principles of enzyme function towards facilitating different catalytic processes, including activation of less active species, hydrolysis, redox reactions, *etc.*

In 1898, William Crookes articulated the necessity to find a new way to replenishing agricultural soil with nitrogen in a form that plants can metabolize. William Ramsay and Le Chatelier later put forward the studies of direct "fixation" of nitrogen, whereas Ostwald and other attempts could not find success. Later, Fritz Haber, after screening ~20,000 catalysts, could finally produce NH_3 for the first time from its elements N_2 and H_2. Haber observed that NH_3 is produced significantly by passing N_2 and H_2 over an osmium catalyst at a high pressure (200 atm) and a temperature of 600 °C. In 1916, Haber and Bosch replaced the costly osmium catalyst with an inexpensive magnetite (Fe_3O_4) catalyst. This was a *Eureka* moment and one of the significant technological breakthroughs of the 20th century that ushered in the green revolution in the world. The fixation of nitrogen from the air and converting it into ammonia is akin to the fundamental biological process of nitrogen fixation done by microbes for soil enrichment. Therefore, ammonia production can be considered as a biomimetic biological process [1 - 3]. Unlike bio-mimetic inorganic complexes or enzyme catalysis, the activation of N_2 to produce NH_3 proceeds through different mechanisms over heterogeneous catalysis and is one of the active areas of research in catalysis.

The precise arrangement of biomimetic catalyst clusters can serve as scaffolds for the predictable spatial arrangement. These can craft functionally active synthetic catalysts to facilitate biological chemistries. Therefore, biomimetic-based catalyst development provides an attractive alternative to well-developed strategies involving small molecule ligands or conventional peptides dubbed organo-catalysts for bioinspired catalysis.

2. NATURE OF CATALYSTS

2.1. Bioinorganic Catalysis by Nitrogenase Mimics

The nitrogenase enzyme is essential in performing one of the most critical processes towards sustaining life on this planet, *i.e.* nitrogen-fixation [4]. The amino acids and nucleic acids need nitrogen as an essential element, which in turn is fixed from the atmosphere to synthesize blueprint molecules necessary to create and sustain life. Therefore, the structure and mechanism of action of the nitrogenase enzyme has been a topic of intense research activity, with a goal of mimicking catalysis for producing ammonia from nitrogen sustainably. Mechanistic studies have revealed that during the natural nitrogen-fixation reaction, one mole of the dinitrogen molecule reacts with eight mole equivalents of protons and electrons to produce two mole equivalents of ammonia and one mole equivalent of dihydrogen as a side product. Therefore, during this reaction with the reduction of dinitrogen molecule to ammonia, a simultaneous reduction of protons to hydrogen must also occur. Towards such an objective, the active site of the nitrogenase enzyme and the heterometallic molybdenum-iron-sulfur cluster, also possess the homometallic iron-sulfur cubane cluster, which acts as an electron capture and proton reduction unit in many enzymatic centers. Therefore, efforts to mimic the nitrogenase activity have focused on synthesizing heterodimeric cubane assemblies of molybdenum, iron, and sulfur atoms.

2.1.1. Composition of the Active Site of Nitrogenase

The nitrogenase active site is composed of distinct homodimeric and heterodimeric cofactor(s), based on their composition.

• The heterotetrameric MoFe protein (FeMoco, present Component I), is the active nitrogenase cofactor, which uses the electrons provided to reduce N_2 to NH_3.

• The homodimeric Fe-only protein (present in Component II) is a reductase-type protein cofactor with high reducing power, and is responsible for the supply of electrons.

Thus, the nitrogenase enzyme composition is ideally suited for electron capture and transport, proton capture, dinitrogen capture, and the reduction of protons and dinitrogen to dihydrogen and ammonia, respectively. Therefore, any catalyst aiming to reduce dinitrogen should possess sites for electron, proton, and dinitrogen binding and redox-active sites for their reduction. Because of such requirements, iron is essential for such catalysts.

CHAPTER 3

Designer Bio-inspired Hydrogels : A Key to Biomedical Challenges

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Abstract: Low molecular weight hydrogelators (LMOHGs) are extremely promising synthons, in the bottom-up fabrication of supramolecular soft materials. In recent years, significant contributions to *Peptide-based hydrogels* coined as *Bioinspired fragments* have been made. In this book chapter, our effort lies to module two different aspects: Firstly the underlying guidelines and principles for the tailoring of scaffolds that would lead to hydrogel formation and an overview of the role of non-covalent interactions/chemical functionalization that are the key components of various self-assembly processes. In the second section, we aim to bring together our recent achievements with designer assembly with respect to their self-aggregation behavior and applications mainly in the biomedical arena like drug delivery carrier design, antimicrobial, anti-inflammatory as well as wound healing properties. We anticipate that this article would provide a conceptual demonstration of the different approaches taken toward the construction of these task-specific designer hydrogels.

Keywords: Anti-inflammatory, Antimicrobial activity, Biocompatibility, Drug delivery carrier, Mechanical strength, Proteolytic stability, Wound healing.

1. INTRODUCTION

Gels are a class of soft materials formed from high molecular weight polymers, that might be natural or synthetic. Based on the nature of the solvent encapsulated in them, they are categorized into Organogels (when the solvent is organic in nature) and Hydrogels (when the solvent is water) [1 - 20]. To begin with, gels have a long history with numerous positivities and lacunas, primarily with polymers as synthons [1 - 20]. In spite of the fact, its diversified applications

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in versatile avenues, overrule the deficiencies and make them appealing candidates to be widely explored [1 - 20].

Our initial efforts were devoted to understanding the factors that lead to the stabilization of the different class of polymeric gels (Fig. **3.1**). The first category begins with *Chemical Crosslinking Polymeric Gels* that are formed by cross-linking through covalent bonds (materials with extensive mechanical integrity). The second classification could be termed *Physical Crosslinked Polymer Gels* (PCPG), which are mainly stabilized by noncovalent forces (materials with weak mechanical properties). *Hybrid double network polymer hydrogels* (HDNPH), which could be categorized as the third group, a combination of the above two. In general small molecular polymeric gels, are much superior because of their very good mechanical integrity contributed by the long covalent chain of the polymer. But at times it lacks biocompatibility which restricts their choice as preferential candidates for biomedical applications.

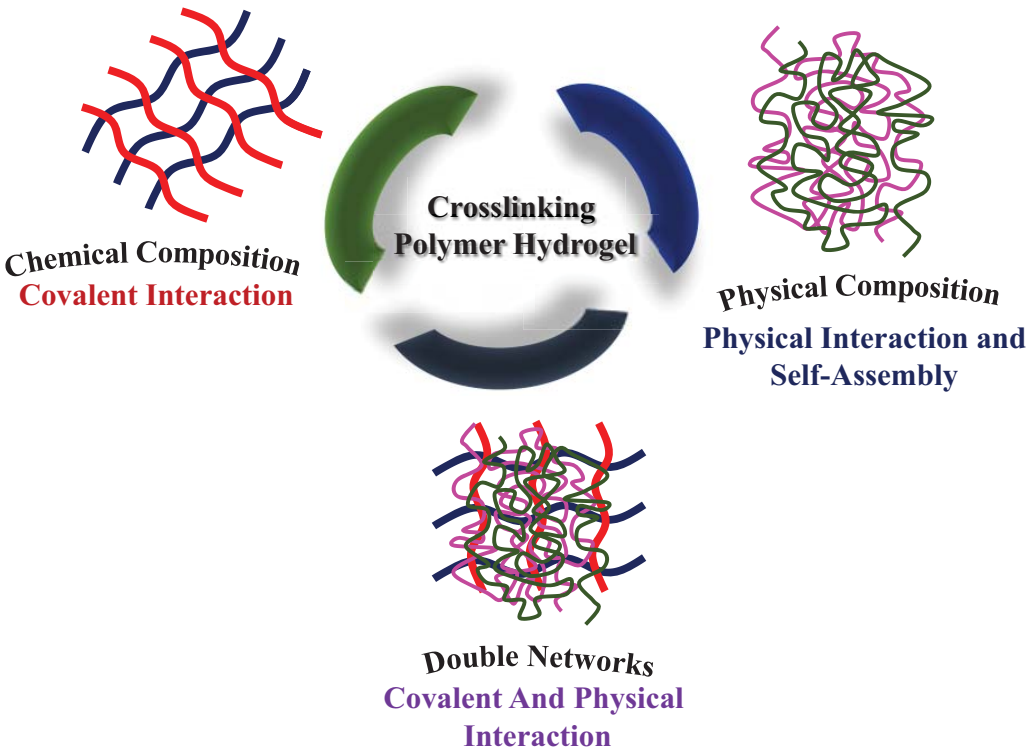

Fig. (3.1). The schematic presentation of the *Gels* fabricated through chemical crosslinking, physical crosslinking or double networks, and a combination of the two.

In this book chapter, our focus would be to discuss Physically Cross-linked Gels for Biomedical Applications……So our synthons are PEPTIDE-BASED HYDROGELS.

1.1. Why Peptide Based Hydrogels?

Peptide based hydrogels find immense importance due to the following reasons [1 - 20].

a. Peptides are formed from eco-friendly amino acids which are of biological origin and possess non-toxic nature.

b. They are biodegradable and biocompatible.

c. Their synthesis protocol is very simple.

d. The ability of peptide molecules to adopt specific secondary, tertiary and quaternary structures provides unique opportunities for the design of nanoscale materials that are not easily available with traditional organic molecules and polymers.

e. The use of amino acids facilitates the easy incorporation of possible bio-functionality into the hydrogel that makes them promising candidates for diversified applications.

f. The most important part is that they are formed through the concept of SELF-ASSEMBLY utilizing non-covalent interactions unlike other polymers that require drastic conditions and complex techniques for their fabrication.

1.2. Principle of Hydrogel Formation

The self-assembly of peptides leading to hydrogelation could be best described as a hierarchical phenomena (Fig. **3.2**) [1 - 20]. All peptide molecules possess a definitive backbone known as the primary structure. In solution, these backbones adopt a specific arrangement known as secondary conformation, stabilized by non-covalent interactions. Many such secondary structures, in the presence of appropriate stimuli or favourable physical conditions, arrange in tertiary structures which give rise to nanofibers. Elongation of these fibers in three-dimensional space leads to thicker and longer fibers (Quaternary structures), which further self-assembles to a fibrillar network (Fig. **3.2**). These pores in the three dimensional networks of peptides are capable of entrapping water molecules in them and form a self-supporting hydrogel. Orchestration of the physicochemical properties of these hydrogels could be achieved by proper choice of the amino acid sequences, thus ending up in control over the synthesized materials.

CHAPTER 4

Natural Biomaterials: An Essential Element for *in vitro* Disease Modeling

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Abstract: In-depth analysis of human diseases, specifically emergent non-communicable ones, needs to be carried out to understand the molecular mechanism and develop sustainable therapeutics. Animals such as small rodents and canines are frequently used as models for clinical trials. However, recent evidence suggests the inappropriateness of such *in vivo* models for human diseases. A new class of human-relevant platforms needs to be established to resolve the issues surrounding the failure of potential drug candidates over the last decades. The development of human-relevant *in vitro* models must abide by the 3R's principles for biomedical research. Modeling diseased tissue requires appropriate matrices such as scaffold, hydrogel, electrospinning mats, and others to mimic the strength and mechanics of the tissue in question. Biodegradable biomaterials from natural sources such as plants and animals are already used widely for tissue engineering, and regenerative medicines can be repurposed to develop a human-relevant disease model. Here we will discuss the current status of such *in vitro* models for a few highly fatal non-communicable diseases like cardiomyopathy, cancer, neuropathy, and others.

Keywords: Biomaterials, Cancer, Cardiopathy, Disease modeling, Extracellular matrix, *In vitro*, Neuropathy, Nephropathy, NCDs, 3Rs.

1. INTRODUCTION

With the advancement of diagnostic and therapeutic approaches, the morbidity and mortality of humans have reduced dramatically over the last century. Interestingly, during this period, the development of antibiotics, significant improvement of hygiene, and altered lifestyle have slowly changed the nature of the global diseases from the communicable ones to the non-communicable (NCDs) ones, which caused roughly, 70% of all deaths now [1]. Fatal NCDs include cardiac, cancer, respiratory, diabetes, and kidney diseases [2]. In addition, other factors such as increasing pollution and accumulation of mutations in old age may influence the emergence of certain conditions such as cancer and neuro-

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-degenerative ones. However, detailed molecular and cellular mechanisms behind these diseases are unknown, hindering successful and cost-effective cure. Therefore, extensive research is needed to understand the causality and progression of these diseases to develop an early-stage diagnosis for a better prognosis and efficient, affordable therapy.

The discovery of potential pathways and candidates for diagnosis and therapy requires a proper model for hypothesis-driven study and validation of the hypothesis. To date, most of the therapeutic targets are validated through the drug discovery pipeline, which starts from silico-driven prediction and proof of concept studies (*in vitro)*, followed by *in-vivo* validation. However, in the last few decades, the development of only a few successful drugs undermined the said pipeline's efficacy [3]. Additionally, it is observed that the very high failure rate (97%) of potential drug molecules might influence the increased death rate and cause a financial burden on the patient [4]. Furthermore, the extensive use of animals such as lower rodents for phase I clinical trials became questionable also due to many reasons, including scientific, ethical, and financial ones [5, 6]. Finally, the recognizable differences between the immune system and pharmacokinetics between human and rodent models made them irrelevant for NCDs and metabolical diseases [7]. Thus, along with the very high failure rate of potential drugs, the emerging problem of drug resistance highlighted a widening knowledge gap between the current hypothesis-driven and the proof-of-concept studies.

As highlighted by a few researchers, the drug discovery pipeline might need a conceptual and technical overhaul. The development of a human-relevant disease model can be one of the approaches to solving this problem [8]. Technological advancements in nanotechnology, microfluidics, and cell and molecular biology can be exploited to develop human-relevant models of diseases to establish the molecular mechanism and cell-cell interaction studies followed by a preliminary screening of possible drug molecules without animal testing [9]. Additionally, the concept of 3Rs (Reduce, Reuse, and Recycle) embedded in international legislation and regulations should be used to prepare a framework for more humane animal research. As observed, the progress in tissue engineering and regenerative medicines was deemed valuable to develop disease models [10]. The development of successful *in vitro* disease models often requires a scaffold or support material to grow the disease-relevant cells for further analysis. Precursor materials for such purposes are known as 'biomaterials' which must be cytocompatible, biodegradable, and cytologically inert or supportive of cellular activity [11]. A multitude of such components is used widely for tissue engineering and biomedical engineering purposes. However, few have been

successfully reused to model different human diseases for research purposes in the last decade.

This chapter will focus on a few such naturally occurring components used as a precursor for disease modeling in recent times and highlight their success. Identification of new and potential biomaterials for diverse purposes will be an additional requirement in the future.

2. BIOMATERIALS

The discovery and development of biomaterials for medicinal purposes began in the eighteenth century when silk-based sutures were used to treat wounds. However, scientific usage of biomaterials can be traced back to the 1960s when biomaterials' requirements were formulated [12]. By definition, biomaterials should be biocompatible and should not exhibit any cytotoxicity when implanted in the body. The primary purpose of using biomaterials was to enhance the functioning of diseased or injured organs by treating or replacing the tissues [13]. First-generation biomaterials are generally referred to as 'nonresponsive or inert' and fabricated to be biostable. Materials such as silicones, ceramics, and metals were frequently used for implants for different physiological requirements during the 1960-80s. Second-generation biomaterials developed in the late 1990s to 2000s are designed to be biodegradable and responsive to the tissue microenvironment. For example, Poly (glycolic acid), poly (lactic acid), and polycaprolactone are developed and used for bone tissue engineering. In recent years, scientists have focused on using naturally occurring biomaterials to incorporate more biologically relevant aspects such as sustained degradation, desired porosity, and ease of fabrication. Naturally available biomaterials exhibit minimal cytotoxicity and other superior qualities such as cell adhesion, proliferation, and migration (Fig. **4.1**). Naturally occurring biomaterials can be of plant or animal origin. The following section will focus on such naturally occurring biomaterials of plant and animal origin and their usage in biomedical and tissue engineering.

2.1. Biomaterials Originated from Plant

Different carbohydrate-based polymers isolated from plant sources belonged to this group due to their capacity to produce diverse 2D and 3D structures under a controlled environment. Such assemblies with controllable pore size and tunable mechanical strength are widely used for tissue engineering and biomedical purposes.

CHAPTER 5

Synthesis and Applications of Bacterial Cellulose Composites

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Abstract: Bacterial cellulose (BC) has been attracting attention for its utilities in a variety of applications. Its nanofibrous nature offers a high surface area for the formulation of composites through physical, chemical, or biological methods. BC composites have been formed by combining with a wide range of molecules to impart additional functions. This chapter summarizes the additives and techniques to modify BC to form nanocomposites for applications in different industrial sectors. The chapter starts with an overview of BC's unique properties that are essential for composite design. The types of additives or reinforcement agents utilized to form composites are discussed, followed by techniques employed to formulate the composites. The last section showcases the applications of BC and BC composites in the areas of pharmaceuticals, food, diagnostics, cosmetics and as a general matrix.

Keywords: Artificial meat, BC bioprocessing, Biosensors, Cellulose nanocomposite, Drug delivery, Optoelectronics.

1. INTRODUCTION

Cellulose is one of the most abundant biopolymers on earth. It is synthesized by a variety of organisms, including plants [1], algae [2], marine animals such as tunicates (urochordates) [3] and bacteria [4], with the plant cellulose (PC) being the most common form of the material. However, the most enigmatic source of cellulose is that obtained from the members of the bacterial family *Acetobacteraceae* of the genus *Acetobacter, Gluconobacter, Gluconacetobacter,*

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and *Komagateibacter.* Most of the cellulose-producing species now come under the genus *Komagateibacter* with the type species *Komogateibacter xylinus* [5]. Similar to PC, cellulose produced by bacteria (BC) is also made up of glucose units linked through β-1,4 linkages [6]. Nevertheless, BC as obtained from the microbes is unique being the purest form of the polymer available in nature, and is synthesized as an extracellular product by the bacteria. The diameter of BC fibers typically ranges from 10-50 nm. When compared to PC, BC exhibits distinct physical characteristics, such as high purity, crystalline nature, higher biodegradability, and higher tensile strength [7, 8]. Furthermore, the naturally obtained nanofibrous structure, biocompatibility, and higher water retention capacity make them attractive for biomedical applications [9 - 11]. The high surface area to volume ratio of the nanofibers mimics the morphology of the extracellular matrix. Modifications to the nanofibers allow not only loading of molecular cargoes (*e.g.,* drugs) but also the modulation of the cargo release increasing its applications in localized drug delivery, tissue regeneration, and as wound healing scaffolds [12].The integration of nanotechnology concepts and functionalization of BC has caught the interest of various industries such as food, paper, packaging, healthcare, and electronics. As a result, BC market has been demonstrating a steady growth over the past decade and is anticipated to reach a market size of USD 1062.6 million by 2028, with a compound's annual growth rate of 13.3 percent during the writing of this review [13].

BC is chemically synonymous with PC. During the microbial fermentation, glucose is metabolized to linear β-1,4-glucan chains. Cellulose consists of methanol group ($-CH_2OH$) at carbon 6 and hydroxyl groups (-OH) at carbons 2 and 3. Despite the presence of these hydrophilic groups, BC is insoluble in common solvents. The widely accepted explanation has been attributed to the strong intermolecular hydrophobic interactions [14] and/or hydrogen bonds of the cellulose chains. These hydrogen bond interactions induce the formation of crystalline regions [15]. The abundance of hydroxyl and methanol groups permits functionalization for the design and development of BC composites. However, in a recent publication, the contribution of hydrophobic interactions have been revisited (REF: https://www.mdpi.com/1420-3049/28/10/4216).

The chapter summarizes a variety of molecules that have been combined with BC to form composites, followed by methods of functionalization (*i.e.,* chemical, physical, biological), including the time point (*i.e.,* during or after fermentation). The advancements in the use of BC and its composite focusing on its applications in the areas of pharmaceuticals, cosmetics, food industry, immobilization platform and diagnostics are also discussed.

2. PROPERTIES OF BACTERIAL CELLULOSE

BC is a nanofibrous matrix typically synthesized by aerobic bacteria of the genus *Komagataeibacter* from the *Acetobacteraceae* family, produced at an optimum temperature range of 25 to 30°C and the pH range of 3 to 7 [16]. Compared to PC, BC has tunable physical properties and is produced in highly pure form, free from hemicellulose, pectin and lignin, simplifying the purification process [17, 18]. The thickness, weight, and porosity of BC can be varied by optimizing the sugar source, bacteria strain, choice of porogens, and incubation duration [6]. The nanofibrous pellicles produced through static culture are processed to obtain BC with different formats such as dry BC film, thin BC film, BC hydrogels, aerogels, or foams by employing different processing methods. The physical properties of BC can be tuned by processing that changes the crystallinity and transparency of BC matrices. The presence of nanofibers in BC provides high surface area to volume ratio. These characteristics extend the opportunity for strong interactions with other substances such as water, biomaterials, nanoparticles, and drug molecules [19]. BC matrix also shows interesting optical properties. It allows light transmission, which is generally impossible for PC [20]. PC requires chemical processing to produce nanocrystals/nanowhiskers-based films to allow light transmission. Inherent BC light transmission property allows for the design of light-sensitive composites.

In its native state, BC pellicle can hold up to 99% water of its own dry weight. However, the water holding capacity of BC changes depending on the drying technique used. For example, 3D matrices obtained from freeze-drying have a higher water holding capacity than those obtained from pressure-based drying. This is due to variations in thickness and volume, which affect the availability of hydroxyl groups to interact with water molecules [21]. The abundance of hydroxyl groups inBC provides higher water absorption and holding ability than PC, which is attributed to inter and intramolecular hydrogen bonding with the nanofibrous matrix [22].This unique property makes BC a suitable material for designing composites for applications that require water absorbing matrices such as wound dressings. Additionally, BC possesses higher tensile strength [200-300 MPa) and higher Young's modulus of 15 GPa when compared to PC [18, 23]. The thermal stability of BC membranes is also high with a decomposition temperature range of 340°C to 370°C – making it a suitable material for designing thermally conductive composites [24]. The water absorption ability and thermal stability of BC can be further modified with additives.Through physical methods, such as impregnation or layering, additives and reinforcement agents can form hydrogen bonds with the hydroxyl groups within the matrix. To form composites, chemical conjugation of additive molecules with the hydroxyl or methanol groups is often employed instead of physical methods.

CHAPTER 6

Biological Membranes: Nature's Own Nanomaterials

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Abstract: Cellular membranes are known to participate in several biological functions in addition to providing cellular integrity. Interestingly, in a small nanometric thickness, they offer a range of polarity, viscosity, and heterogeneity in addition to their lateral organizational diversity, which makes biological membranes a unique medium to carry out several cellular reactions. In this chapter, we have discussed the membrane architecture, physical properties, and its contribution to several biological functions.

Keywords: Acylation of proteins, Biomembrane architecture, Electron transfer, Glycosylation, Lipid biosynthesis and sorting, Membrane heterogeneity, Membranes, Oxidative phosphorylation, Protein sorting, Signal transduction.

1. INTRODUCTION

Membranes separate the interior of a cell from its external environment and ascertain the integrity of internal compartments, such as the nucleus and cytoplasmic organelles [1]. Additionally, it lends selective permeability to cells for various molecules and ions. Lateral heterogeneity along the bilayer normal offers a unique feature to the membrane for its selective permeability. Interestingly, the membrane provides a dramatic gradient of polarity, fluidity, segmental motion, and water penetration along a 20 Å thickness of half [2, 3]. Moreover, the membrane provides a meeting point for lipids and proteins, which is essential for the cellular functions of several membrane proteins [2, 4]. In the last couple of decades, material science research has accumulated tremendous momentum in developing function-driven nanomaterials. However, we are yet to match the functional diversity of biomembranes. Biological membranes are mechanically stable and optimized to function on nanometer to micrometer length

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scales, like other materials and nanomaterials. Interestingly, biological membranes are tunable through the modulation of their lipid composition [5]. Membranes provide a platform for the functioning of several membrane proteins. The function of membrane proteins depends on the physicochemical properties of the biological membranes, which can be modulated by altering the lipid composition [6]. Cholesterol is an important constituent of biological membranes whose abundance changes with age and different pathophysiological conditions. Therefore, membrane proteins, especially receptor proteins demonstrate attenuated functions with increasing concentrations of membrane cholesterol [7, 8]. Overall, like any other material, the physical and functional properties of biomembranes are regulated by their lipid composition. The vast diversity of membrane lipids offers unlimited opportunities to tune the physical properties as well as functions of biomembranes.

1.1. Architecture of Biomembranes

A general representation of the biomembranes, where associated and transmembrane proteins are interacting with the lipid bilayer, is shown in Fig. (**6.1**). The membrane provides an exclusive environment for proteins to assume biologically active structures, display dynamics, and carry out appropriate biological functions with great precision and high yield. Membrane proteins respond to external stimuli, help in the selective transport of molecules, and participate in electron transport [1].

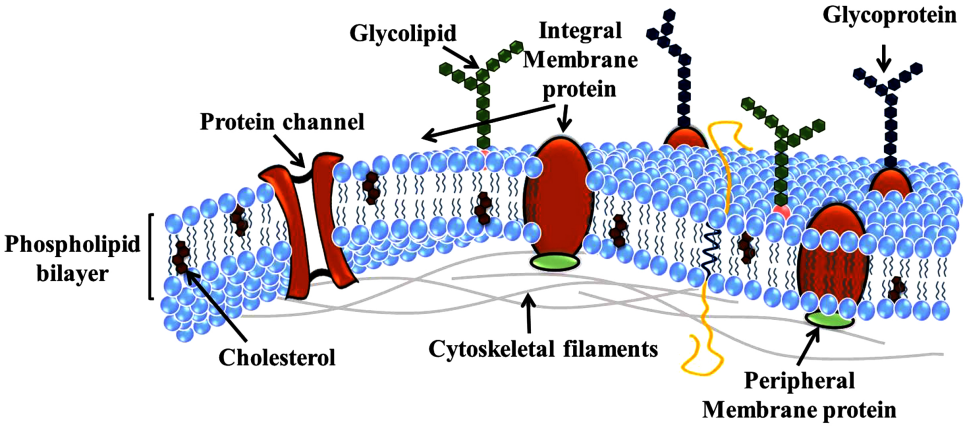

Fig. (6.1). Representative structure of biomembranes, where the membrane is encompassing the associated and transmembrane proteins.

Generally, lipids are classified into three types, *viz.,* phospholipids, glycolipids, and sterols. Phospholipids shown in Fig. (**6.2a**) have two hydrophobic fatty acyl

chains linked to a glycerol backbone through an ester bond, and the polar head group is attached to the phosphate backbone through phosphor-ester linkage [9]. Separated hydrophilic (head group) and hydrophobic (fatty acyl tail) regions make a lipid molecule amphipathic in nature, which is critical for spontaneous bilayer formation. In a bilayer, hydrophilic heads are exposed to water, whereas hydrophobic tails are pointed toward each other and hidden in the bilayer [9]. This self-assembly of the phospholipid bilayer segregates the internal constituents of the cell from the external environment. The same principle is recapitulated in the formation of distinct organelles [6]. Commonly found phospholipids in biological membranes are phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylinositol (PI), and sphingomyelin (SM) [1]. Glycolipids shown in Fig. (**6.2b**) unlike phospholipids either contain glycerol or sphingosine backbone and sugar instead of phosphate head [9]. The abundance of glycolipids is only 2-10% of the plasma membrane [10]. Cholesterol (sterol) comprises a hydroxyl group (hydrophilic head), a four-ring steroid structure, and a short side chain (hydrophobic tail) as shown in Fig. (**6.2c**) [9]. The polar hydroxyl group of cholesterol remains close to the phospholipid head group, and the steroid ring interacts with the fatty acyl chain near the interfacial region, thereby reducing the mobility near the phospholipids head group region. It also hinders the interaction between fatty acyl tails of phospholipids and maintains the membrane fluidity at a lower temperature [1].

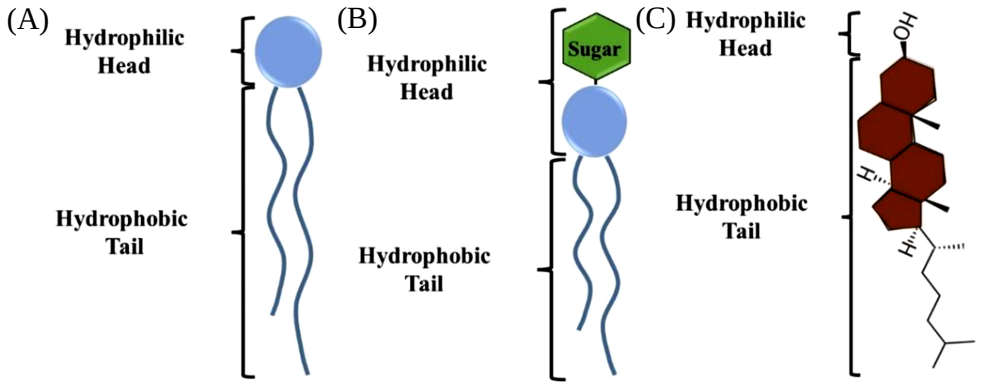

Fig. (6.2). Schematic representation of (**A**) Phospholipid (**B**) Glycolipid and (**C**) Cholesterol.

The fluid mosaic model proposed the rotational and lateral diffusion of lipids and proteins within the bilayer [11]. The diffusion of either lipid or protein in the bilayer can easily be visualized from fluorescence recovery after photobleaching (FRAP) experiments utilizing different fluorescent markers [12]. Further, membranes with short-chain fatty acids remain fluid at low temperatures, because

CHAPTER 7

An Overview of Microbe-Based Drug Delivery Systems

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Abstract: Drug delivery systems are cargos delivering drugs to desired cells, tissues, organs and sub-cellular organelles for better drug release and absorption. These were introduced to improve the pharmacological activities of therapeutic drugs, and overcome problems like low bioavailability, lack of selectivity, drug aggregation, poor biodistribution, limited solubility, and reduced side effects associated with therapeutic drugs. Novel drug delivery systems have contributed immensely towards improving the lifestyle of patients suffering from varied pathological conditions, but drug resistance developed during the treatment becomes a major concern, fueling the need to find an alternative effective transport system. Numerous advancements have led to the development of active carriers for more targeted action along with improved pharmacokinetic behavior. Microbe-based drug delivery systems are one such system providing non-toxic, safe, site-specific targeted actions with minimal side effects. For the development of highly effective delivery carriers, microorganisms' properties like self-propulsion, *in-situ* production of therapeutics, increased immunity, tumour cells' penetration, *etc*, play an important role. The microbe-based drug–delivery systems can be classified into- bacterial, fungi, viral and algae-based drug-delivery systems. Intra-tumor injection, nasal administration and oral administration are preferred routes of administration for such delivery systems depending upon the drug's nature, administration ease, and intended location. Bacteria, anticancer oncolytic viruses, viral immunotherapy and viral vectors are engaging areas of biotechnological research. The microbe-based drug delivery system with reduced toxicity and side effects will surely serve as a futuristic advanced carrier to improve patient's health. The chapter provides a general overview of the novel approach of microbe-based drug delivery and its applications.

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Keywords: Active carriers, Bacteria, Bio-hybrids, Bio-nanocapsules, Bactofection, Envelopes, Intra-tumor, Targeted drug delivery, Microbe-based drug delivery systems, Microbes, Novel drug delivery systems, Oncolytic immunotherapy, Oncolytic virotherapy, Polymers, Peptides, Phages, Routes of administration, Stimuli, Spores, Viral delivery.

1. INTRODUCTION

Conventional drug delivery systems spanning tablets, capsules, injections *etc.* have been subject to numerous undesirable effects, along with a decrease in therapeutic efficacy, owing to their lack of target specificity and tendency to interact with receptors at sites other than the target region. Oral or parenteral administration of antineoplastic drugs, for example, has by severe side effects, ranging from nausea to organ damage. To overcome these limitations, attention has been shifting toward the development of novel delivery systems [1].

Novel Drug Delivery System (NDDS), are specialized drug delivery systems that have been designed in order to improve conventional systems. They are used to improve the efficiency of drug targeting and delivery, in a way to maximize the therapeutic effect, while keeping the adverse effects to a minimum. The concept of NDDS has been subject to a number of modifications and transformations, each of which has been aimed at further perfecting the efficacy and compliance, while also reducing any unwanted complications. The ultimate goal of many advances in the field, from micro-encapsulation and liposomal technology to epithelial and transdermal targeting and extracellular matrices, has been the effective administration of drugs for safe and clinically sound therapeutic effects [2].

One such avenue which is being explored is the use of microbes as drug carriers. Bacteria, viruses, and even fungi to some extent, are being employed to carry drugs to the target site (Fig. **7.1**). Their growing popularity is backed by their easily manipulative nature, especially when it comes to disarming pathogenic strains and instead using their mechanisms to achieve delivery.

The most frequently utilized organisms are bacteria, ranging from whole cells to cell toxins and ghost cells (which essentially comprise only the outer shell of the bacteria, surrounding a drug core). The rationale behind their use includes their ability to effectively enter the target cells. An example of such a bacterium is *Clostridium novyi NT,* which can enter and kill tumour cells. Viral carriers have been tried for the delivery of biomolecules, especially genes and nucleic acids, and polypeptides, in systems known as ‘Virosomes'. Fungi, while not directly used as carriers, act as a source of chitin and chitosan, and some other polymers, which are widely used in designing drug delivery systems, such as nanoparticles.

While the use of microbe-based drug delivery systems is still new, and a lot of research is still pending in the domain, their most important applications are in the therapy of cancer and inflammatory bowel disease [1].

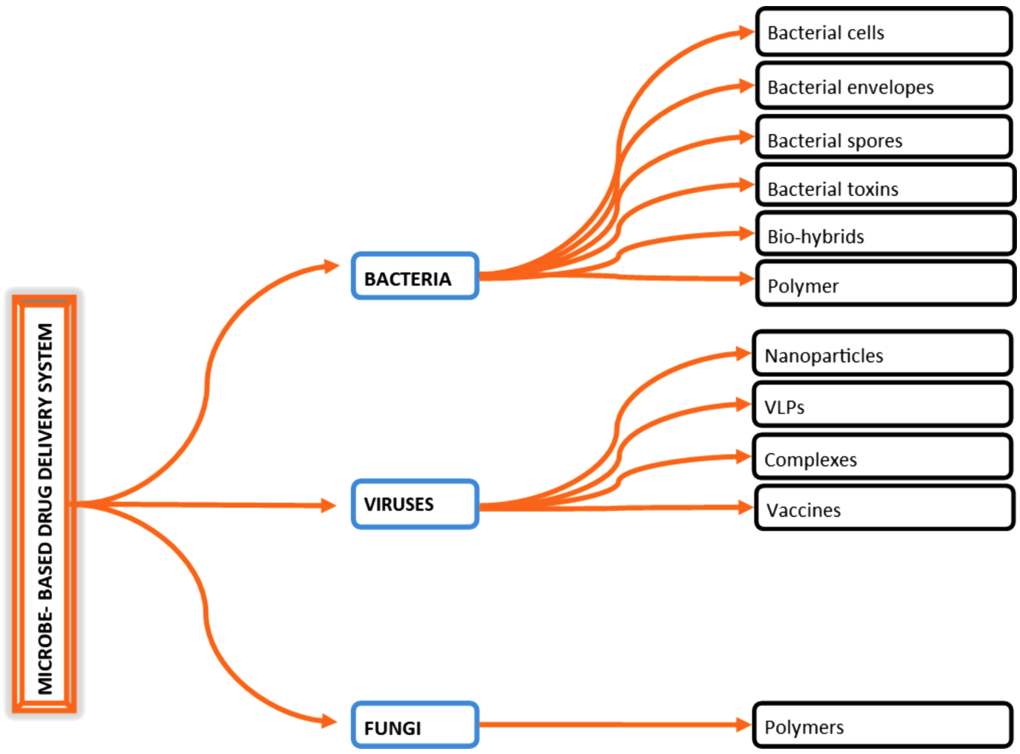

Fig. (7.1). Microbe-based drug delivery system.

2. HISTORICAL ASPECTS OF MICROBE-BASED DRUG DELIVERY SYSTEMS

The use of microbes as therapeutics in the treatment of contagious diseases was first documented by Vautier in 1813. Following this, during the treatment of cancer patients, *Clostridium perfringens* were used to produce gas gangrene to kill tumour cells. Later, it was discovered that a number of bacteria, such as *Bifidobacterium spp., L. monocytogenes, E. coli*, Mycobacterium bovis and *Clostridium,* showed a tendency to accumulate at the site of tumour. A major advancement in the use of bacterial drug delivery systems (DDSs) was the discovery of magnetotactic bacteria and their specialised magnetosomes, by Salvadore Bellini, in 1958. This group of bacteria can be used for magnetic guiding.

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