

## Review Article

# Natural Products: A Minefield of Biomaterials

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The development of natural biomaterials is not regarded as a new area of science, but has existed for centuries. The use of natural products as a biomaterial is currently undergoing a renaissance in the biomedical field. The major limitations of natural biomaterials are due to the immunogenic response that can occur following implantation and the lot-to-lot variability in molecular structure associated with animal sourcing. The chemical stability and biocompatibility of natural products in the body greatly accounts for their utilization in recent times. The paper succinctly defines biomaterials in terms of natural products and also that natural products as materials in biomedical fields are considerably versatile and promising. The various types of natural products and forms of biomaterials are highlighted. Three main areas of applications of natural products as materials in medicine are described, namely, wound management products, drug delivery systems, and tissue engineering. This paper presents a brief history of natural products as biomaterials, various types of natural biomaterials, properties, demand and economic importance, and the area of application of natural biomaterials in recent times.

## 1. Introduction

A biomaterial is regarded as any nondrug material that can be used to treat, enhance or replace any tissue, organ, or function in an organism [1]. While the definition of biomaterial was reframed as a *nondrug substance suitable for inclusion in systems which augment or replace the function of bodily tissues or organs* [2]. This definition explicitly described biomaterial in relation to drugs and as such, there is a need to clarify the impression that natural products are synonymous with drugs. The definition implies that natural products can be applied as biomaterials by eliminating the ambiguity always associated with natural products as drugs. It must be emphasized that this definition is not regarded as one of the most popular and is not often cited as this one which defines *biomaterial as a nonviable material that intends to interact with physiological environment* [3]. However, in this study, the following definition will be adopted: *biomaterial can be defined as any substance (other than a drug) or combination of substances synthetic or natural in origin, which can be used any time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ or function of the body* [4]. It must be noted that in this study the substances are natural in origin.

**1.1. Economy.** The field of biomaterials working under biological constraints is rapidly expanding. It is considered that this domain represents 2-3% of the overall health expenses in developed countries [5]. There are over 13 million medical device implants annually in USA. However, all these devices are prone to incomplete or nonspecific cellular healing which may lead to the ultimate failure of the device [6].

**1.2. History.** The new interest in natural biomaterials could really be considered as a renaissance. Historians have traced the use of sutures made from animal sinew to ancient Egypt, while some say they were used even earlier [7]. The ancient Egyptians were regarded as the first to use biomedical materials, employing coconut shells to repair injured skulls; wood and ivory as false teeth and these dated as far back as 3000 BC [8]. Some of the earliest biomaterial applications were as far back as ancient Phoenicia where loose teeth were bound together with gold wires, tying artificial teeth to neighbouring teeth [2].

As early as the first century AD in both Greece and India, physicians were using natural biomaterials while performing plastic surgery to repair mutilations from battle

and punishment. There are even accounts of some of these physicians treating disemboweled soldiers to good effect [7]. The earliest recorded hip replacement surgery took place in Germany in 1891 AD, and in this instance ivory was used. This material is favoured for its relatively inexpensive cost although it also turned out to have useful biomechanical bonding qualities, which makes it well suited to work with human body tissue [8]. From as early as a century ago artificial, materials and devices have been developed to a point where they can replace various components of the human body. These materials are capable of being in contact with body fluids and tissues for prolonged periods of time, whilst eliciting little if any adverse reactions occur [9].

In the early 1900's, bone plates were successfully implemented to stabilize bone fractures and to accelerate their healing. While by the time 1950's and 60's, blood vessel replacement was in clinical trials artificial heart valves and hip joint were in development [2]. It is believed that by knowing the history of the development of biomaterials we can have a better perspective of how the state of the art is progressing. The big question with biomaterials is *How will this product perform better than those available today?* It is all too easy when performing research in today's compartmentalized and specialised society to forge the bigger picture. In the past, the research approach to biomaterials was spurred on by innovative and creative doctors who used whatever they thought might work to fix a problem sometimes with wonderful results but with extremely high risk. Today's researchers are much more focused into improving medicine methodically and with as little risk to patients as possible. The road has been long and treacherous; nature has given us many amazing remedies put together by millions of years of evolution [10].

Theoretically, any material natural or man made can be a biomaterial as long as it serves the stated medical and surgical purposes. The development of biomaterials is not a new area. It encompasses elements of medicine, biology, chemistry, tissue engineering, and materials science. Nevertheless, the demand for biocompatible, biodegradable, and bioresorbable materials has increased dramatically during the last decade. An ideal biomaterial is one that is nonimmunogenic, biocompatible, and biodegradable, which can be functionalized with bioactive proteins and chemicals. In particular, biodegradability is one of the essential properties of the biomaterials [11]. It must be emphasized that the key factors in biomaterial usage are its biocompatibility, biofunctionality, and availability to a lesser extent.

Biomaterials are ultimately intended for implantation in or on the human body. They can be designed with a range of properties that are capable of either promoting or inhibiting specific host cell and tissue responses [12]. Biomaterials also refer to biologically-derived materials used for their structural rather than biological properties, for example, collagen (a protein found in the skin, connective tissues, and bone) as a cosmetics ingredient. Also carbohydrates (biotechnologically modified) are being used as lubricants for biomedical applications and as bulking agents in the food industry [1]. Not until recent times have naturally derived biomaterials been explored as facilitators and promoters of

healing and regeneration. Today, biomaterials of all types are being used for everything from wound dressing to tendon and ligament repair. Extensive experimentation has been undertaken to identify the composition, mechanical properties, and in vivo response of naturally derived biomaterials. The choice of biomaterials depends on the type of procedure being performed, the severity of the patient's condition, and the surgeon's preference. To be successful, the implant should effectively repair the defect it covers without eliciting an adverse tissue reaction while maintaining mechanical and biological integrity for a desired amount of time from a few weeks to several years. The prime reason biomaterials have come about is to provide a remedy for surgical problems [10].

Biomaterials research is one of the most important fields of modern medicine. Biomaterials are used in organ implants, wound healings, drug delivery, and so forth. It was suggested that for many reasons natural biomaterials are the most preferred ones; they are biodegradable, biocompatible, and nontoxic [13]. Biomaterials can be divided into four major classes of materials, namely; polymers, metals, ceramics (including carbons, glass-ceramics, and glasses), and natural materials (including those from both plants and animals). Composite materials are the ones which are comprised of two or more different classes of materials and they are regarded as the fifth class of biomaterials [14]. It is observed that metals rarely occur in nature as a single entity; hence, they are synthesized from their compound ores such as oxides, sulphides, and carbonates with the exception of rare metals like gold, and platinum. Natural metals have found application as dental materials in ancient times. Recently, the applications of metals as natural biomaterials are not documented. There is an international resurgence of interest in natural products as a source of novel bioactive substances for the development of novel drugs and therapies, the same trend is observed in the application of natural products as materials in medicine. By 2020, Ireland will have a leading capacity in the utilization of natural biomaterials and nutraceuticals [15].

There are several materials derived from the animal or plant world being considered for use as biomaterials and they are called natural biomaterials. One of the advantages of using natural materials for implants is that they are similar to materials, and are familiar to the body systems. In this regard, the field of biomimetics (or mimicking nature) is growing. However, natural materials can be subjected to problems of immunogenicity. Another problem faced by these materials, essentially natural polymers, is their tendency to denature or decompose at temperatures below their melting point. This severely limits their fabrication into implants of different sizes and shapes. Natural materials do not usually offer the problems of toxicity often faced by synthetic materials. Also, they may carry specific protein binding sites and other biochemical signals that may assist in tissue healing or integration [16]. This paper intends to highlight the different types of natural products that are currently being employed as biomaterials, state their advantages and disadvantages, and also to summarize the areas of application in the medical industry.

## 2. Natural Products

Biological structures have always been a source of inspiration for solving technical challenges in architecture, mechanical engineering, or materials science. Nature has developed—with comparatively few base substances, mainly polymers and minerals—a range of materials with remarkable functional properties [17]. Natural was defined as something that is present in or produced by nature and not artificial or man made, and most often the definition is assumed to mean something good or pure [18].

The term natural products is quite commonly understood to refer to herbs, herbal concoctions, dietary supplements, traditional medicine, or alternative medicine [19]. It must be stated that while the stories of herbs and drugs are very much intertwined, it needs to be fully appreciated that the use of herbs as natural product therapy is different from their use on the platform of drug discovery and further development [20]. Natural products are regarded as chemicals, but they are not just accidents or products of convenience of nature. More than likely, they are a natural expression of the increase in complexity of organisms [21]. There are several definitions of natural products, and the common trend is that a natural product is a chemical compound or substance produced by a living organism. The living organism is regarded to be found in nature, and that they have pharmacological or biological activity for use in pharmaceutical drug discovery and drug design. A natural product can be considered as such, even if it can be prepared by total synthesis. It must be recognized that not all natural products can be fully synthesized, and many natural products have very complex structures that are too difficult and expensive to synthesize on an industrial scale. Such compounds can only be harvested from natural sources—a process which can be tedious, time-consuming, and expensive as well as being wasteful of the natural resource [22, 23]. It will be realised that natural products are regarded as only beneficial to the pharmaceutical industry at the expense of others like agriculture, food and even the chemical industry. Hence, there is a need to redefine natural products, and according to the biology dictionary definition, natural products depend on the industry; medicine and pharmaceuticals; healthcare and nutritional supplement; agrochemical; food and flavouring. In this study, *natural products are regarded as chemical substances that are produced by living organisms with the intent of their application in/as biomedical materials.*

It must be noted that interest in natural sources to provide treatments for pain, palliatives, or curatives for a variety of maladies or recreational use dates back to the earliest parts of history. Also, several sources of information on natural products such as pharmaceutical products are well recorded and documented [20]. There are numerous studies on the applications of natural products as biomaterials, but a comprehensive summary has not been reported. Hence this paper intends to give a comprehensive review of natural product usage as biomedical materials.

Natural products can come from anywhere; generally, they are either of prebiotic origin or originate from microbes,

plants/animal sources [24]. Suffice it to say that natural products can come from any point or level on the phylogenetic tree. When searching for natural products, one should never feel that a form of life is too low, simple or grotesque to provide a compound of interest. However, before one goes marching out into the woods, sailing out into the sea, climbing the highest mountains, or descending into the deepest caves, it is appropriate to perform a little bit of research, and hence a visit to the library becomes the first step in any search for a natural product. Ideally, it is important to know the history, folklore, origin of use, source, chemical structure, availability, and method of preparation, pharmacology, toxicology, and therapeutics of any natural products [20]. It is observed that it can be challenging to obtain information from practitioners of traditional medicine—which is always well versed in natural products—unless a genuine long-term relationship is made. Natural products may be extracted from tissues of terrestrial plants, marine organisms, or microorganism fermentation broths. A crude extract from any one of these sources typically contains novel, structurally diverse chemical compounds. The sources of natural products are as outlined after which a brief introduction of biomaterials will come up in the next section.

It is noted that several opportunities abound in nature that can provide natural products, and these opportunities can present themselves from almost any niche of nature and most likely some that have not even yet been discovered.

Microorganisms have proven to be an excellent source of natural products including polyketide and peptide antibiotics as well as classes of other biological active compounds [25]. It is noteworthy that some of these compounds when originally discovered failed in their development and their original uses as either antibiotics or as agricultural fungicides [20]. Microbes can be of any sources be it aerial, terrestrial, or even marine. It has been well reported in a wide range of applications in drug synthesis and design. Also, it is used in the biomedical industry as materials for wound management and drug delivery system among others. The diversity of microorganisms is of a staggering quantity, and only an extremely small proportion of bacteria and fungi have been examined for the production of potentially useful secondary metabolites. Bacteria, smuts, nests, yeasts, moulds, fungi, and many other forms of what we consider to be primitive life can be very useful [20].

People most commonly think of plants first when talking about natural products, but trees and shrubs can also provide excellent sources of biomaterials. Plants produce a variety of different types of compounds including biologically active proteins. Some of these types of compounds are even shared with other organisms, and they include such chemical families as lectins, defensins, cyclotides, and ribosome-inactivating proteins [25]. Ribosome-inactivating proteins are a group of proteins exhibiting a wide spectrum of biological activities, including a ribonucleolytic activity for which the group is named. Plant antimicrobial peptides comprise another large group of biologically active compounds. This group of compounds can be further subdivided into thionins, defensins, cyclotides, and lectins. Thionins are

small proteins that selectively form disulfides bridges with other proteins or form ion channels in membranes. This ability to make membranes more permeable suggests the potential for antimicrobial activity. Defensins are cysteine-rich peptides that also permeabilize membranes but appear to be very specific in their activity. Finally, lectins are proteins that have a noncatalytic domain that binds reversibly to specific carbohydrates; this activity encompasses potentially a wide spectrum of biological activities. Plants have been, over time, an extremely popular source of natural products [26–29]. Compounds isolated and identified from this source will undoubtedly continue to make strong contributions. Plants as biomedical materials have found applications in wound management, drug delivery systems, and medical fibres and textiles.

Various polypeptides of interest have been isolated from the venom of arachnids and anthropods that prey on insects [25]. Insect peptides have been the subject of research into the immune defense of insects but have not yet been investigated for effects and potential benefit in humans. Compounds from this peptide group include such sources as the termite (*Pseudacanthotermes spiniger*), the mosquito (*Anopheles gambiae*), the moth (*Heliothis virescens*) and the beetle (*Oryctes rhinoceros*) [20]. Insect derived natural products offer another strong potential avenue for the development of future biomaterials. However, silk produced by silkworm, *Bombyx mori*, has excellent properties such as biocompatibility, biodegradation, nontoxicity, and adsorption properties. It has been commercially used as a biomaterial suture for decade and its application also includes wound management, enzyme immobilization matrices, vascular prostheses, structural implants among others [11, 30–35].

Animals, whether highly developed or poorly developed, whether they live on land, in the sea, or in the air can be excellent sources of natural products [20]. Research into a variety of antimicrobial peptides, such as megamins, defensins, cathelicidins, and protegrins generated by vertebrates has, over recent time, become popular. Cathelicidins-type peptides are a broad range of antimicrobial proteins that have been isolated from rabbits, mice, sheep, and humans. Some compounds have been the subject of substantial research, and they offer potential opportunities in the areas of cardiovascular function, immune and central nervous system functions. A typical application is in the area of tissue engineering and these include the use of tissue replacement from animals, dead corpses, and the man himself. These methods are known as xenograft, autograft, and allograft respectively.

The first discovery of a marine-based biologically active compound of interest was really quite by accident approximately 10 years after the end of World War II [36]. The marine environment, arguably the original source of all life, is a rich source of bioactive compounds [37–43]. More than 70% of our planet's surface is covered by oceans, and some experts feel that the potentially available biodiversity on the deep sea floor or coral reefs are greater than those existing in the rainforests [44]. The search for new biomedical from marine organisms resulted in the isolation of more or less 10,000 metabolites with a broad spectrum of biological

activities [45, 46]. There are wide applications of natural products obtained from the marine world such as biomedical materials. A typical example is the successful use of natural coral as a bone graft substitute in tissue engineering.

### 3. Bioceramics

It has been accepted that no foreign material placed within a living body is completely compatible. The only substances that conform are those manufactured by the body itself (autogeneous) and any other substances are recognized as foreign, they initiate some type of reaction (host tissue response). Bioceramics are classified according to their bioactivity, and they are, namely, bioinert (alumina dental implant), bioactive [hydroxyapatite,  $\text{Ca}(\text{PO}_4)_2$ ], surface active (bioglass), and bioresorbable [tricalcium phosphate implant,  $\text{Ca}_3(\text{PO}_4)_2$ ] [2].

In the early 70's, bioceramics were employed to perform singular biologically inert roles, such as to provide parts for bone replacement. The demands of bioceramics have changed from maintaining an essentially physical function without eliciting a host response to providing a more integrated interaction with the host. Bioceramics potentially can be used as body interactive materials, helping the body to heal, or promoting regeneration of tissues, thus restoring physiological functions. Ultimately, the field of bioceramics is fundamental to advances in the performance and function of medical devices and is a critical part of medicine and surgery. The correlations between material properties and biological performance will be useful in the design of improved bioceramics, particularly to overcome the problems of implant rejection and related infection [2]. Bioceramics have been proposed for biomedical applications such as dental restorations, middle ear reconstruction, rebuilding of facial and cranial bones, and filling of bony defects, to name a few [2, 47]. It was reported that commercially available porous bioceramics originate from two sources, namely; hydroxyapatite (e.g., Pro osteon) or bone (e.g., Endobon) [48].

In this paper, bioceramics that are sourced from natural products are to be considered and there are potentials in shells, coral, bone and soil/mineral.

**3.1. Bone.** Bone consists of a compact tissue type (cortical bone) and a spongy porous material (trabecular bone). In both tissue types, the basic building block is a bone lamella, typically about  $5\ \mu\text{m}$  thick. In cortical bone, lamellae form laminated cylindrical composite structures built around blood vessels, which are denoted as secondary osteons [49]. The mechanical performance of bone, often coined bone quality, does not only depend on the shape and the amount of the bone (as estimated by the bone mineral density, BMD), but also on its architecture and on the quality of the bone material [50, 51].

Bone can be utilized as a biomedical material when it is used to substitute a damaged part. The grafting involving the use of the patient's own bone in replacing the fractured part is known as *autografting*, while *allografting* is the use of another human being's bone and often it involved the utilization



TABLE 1: Chemical composition of some calcium phosphates minerals.

Ca:P	Mineral name	Formula	Chemical use
1.0	Monetite	$\text{CaHPO}_4$	Dicalcium phosphate (DCP)
1.0	Brushite	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	Dicalcium phosphate dihydrate (DCPD)
1.33	—	$\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$	Octacalcium phosphate (OCP)
1.43	Whitlocksite	$\text{Ca}_{10}(\text{HPO}_4)(\text{PO}_4)_6$	—
1.5	—	$\text{Ca}_3(\text{PO}_4)_2$	Tricalcium phosphate (TCP)
1.67	Hydroxyapatite	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	—
2.0	—	$\text{Ca}_4\text{P}_2\text{O}_9$	Tetracalcium phosphate

of cadaver. Lastly, when animal bones such as rabbit, pig, dog among others are used as replacement this is known as *xenografting* [14].

Bone typically consists by weight of 25% water, 15% organic materials and 60% mineral phases. The mineral phase consists primarily of calcium and phosphates ions, with traces of magnesium, carbonate, hydroxyl, chloride, fluoride, and citrate ions. Hence, calcium phosphates occur naturally in the body, but they occur also within nature as mineral rocks, and certain compounds can be synthesized in the laboratory. Also, certain compounds are useful for implantation in the body since both their solubility and speed of hydrolysis increase with decreasing calcium-to-phosphorus ratio [48]. Table 1 summarizes the mineral name, chemical name, and compositions of various phases of calcium phosphates. Driessens stated that those compounds with a Ca/P ratio of less than 1 : 1 are not suitable for biological application [52].

The main crystalline component of the mineral phase of bone is a calcium-deficient carbonate hydroxyapatite.

**3.2. Hydroxyapatite.** This has been a well-known biomaterial since the 1960's, and it is universally accepted for the excellent biocompatibility, nondegradability, good haemocompatibility, noncarcinogenic, and nonimmunogenic reaction. It also releases calcium and phosphate ions, and it leads to osteoinduction. Hydroxyapatites are inorganic materials and based on their properties that are widely used in tissue engineering and bone replacement, it is also used as a coating for fixing prostheses [53, 54]. Hydroxyapatite has been used clinically in a wide range of forms and applications. However, one of the major contributions of clinical application of hydroxyapatite is in the form of filler in a polymer matrix [48]. The natural sources of hydroxyapatite are regarded to be safer due to their cross-reaction and other immunological reaction as compared to synthetic hydroxyapatite [54].

**3.3. Coral.** Natural coral (Porites) consists of a mineral phase principally calcium carbonate in the structural form of aragonite with impurities such as strontium, magnesium and fluoride ions, and an organic matrix. Commercially available coral (Biocoral) is used as bone graft material and has been reported to be biocompatible and resorbable [55, 56]. Natural coral graft substitutes are derived from the exoskeleton of marine madreporic corals. Researchers first started evaluating coral as a potential bone graft

substitute in the early 1970s in animals and in 1979 in humans. The structure of the commonly used coral Porite, is similar to that of cancellous bone, and its initial mechanical properties resemble those of bone. The exoskeleton of these high content calcium carbonate scaffolds has since been shown to be biocompatible, osteoconductive, and biodegradable at variable rates depending on the exoskeleton porosity, the implantation site and the species. Although not osteoinductive or osteogenic, coral grafts act as an adequate carrier for growth factors and allow cell attachment, growth spreading, and differentiation. When applied appropriately and when selected to match the resorption rate with the bone formation rate of the implantation site, natural coral exoskeletons have been found to be impressive bone graft substitutes [57]. There are several natural sources of coral and coral-derived materials, and they are resorbed slowly and substituted by host bone. Only two of the naturally occurring coral-based materials will be discussed.

Coralline apatites can be derived from sea coral and they are a naturally occurring structure with optimal strength and structural characteristics. It is known that the pores structure of coralline calcium phosphate produced by certain species is similar to human cancellous bone, making it suitable material for bone graft applications. Coral and converted coralline hydroxyapatite have been used as bone grafts and orbital implants since the 1980s, as the porous nature of the structure allows ingrowth of blood vessels to supply blood to the bone, which eventually infiltrates the implant. Several methods have been developed in producing hydroxyapatite directly from corals but two of such processes are widely utilized and reported. These techniques are hydrothermal and microwave processes, although others such as sol-gel coating are also in use among others [53].

Coral sands have the potential for a range of biomedical applications where calcium phosphates are used. There is difficulty associated with manufacturing of spherical porous powders which has increased the interest in discovering possible alternatives in nature. It was reported that under controlled hydrothermal exchange, a mix product of calcite and  $\beta$ -tricalcium phosphate can be derived from coral sand grains, and they were able to retain their porous structures. This makes them suitable for potential biomedical application as biodegradable material [58].

Corals, including those of Indian and Australian origin, have been converted to coralline hydroxyapatite successfully in the past [59, 60]. Considerable efforts are needed in order

to consider the possibilities of converting African corals to coralline hydroxyapatite especially in the west coast of the continent where these substances are present in abundance. Coral has architectural properties such as interconnected macroporosity, which can be adapted to the biological requirements of the receiver bone. Natural coral implanted into bony tissue is gradually resorbed and replaced by newly formed bone [61].

Coral has been used clinically with good results in spinal fusion or to fill periodontal defects [62–64]. The exoskeleton of coral contained a high proportion of calcium carbonate, and this has been shown to be biocompatible, bioactive, osteoconductive and biodegradable at variable rates depending on the exoskeleton porosity, the implantation site, and the species [55, 65]. Natural coral, submitted to rigorous protocols of preparation and purification can be used as a replacement for bone grafts in both orthopaedic surgery and maxilla-cranial-facial surgery.

**3.4. Shell.** There are numerous shells in nature, and some of them have been evaluated for possible biomedical applications. *Barnacle shells* are very complex and strong composite bioceramic composed of different structural units which consist of calcite microcrystals of very uniform size. These are organized in a massive microstructure toward the external shell and in mineral layers separated by organic sheets toward the internal shell. It was observed that in contrast to nacre, barnacle shell contains calcite microcrystals (instead of aragonite microcrystals and has considerable porosity when compared with nacre which is a very dense material. The different composition and microstructural characteristics should affect dissolution behaviour in the body fluids (calcite being less soluble than aragonite)-and porosity could favour binding of this material with bone [66]. An investigation showed that calcium phosphate-based bioceramics have been synthesized by using *eggshell*-derived raw materials and phosphoric acid at different mixing ratios. The mineral composition of cockle shell is almost similar to that of coral and it was suggested that cockle shell has the potential to be used as a material for orthopaedic applications [53, 65].

The shell formation process in *molluscs* is a promising model for the development of bioinspired ceramics for a wide variety of applications in fields as varied as adaptive surface coatings, corrosion inhibition, hybrid composite materials, and more. The hybrid nature of the mollusc shell in terms of both mineral and organic components makes it an ideal bioceramic materials candidate: it is porous, it is a result of sophisticated structure, and exhibits exceptional flexural, fracture strength, and toughness [66].

*Cowrie shells* of West African origin are currently being evaluated for possible applications in orthopaedics as well as dental materials. The preliminary results have shown that these shells have great potential as biomedical materials.

**3.5. Soil.** It can be deduced from Table 1 that most of the calcium phosphates are inorganic, and they do exist as minerals. It was based on this that one of the authors believed that there is the possibility of obtaining these materials from

nature. The investigation of some naturally occurring clays show that they contain some of these minerals, and also the fact that some natural practitioners employed a special type of clay in bone fracture and spinal management. Currently, work is on-going on the possibilities of using anthill as a biomedical material.

## 4. Biopolymer

Polymers play a central role both in the natural world and in modern industrial economies. Some natural polymers such as nucleic acids and proteins carry and manipulate essential biological information, while other polymers like polysaccharides—that is nature's family of sugars—provide fuel for cell activity and serve as structural elements in living systems [67]. The advantages of synthetic polymers include predictable properties, batch-to-batch uniformity, and they can be tailored easily but they are too expensive. The growing reliance on synthetic polymers has also raised a number of environmental and human health concerns. It was concluded that the focus should now be on natural polymers which are inherently biodegradable and can be promising candidates to meet different requirements [67, 68]. Emerging applications of biopolymers range from packaging, industrial chemicals, medical implant devices, to computer storage media. In this paper, the utilization of natural polymers biomedical materials will be considered. The major problems yet to be overcome with natural starting materials are their propensity for calcification and eventual biodeterioration [69]. Some of the disadvantages and advantages associated with natural biopolymers are as listed in Table 2. A study stated that polymers from natural sources are particularly useful as biomaterials, given their similarity to the extracellular matrix (ECM) other polymers in the human body [70]. Natural polymers include both ECM proteins derivatives (e.g., collagen) and some materials derived from plants and seaweed among others [71]. Biopolymers have wide applications as implantable biomaterials, controlled disease carriers or scaffold for tissue engineering.

Throughout history, humans have relied extensively on biological materials like wool, leather, silk, and cellulose, and these materials are natural polymers. Polymers are substances composed of repeating structural units that are linked together to form long chains [67].

**4.1. Economics and Applications.** Biopolymers are a diverse and versatile class of materials that have potential applications in virtually all sectors of the economy; typical examples are adhesives, absorbents, lubricants, soil conditioners, cosmetic, drug delivery vehicles, textiles, high-strength materials, and even computational switching devices [67]. The structure and some functions of natural polymers are as shown in Figure 1 [72]. It is reported that commercially available biopolymers are quite expensive but their application in specialized fields such as medical materials justified the relatively high costs. Also, the commercialization difficulties facing biopolymers in many ways resemble the problems confronting other emerging technologies such as photovoltaic cells and fuel cells. In this study, the utilization

TABLE 2: The advantages and disadvantages of natural polymers [72].

S/N	Advantages	Disadvantages
1	No problem with toxicity or foreign body response	A major issue is immunological reaction. Body’s immune system recognizes foreign material and tries to destroy it
2	Can function biologically at molecular level, not just macroscopic level	High natural variability
3	If desired, natural degradation can occur in the body via natural enzymes. Can also add cross-links to make less degradable	Structurally more complex than traditional materials. Technological manipulation is more elaborate

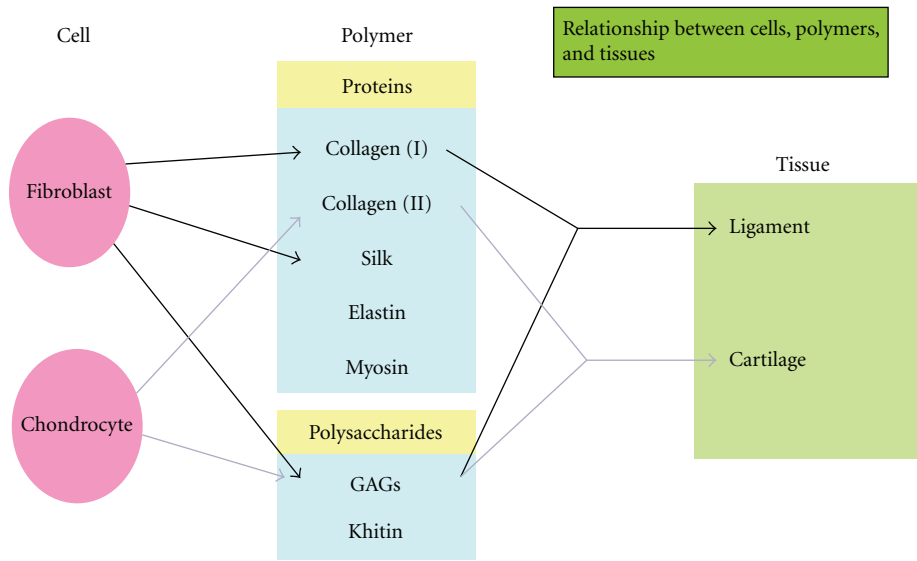


FIGURE 1: Natural polymers: structure and function.

of biopolymers from natural products in the area of medicine is reviewed.

4.2. Demand. It was forecast that natural polymer demand is expected to grow by 5.9% annually to \$3.6 billion in 2010, reaching £1.7 billion. It was also stated that the threats to further growth include mature applications and variable supplies for products due to climatic and political uncertainties [73]. Polymers are regarded as a class of giant molecules consisting of discrete building blocks linked together to form long chains. Simple building blocks are called monomers, while the more complicated building blocks are sometimes referred to as “repeat units.”

Generally, biopolymers fall into two principal categories:

- (i) polymers that are produced by biological systems such as micro-organisms, plants and animals, in short natural products;
- (ii) polymers that are synthesized chemically but are derived from biological starting materials such as aminoacids, sugars, and natural fats or oils. This can sometimes be referred to as synthetic natural product based polymers.

In this study, the emphasis is only on the first category of biopolymers. Exhaustive classifications are dealt with and

their potential applications. Many types of polymers are widely used in biomedical devices that include orthopaedic, dental, soft tissue, and cardiovascular implants. Polymers represent the largest class of biomaterials, and they may be derived from natural sources, or from synthetic organic processes. The wide variety of natural polymers relevant to the field of biomaterials includes plant materials such as cellulose, sodium alginate, and natural rubber; animal materials like tissue-based heart valves and sutures, collagen, glycosaminoglycans, heparin and hyaluronic acid; and other natural materials, deoxyribonucleic acid (DNA), the genetic material of all living creatures [74]. Table 3 lists the various types of naturally occurring biopolymers and defines them on the basis of the chemical structure of their monomeric units and indicates the functions that these polymers serve in living organisms.

Natural polymers were viewed to offer the following properties: they are often identical, very similar to macromolecular substances which the biological environment is prepared to recognize and deal with metabolically. As a result, the problems of toxicity and simulation of chronic inflammatory reaction, which provoked by many synthetic polymers are suppressed. Furthermore, there is capability for designing those biopolymers at molecular rather than the macroscopic level, equal biopolymers are degradable.

TABLE 3: Biopolymers found in nature and their functions [67].

Polymer	Monomer	Function(s)
Nuclei acids (DNA and RNA)	Nucleotides	Carriers of genetic information, universally recognized in all organisms
Proteins	$\alpha$ -aminoacids	Biological catalysis (enzymes), growth factors, receptors, structural materials (wool, leather, silk, hair, and connective tissue); hormones (insulin); toxins; antibodies
Polysaccharides (Carbohydrates)	Sugars	Structural materials in plants and some higher organisms (cellulose and chitin); energy storage materials (starch and glycogen); molecular recognition (blood types); bacterial secretions
Polyhydroxylalkanates	Fatty acids	Microbial energy reserve materials
Polyphenols	Phenols	Structural materials in plants (lignin); soil structure (peat and humics); plant defense mechanisms (tannins)
Polyphosphates	Phosphates	Inorganic energy storage materials
Polysulfates	Sulfates	Inorganic energy storage materials

TABLE 4: General properties of certain natural polymers [67].

Polymer	Incidence	Physiological Functions
(A) Protein		
Silk	Synthesized by anthropods	Protective cocoon
Keratin	Hair	Thermal insulation
Collagen	Connective tissues (tendon, skin)	Mechanical support
Gelatin	Partly amorphous collagen	Industrial product
Fibrinogen	Blood	Blood clotting
Elastin	Neck ligament	Mechanical support
Actin	Muscles	Contraction motility
Myosin	Muscles	Contraction motility
(B) Polysaccharides		
Cellulose	Plants	Mechanical support
Amylose	Plants	Energy reservoir
Dextran	Synthesized by bacteria	Matrix for growth of organism
Chitin	Insects and Crustaceans	Provides shape and form
Glycosaminoglycans	Connective tissues	Contribution to mechanical support
(C) Polynucleotides		
Deoxyribonucleic acids (DNA)	Cell nucleus	Direct protein biosynthesis
Ribonuclei acids (DNA)	Cell nucleus	Direct protein biosynthesis

However biopolymers suffer from immunogenicity, elaborate technological manipulation, decomposition or modification and natural variability in structure from the sources. These divergent factors have produced some unique biomedical materials with outstanding performance. Table 2 shows the general properties of certain natural polymers [75]. A comprehensive overview of the family of natural polymers is listed in Table 4. In this study the broad classification, presented in Table 5, will be adopted for biopolymers and they are grouped into proteins, polysaccharides, and polynucleotides. Polynucleotides are used for purposes such as nanostructural materials and assembling as well as for their electrical properties, but this is not currently of interest in the field of biomaterials. Hence, this paper will be limited to proteins and polysaccharides.

**4.3. Proteins.** Proteins are polymers that are composed of amino acids. The specific amino acids used and the sequence of amino acids in a protein polymer chain are determined by the corresponding deoxyribonucleic acid (DNA) template. Proteins are also referred to as polypeptides, these are complex copolymers composed of up to 20 different amino acids building blocks. There are virtually a limitless number of proteins that can be formed from these 20 monomers. Proteins can contain a few hundred amino acid units or thousands of units. Protein polymers are unique in that the sequence of the monomers in the polymer chain is predetermined by the template-specific reamer of the polymerization process [14, 67].

Many proteins are of commercial interest because of their catalytic (enzymatic) or pharmaceutical properties.



TABLE 5: A Snapshot of the biopolymer family.\*

<i>Polyesters</i>	<i>Polysaccharides (fungal)</i>	<i>Lipids/surfactants</i>
Polyhydroxyalkanoates	Pullulan	Acetoglycerides, waxes
Polylactic acid	Elsinan	Surfactants, emulsan
	Yeast glucans	
<i>Proteins</i>	<i>Polysaccharides (plant/algal)</i>	<i>Polysaccharides (bacterial)</i>
Silks	Starch (amylose/amylopectin)	Xanthan
Collagen/gelatine	Cellulose	Dextran
Elastin	Agar	Gellan
Resilin	Alginate	Levan
Adhesives	Carrageenam	Curd lan
Polyaminoacids	Pectin	Polygalactosamine
Soy, zein, wheat gluten, casein, and serum albumin	Konjac	Cellulose (bacterial)
	Various gums (guar)	
<i>Polyphenols</i>	<i>Polysaccharides (animal)</i>	<i>Specialty Polymers</i>
Lignin	Chitin/chitosan	Shellac
Tannin	Hyaluronic acid	Poly- $\gamma$ -glutamic acid
Humic acid		Natural rubber
		Synthetic polymers from natural fats and oils (nylon from castor oils)

\* Adapted from Herdman (1993) from p20.

Nature has provided a vast array of proteins whose principal function is to form structural materials in living organisms. Some of the more familiar protein materials include wool, leather, silk, and gelatine. Also, elastomeric proteins occur in a wide range of biological systems where they have evolved to fulfil precise biological roles. The best known include proteins in vertebrate muscles and connective tissues, such as titin, elastin, and fibrillin, and spider silks. While some other examples are byssus and abductin from bivalve, molluscs, resilin from arthropods, and gluten from wheat [67, 76].

**4.3.1. Gelatin.** This is obtained through a controlled denature of the fibrous insoluble protein, collagen which is the major component of skin, bone, and connective tissue. It is characterized by having no antigenicity in comparison to its precursor. Gelatin is widely used as scaffold for tissue engineering and also has been frequently used in medicine as a wound dressing, and as an adhesive, absorbent pad for surgical use [77, 78].

**4.3.2. Collagen.** Collagen is an example of natural material which exists mostly in fibril form; it has a characteristic triple-helix structure and is the most prevalent protein in the animal world. It is the most abundant of all proteins found in mammals typically accounting for more than 30 percent of body protein. It forms a significant component of connective tissue such as bone, tendons, ligaments, and skin. There are at least 10 different types of collagen in the body. The arrangement of collagen fibres is arranged parallel to one another to give a structure with the tensile strength of a light steel wire. In skin, where strength and flexibility are required, collagen fibres are randomly oriented and woven together like felt [16, 67]. Collagen is a protein that acts

as a structural support in a wide range of tissues including skin, bone, tendons, ligaments, cartilage, blood vessels, and nerves. It is usually implanted in a sponge form that does not have significant mechanical strength or stiffness. It has shown good promise as a scaffold for neotissue growth and is commercially available as a product for wound healing. Injectable collagen is widely used for the augmentation or buildup of dermal tissue for cosmetic reasons. In particular, collagen and its degradation products are often used for the attraction of fibroblasts in vivo during wound repair, fracture healing, and embryogenesis [16, 78, 79].

**4.3.3. Silk.** Silk is natural fibrous protein which is spun by *Lepidoptera larvae* such as silkworms, spiders, scorpions, mites, and flies [80]. Several attempts to produce silk by bacteria, yeast and plants by inserting genes in them gave insoluble silk proteins, which slumped inside cells [13].

It is well known that silk fibres are composed of at least two main proteins: sericin and fibroin. Silk fibroin shows excellent physical and chemical properties. Silk without sericin showed higher stability than others. Also, silk fibroin can be prepared in various forms; gel, powder, film, matrix, or fibre depending on the applications [80, 81]. Silk has always been a material of great fascination. Spiders can process silk protein into a material that has a tensile strength 16 times greater than that of nylon and a very high degree of elasticity. Silkworm silk is about 2 or 3 times greater than that of nylon. Silk also possesses the ability to super contract especially when they are put into liquid [67]. The breaking stress and strain for different silks are presented in Table 6 [13].

It is observed that the most interesting silk for engineering is viscid silk of *Adameus Diamantus* since it has

TABLE 6: Stress and strain of different types of silk.\*

Silk type	Stress (Gpa)	Stress (Gpa)
<i>Bombyx mori</i> cocoon silk	1.1	0.24
<i>Nephila claripe</i> MAS	1.75	0.15
<i>Nephila maculate</i> dragline	1.1	0.46
<i>Arameus serratus</i> framesilk	0.81	0.24
<i>Araneus diadematus</i> radial silk	1.2	0.40
<i>A. serratus</i> viscid silk	1.0	2.00
<i>A. diadematus</i> viscid silk	1.4	4.76

\* Adapted from Ivanova (2005) [13].

greater stress and strain at breaking point. The strength and toughness of silk is known to be remarkable, and some of the mechanical properties of biodegradable materials are presented in Table 7 [11].

Generally, silk has been investigated for use as biomedical resource due to its unique properties which include nontoxicity, biocompatibility, and biodegradability. It must be noted that it is quite hard and expensive to produce silk from these natural sources in large quantities. Silk has been used as a biomaterial in various forms such as films, membranes, gels, sponges, powders, and scaffolds. They have been commercially applied as scaffolds, vascular prostheses, structural implants, nets, and sutures among others [30, 31, 67].

**4.3.4. Keratins.** The structural integrity and solubility of keratin as well as its natural biocompatibility, controllable biodegradability, and bioactivity makes it an ideal material medical polymer. A proposal was made that keratin extracts from hair and wool could be used as platform technology to make a new family of biomaterials used for biomedical applications such as wound healing and bone regeneration, scaffold for tissue engineering, and coatings for medical devices. This proposal was a challenge to the long-standing notion that these animal-derived proteins would not be compatible with human biological systems. It was proved that the carefully extracted keratin molecule did not elicit an adverse biologic response [82]. These are a class of biomaterials that can be derived by extraction of proteins from human hair. They have haemostatic characteristics, and it was hypothesized that a keratin hydrogel having the ability to absorb fluid and bind cells may be an effective haemostat [83]. Also the usage of keratins to mediate a robust nerve regeneration response in part through activation of Schwann cells was reported [84]. They also suggested that keratins derived from human hair are neuroinductive and can facilitate an outcome comparable to autograft in a nerve injury model.

**4.3.5. Elastin.** The best known and most widely distributed protein elastin is elastin. It is responsible for the elasticity of the aorta and skin of mammal, and is also present in the *ligamentum nuchae* which is involved in raising the heads

of grazing hoofed animals. Elastic fibres are elastic, load-bearing protein polymers found in connective tissue such as ligaments. This rubber-like material responds to changes in temperature and is able to convert chemical energy into mechanical energy. As a consequence, the material could be used as a replacement for ligament tissue, blood vessels, or any other tissues requiring the contractile properties of elastin [67, 76].

**4.3.6. Natural Rubber Latex.** It was recently claimed that the natural rubber latex, extracted from *Hervia brasiliensis*, is a strong candidate for use as a biomaterial. This biologically compatible material can be used in contact or inside the human body, and it has been shown that natural rubber latex performs a biological action that accelerates the healing process, being a powerful stimulator of cicatrization. It is well known that dried latex, in the rubber form, presents high resistance; high elasticity; and is an easy-shaping material, which increases its appeal for use in the fabrication of vascular prostheses [85, 86].

**4.4. Polysaccharides.** Polysaccharides are inexpensive, natural biopolymers which are widely used as raw materials in several industries and being a natural compound, most polysaccharides are easily biodegradable. 75% of all organic material on earth is present in the form of polysaccharides [87, 88]. Polysaccharides are polymers or macromolecules composed of simple sugars, and they have two principal functions. Some such as cellulose serve as structural materials in living systems. Polysaccharides can be utilized as materials in medicine which include wound management, tissue engineering, drug delivery systems, and haemostatic devices among others. It can be classified as listed in Table 8.

**4.4.1. Starch.** Starch is one of the most abundant and cheap polysaccharides. Natural starch occurs in a granular form, and it is a principal carbohydrate storage product of plants. It is found in cereal and tuber plants such as maize and potatoes, respectively [67, 87, 89]. The content of amylose and amylopectin in starch varies and largely depends on the starch source. Most often, starch consists of about 30% amylose [a linear  $\alpha$ -(1-4) glucan] and 70% amylopectin (dendritically branched version) [89-92]. The structure of starch is shown in Figure 2, and it is adapted from Nair and Laurencin [93]. The ratio of amylose and amylopectin in the starch may affect the starch behaviour during processing and the properties of the end product. As the amylose content increases, it will also increase the crystallinity of starch based products and this resulted in texture firming. It must be emphasized that starch is an established and widely used biodegradable polymer. Also starch possesses some properties which enable it to be compounded with other biopolymers with resultant improved products. Starch is insoluble in cold water, but it is very hygroscopic and binds water reversibly. It is renewable, biodegradable, inexpensive, and as such can play an important role in the medical field. They are studied in several biomedical applications ranging from bone replacement implants, bone cements to drug delivery systems and tissue scaffolds [94, 95].

TABLE 7: Mechanical properties of biodegradable materials.\*

Source of biomaterial	UTS (MPa)	Modulus (GPa)	Strain (%) at breakage
<i>Bombyx mori</i> silk (with sericin)	500	5–12	19
<i>Bombyx mori</i> silk (without sericin)	610–690	15–17	4–16
<i>Bombyx mori</i> silk	740	10	20
Collagen	0.9–7.4	0.0018–0.046	24–68
Cross-linked collagen	47–72	0.4–0.8	12–16
Polylactic acid	28–50	1.2–3.0	2–6

\* Adapted from Cao and Wang (2009) [11].

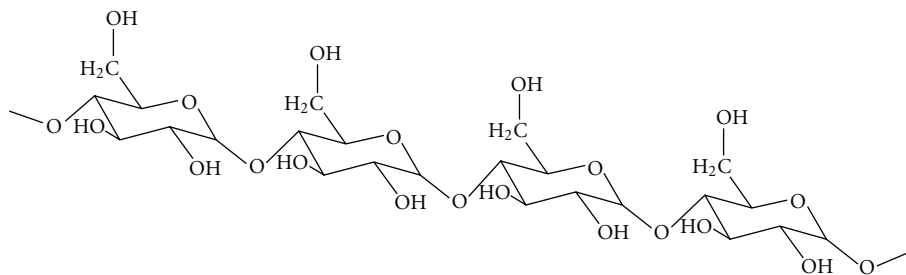


FIGURE 2: Structure of starch.

TABLE 8: Types of polysaccharides.

Types	Examples
Bacterial	Xanthan, dextran, gellan, and cellulose
Fungal	Pullulan, elsinan, yeast, and glucan
Plant	Starch, alginate, and tannin
Animal	Chitin, chitosan, hyaluronic acid, lignin, and tannin

**4.4.2. Chitin and Chitosan.** Chitin is a nitrogen-containing polysaccharide, related chemically to cellulose, and it is insoluble in most solvents. Controlled deacetylation is used to produce chitosan which is a derivative with approximately 50% free amine. Chitins are regarded as the second most abundant natural polymer after cellulose and there are three possible sources of chitin as raw materials. They are isolation from traditional shellfish sources such as crabs and shrimps; harvesting of fungal mycelia from bioreactor processes, a typical example is mushroom; synthesizing from monomeric/dimeric units using chemical and/or enzymatic strategies. However in this paper, the third source of obtaining chitin will be neglected because it involves chemical synthesis. Recently, studies have shifted from the traditional shellfish to exciting and novel shell materials like eggshell and cowry shell. This may be attributed to the environmental pollution and the concern for the amount of residual protein [96–98].

Chitosan is currently obtained by the deacetylation of chitin-9poly- $\beta$ -(1–4)-N-acetyl-D-glucosamine). Chitosan (1,4 linked 2-amino-2-deoxy- $\beta$ -D-glucan) comprises of glucosamine and N-acetylglucosamine. The latter is the water soluble chitin called chitosan [99], which is a moiety of glycosaminoglycans (GAGs). The structure of chitosan and

chitin is shown in Figure 3 [93]. Meanwhile, chitin and chitosan are regarded as natural resources waiting for a market and sourced from the canning industry especially the crustaceans [100]. They stated that there are four chronological steps by which chitosan can be processed from crustacean shells. The steps are as shown in Figure 4, and they are, namely, deproteinization, demineralization, decolouration, and deacetylation. Chitin and chitosan are biologically stemmed aminopolysaccharides which exhibit multiple bioactivities, for example, low toxicity, biocompatibility, biodegradable, antimicrobial, and wound-healing properties. Moreover, chitosan elicits minimal foreign body reaction. Chitosan favours both soft and hard tissue regeneration [80, 101].

Chitins have various biofunctionalities including antithrombogenic, haemostatic, immunity enhancing, and wound healing. Research has shown that chitin and chitosan are nontoxic and nonallergenic, so the body does not reject these compounds as foreign invaders. Biocompatibility, biodegradability, and adsorption properties of chitin and its derivatives are much higher than synthetically substituted cellulose. The native chitin molecule has strong inter- and intra-molecular hydrogen bonds with partial N-deacetylation [102]. Chitin is a biocompatible and biodegradable polymer which demonstrates bacteriostatic and analgesic effects, which in addition, shorten the time of wound healing and the rebuilding of connective tissue. The only disadvantage of natural chitin application is its insolubility in the common solvents generally available, and the enormous related difficulties connected with chitin processing [103].

The chitin family of polymers is being widely used in various applications such as medicine, manufacturing,

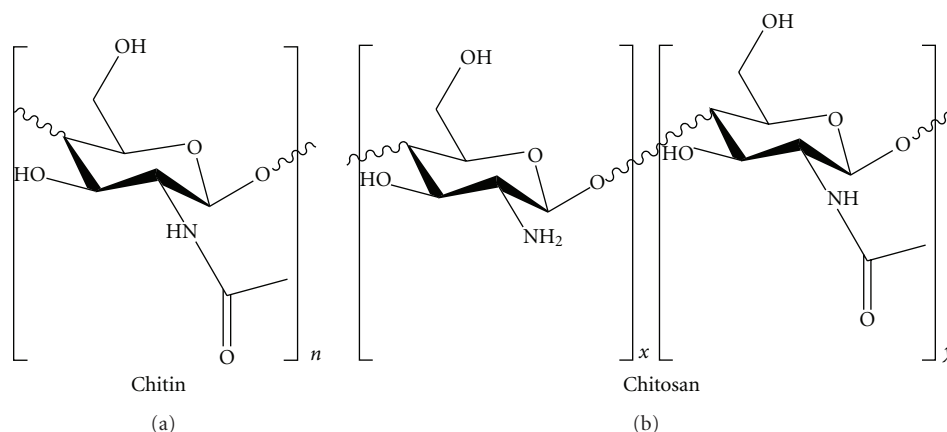
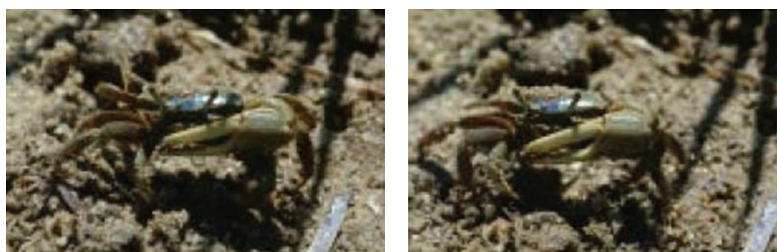


FIGURE 3: Structure of chitin (a) and structure of chitosan (b).



Crustacean shells  $\longrightarrow$  size reduction  $\longrightarrow$  protein  
separation  $\longrightarrow$  (NaOH)  $\longrightarrow$  washing demineralization  
(HCl)  $\longrightarrow$  washing and dewatering  $\longrightarrow$  decolouration  
 $\longrightarrow$  chitin  $\longrightarrow$  deacetylation (NaOH)  $\longrightarrow$  washing and  
dewatering  $\longrightarrow$  chitosan

FIGURE 4: The processing stages in producing chitosan from crustacean shells.

agriculture, and waste treatment. In the biomedical area, chitosan and its derivatives have been successfully used in wound dressings, drug delivery systems, and as materials for tissue engineering. They have been reported to be a promising candidate as a scaffold material for engineered human tissue such as skin, cartilage, and bone due to its biocompatibility, and resorbability. Chitosan is used as an intraocular lense material because of its oxygen permeability and it has also been found to expedite blood clotting. It is also being evaluated for use in the bioremediation of toxic phenolic compound [67, 104, 105].

**4.4.3. Hyaluronic Acid.** Hyaluronic acid (HA) is a natural polysaccharide polymer belonging to the same class of compounds as starch and cellulose. The substance is found naturally in the extracellular matrix of skin, cockscomb, cartilage, vitreous humor, and other body tissue and plays a role in the movement and proliferation of cells. It also occurs as an extracellular polysaccharide in a variety of bacteria [67, 106]. HA was discovered in 1934, and it is a long unbranched polysaccharide chain, composed of repeating twin sugar units. Due to the high density of negative

charges along the polymer chain, HA is very hydrophilic and adopts highly extended random coil conformations. It is extremely flexible, has a high viscosity, and structure is shown in Figure 5 [67, 93]. HA consists of 2-acetamide-2-deoxy- $\alpha$ -D-glucose and  $\beta$ -D-gluconic acid residues linked by alternate (1,3) and (1,4) glycoside bonding and has the high capacity of lubrication, water sorption, and water retention, and influences several cellular functions such as migration, adhesion, and proliferation. HA is water-soluble, and must be cross-linked or otherwise modified to form a scaffold [71, 78].

It is an extremely attractive polymer material because it is a natural product that degrades into simple sugars. Recent biomedical applications of hyaluronic acid include scaffolds for wound healing and tissue engineering, as well as ophthalmic surgery, arthritis treatment, and as a component in implant materials. It is also used as a lubricating fluid in joints and serves as a regulator in the lymphatic system. Based on its *in vivo* functions, HA has been adapted to commercial compounds for treating a number of tissue-related conditions, including osteoarthritis of the joints, and facial wrinkles and folds of the skin [67, 78, 107].



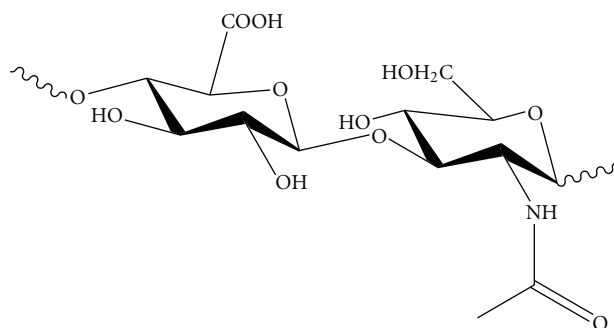


FIGURE 5: Structure of hyaluronic acid.

**4.4.4. Pullulan.** Pullulan is water-soluble polysaccharide produced outside the cell by several species of yeast, most notably *Aureobasidium Pullulans*. It is a linear polymer made up of monomers that contain three glucose sugars linked together [67, 108]. It is claimed that pullulan is a nonionic exopolysaccharide of fungal origin and is currently exploited in the food industry due to its many unique characteristics [109]. It is nontoxic, nonimmunogenic, nonmutagenic, and noncarcinogenic; hence there are attempts to explore pullulan for various biomedical [110].

Pullulan acts as a plasma extender without undesirable side effects. After metabolic turnover, it is completely excreted, and it was reported that pullulan to be used as plasma blood expander should have a molecular weight of about 60 kDa. Pullulan is biodegradable, impermeable to oxygen, nonhygroscopic, and nonreducing. Recently, the role of polysaccharides in developing controlled drug delivery systems has increased significantly, and pullulan is gaining lot of attraction for this application [111]. Tissue engineering requires scaffolds or artificial extracellular matrix (ECM) that can accommodate cells and regulate their growth leading to three-dimensional tissue regeneration. It was concluded that heparin-conjugated pullulan material can thus be used for the proliferation of vascular endothelial cells and to inhibit the proliferation of smooth muscle cells (SMCs) [108]. Pullulan has very important applications in surface modification of polymeric materials so that they can be made more blood compatible and bioinert. Pullulan being adhesive is also tried for wound dressing applications. The thermal stability and elastic properties of pullulan allow it to be utilized in many different ways [109, 112, 113].

## 5. Biocomposite

Naturally, animals and plants synthesize biocomposites with high strength consisting of fibrous biopolymers. A classic example is cellulose which consists of whisker like microfibrils that are synthesized and deposited in a definite manner which imposes high strength. Living tissues are composites themselves with a number of levels of hierarchy. Reinforcement of polymer with nanosized particles or fibres is a promising technique that is capable of yielding materials with enhanced performance but without involvement of expensive synthesis procedures [103]. Bone is regarded as

a biocomposite which comprises of mainly nanohydroxyapatite crystallite orienting along collagen fibres [77].

There is no really adequate definition of a composite material; however, there are three criteria that have to be satisfied before a material can be said to be a composite. Firstly, the constituents have to be present in reasonable proportions and secondly, the constituent phases must have different properties and as such ultimately leading to properties that are superior and possibly unique in some specific respects, to the properties of the individual components. Lastly, the processing technique must be (in such a way that) able to be carried out under controlled conditions. There are several means by which composites can be classified and in this paper, we are interested in natural composite materials. Some typical examples of this class are wood, bone, muscle, and other tissues. Bone is a composite material composed primarily of organic fibres, small inorganic crystals, water, and fats. The proportions of these components will vary with the type of bone, animal species, and age, but typically about 35% of the dry, fat-free weight of bone is the organic fibre, collagen. Collagen is a fibrous protein and located around the outside of the collagen fibres are small rod-like crystals of hydroxyapatite with dimensions of the order of  $5 \times 5 \times 50$  nm. Therefore at this microscopic level we have a hydroxyapatite-reinforced collagen composite and this may be considered to be the basic "building block" of bone [114, 115].

It must be realised that to classify composite within the context of this work is severely restricted. This is due to the fact that only combinations of biopolymers and bioceramics are possible. Thermodynamically, metals are stable in combined state as ores (i.e., oxides, sulphides, and carbonates), and they rarely exist in their pure form; hence only precious metals are available as natural materials for biomaterials application. This paper will consider combination of biopolymer with biopolymer, biopolymer with bioceramics; there have been little or no reports on the application of two bioceramics as biocomposites.

**5.1. Biopolyme-Biopolymer.** Biopolymers occur abundantly in nature, and they have several applications as materials in medicine. Chitosan is regarded as a biodegradable and nontoxic hydrophilic polysaccharide with excellent mucoadhesive and permeation-enhancing properties. Alginate is the name given to a family of linear polysaccharides found in brown algae and is composed of guluronic and mannuronic units [106]. Meanwhile, there has been increasing interest in the study of alginate-chitosan microparticles as carriers for controlled release of proteins and drugs due to its biocompatible, biodegradable, and mucoadhesive properties. It was shown that the stability of alginate-chitosan capsules depended strongly on the amount of chitosan bound to the capsules [116]. The superporous hydrogel foams containing chitosan and gelatine have a lot of interesting food and medical applications. The superporous structure and mechanical properties are especially proper for scaffold preparation [105].

Chitosan/gelatine hydrogels are being developed for tracheal epithelia. A company in Italy is reported to have

developed a series of modified hyaluronate esters by adding hydrophobic moieties to the carboxyl groups so as to control degradation, and it is marked as tissue engineering polymers which are being applied to bone growth and cartilage [71]. An investigation concluded that the artificial dermal skin is composed of gelatine and polysaccharides such that hyaluronic acid and  $\beta$ -glucan will be useful to promote wound healing [78]. While a combination of flexible protein and rigid polysaccharide results in a series of biomimetic chitosan/gelatine based biomaterials covering surface modifier and nonviral vector for gene therapy. They hold promising prospect in tissue engineering [77].

Cellulose-based hydrogels are advantageous over cellulose sponges and fabrics as their bulk chemistry can be easily modified. Independent investigations have reported the synthesis of novel biomimetic hydrogels, based on cross-linking cellulose derivatives with hyaluronic acid [117, 118]. Although mainly proposed as postoperative adhesion barriers, such hydrogels also show potential as scaffolds for regenerative medicine, with a tunable degradation rate. Indeed, the presence of hyaluronic in the cellulose network provides enzyme-sensitive degradation sites, whose density in the bulk of the hydrogel can be easily controlled [119].

The blending of polymers with starch under controlled conditions leads to copolymerization that in turn results in high-molecular polymers with thermoplastic properties. Though, the mixing or blending needs special machinery, such as an extruder, the products (polymer blend) can be handled as easily as conventional plastic resin [94]. Although starch such as that of cassava is used as a polymer, other polymers are frequently used in the blend. Polycaprolactone blend is the most commonly used polymer/starch blend because of its low-melting temperature ( $T_m$ ) and high susceptibility to amylase and lipase hydrolyses [120, 121]. It must be noted that starch as polymer has been marketed under various names, and most patents describe a generic starch, this includes cassava [100].

Natural polymers such as chitosan and cellulose, and their derivatives are inherently biodegradable, and exhibit unique properties. Starch and chitosan are abundant naturally occurring polysaccharides. Both of them are cheap, renewable, non-toxic and biodegradable [122]. Bourdoom and Chinnan (2008) concluded that the starch/chitosan blend exhibits good mechanical properties, while water barrier properties, and miscibility of biodegradable blend films are affected by the ratio of starch and chitosan.

One problem associated with starch-based blend is that starch and many polymers are nonmiscible which leads to the mechanical properties of the starch/polymer blends generally becoming poor. Thus, chemical strategies are taken into consideration in order to improve the properties [123]. Starch-based biodegradable polymers have some advantages for use as medical materials such as good biocompatibility, biodegradable, and its degradation products are non-toxic, proper mechanical properties and degradation as requirement. Starch-based biodegradable polymers have been widely investigated in bone tissue engineering.

Starch-based biodegradable bone cements can provide immediate structural support and degrade from the site of

application. In addition, starch-based biodegradable polymers can also be used as bone scaffold and when they are in the form of microsphere or hydrogel they are suitable for drug delivery systems. There is no need for surgical removal of the device after drug depletion. The unique properties such as hydrophilicity, permeability, biocompatibility, are to some extent similar to soft biological systems, all these make starch-based hydrogel to be useful for various biomedical applications [124–129]. Biodegradable polymers such as poly (lactic acid), poly (glycolic acid), and their respective copolymers have been used in several drug delivery systems. However, few attempts have been made to use starch-based polymers in these types of applications; despite being well known that they are biodegradable materials; they have been proposed in several works to be used as biomaterials [130–133].

**5.2. Biopolymer-Bioceramics.** A composite made of bioceramic-polymer composite was introduced, and it was based on the concept that cortical bone itself comprises an organic matrix reinforced with a mineral component. The material they developed has been used as an orbit implant for orbital floor fractures and volume augmentation, also it is now being used in middle ear implants, commercialized under the trade name HAPLEX [134, 135].

Polymers such as alginates showing low toxicity and high biocompatibility and hydroxyapatite have been reported with osteoinductive or osteoconductive potential. Composites binding these properties could be a good choice for the development of new materials for medical application. This composite is considered to be biocompatible and partially resorbable [136].

The association of bioceramics and fibrin sealants may develop the clinical applications of bone substitutes. The physical, chemical, and biological properties of both bioceramics and fibrin glue may be cumulated for preparing advance bone substitutes. The ideal bone substitute should be biocomposite, biodegradable at the expense of bone growth and mouldable, with sufficient mechanical properties to fill and restore bone defects [137]. These biological properties can be tailored for both bioceramics and fibrin glue by changing the composition; porosity and network cross-linking. The positive effects of the combination of fibrin sealant with ceramic biomaterials have essentially been observed in clinical studies. Fibrin sealants improve the surgical handling of biomaterials and widen their field of application in bone surgery. Furthermore, the future development of this composite may be in combination with bone growth factors [138].

One of the naturally occurring biocomposites that has been deployed as biomedical materials is *nacre*. It is secreted only by the molluscan classes, *Gastropoda*, *Bivalvia*, *Cephalopoda*, and to a minor extent, *Tryblidiida*. Nacre has a lamellar structure consisting of alternating tablets of aragonite and organic interlamellar membranes which have a core of  $\beta$ -chitin surrounded by acidic proteins [139]. It is now clear that the sequence of nacre formula involves the secretion of interlamellar membranes separated by a liquid rich in silk fibroin such that subsequently the liquid

TABLE 9: Some applications of natural biomaterials.

Application	Natural biomaterial
Artificial heart valves	Bovine pericardium, Intact porcine aortic valves
Hernia repair devices	Porcine small intestinal submucosa, porcine urinary bladder mucosa, Porcine dermal grafts
Sutures	Catgut (porcine or bovine intestinal wall) and porcine dermal grafts
Skin repair/wound care	Dermal allograft, porcine small intestinal submucosa, and porcine dermal grafts
Vascular prostheses	Bovine ureter, porcine small intestinal submucosa, and Ovine arteries
Urethral repair	Porcine bladder
Breast reconstruction	Dermal allograft
Ligament repair	Dermal allograft, porcine small intestinal submucosa, and fetal bovine skin
Spinal fusion/bone healing	Bone allograft

is replaced with mineral. This pattern is the same for the bivalves and gastropods, so too for the other nacre-secreting molluscs, although this is yet to be determined. There are, however, structural differences between bivalve and gastropod nacre [140].

Nacre is by far the most intensively studied nonhuman organomineral biocomposite. It has a high proportion, approximately 5% of organic matter (proteins and polysaccharides), the mineral fraction being exclusively in the form of aragonite. The aragonites work of fracture is estimated to be as high as 3000 times that of inorganic aragonite but this figure is considered to be lower in reality. Nacre has found possible applications in the biomedical industry due to their superior biomechanical properties [140]. Nacre is able to form a tight bond of bone without soft and fibrous tissue formation. It is gradually and centripetally dissolved but not resorbed by cells because it is not porous [141, 142].

## 6. Application of Natural Products in Biomaterials

There are various uses of natural products in materials for medical applications, some of which are bioelectrodes, dental implantation, orthopaedic applications, adhesive and sealant, ophthalmological applications, intraocular lens implants, burn dressings, and skin substitutes among others. Table 9 lists some of the natural biomaterials and their areas of application [10]. There are three principal market segments for natural biomaterials: wound management products, drug delivery systems (DDSs), and tissue engineering. In this paper, all these three will be discussed and another important area of application will be highlighted. Biotextiles have utilized natural product-based proactive agents such as chitosan, natural dyes, neem extract, and other herbal products for antimicrobial finishing of textile substrates [143]. Biotextiles also provide a good platform to demonstrate the limitations and challenges of natural products as materials in medicine.

**6.1. Wound Management.** This segment is regarded to grow at an astronomical rate, and it represents a sizeable portion of

biomedical materials. Hyaluronic acid is an extremely attractive polymer material used in wound-healing preparations, aids tissue formation and repair, provides a protective matrix for reproductive cells, serves as a regulator in the lymphatic system, and acts as a lubricating fluid in joints. Zein, which is a major storage protein of corn, has been used widely as an adhesive, fibre, cosmetic powder, and ink [67]. Hide glue derived from gelatin has been in used for centuries. Lastly, mention must also be made of burn dressings methods like autografts, allografts from cadavers, and xenografts of which domestic swine is the most commonly used as a temporary wound closure material [14].

**6.2. Drug Delivery System.** The discovery of new drugs has been the major thrust in drug research, and although this trend will continue for a while, there is an increasing emphasis being placed on the development of novel drug delivery systems. The use of biopolymer materials for drug delivery can minimize tissue reaction and allow drugs to be administered in nonconvexional ways. The use of biopolymers in these formulations has thus far been restricted to a narrow set of applications [67]. Natural polysaccharides due to their outstanding merits have received more and more attention in the field of drug delivery systems. In particular, polysaccharides seem to be the most promising materials in the preparation of nanometric carriers. In nature, polysaccharides have various resources from algal origin (e.g., alginate), plant origin (e.g., pectin and guar gum), and microbial origin (e.g., chitosan and chondroitin). Among various polysaccharides, chitosan is the early one to be used to prepare nanoparticles [144, 145]. Also, the main applied form of albumin for biomaterials is pharmaceutical microspheres, which has been extensively investigated for drug targeting to various organs and tissues [146, 147].

**6.3. Tissue Engineering.** One key area of research gaining significant attention over the past several years is tissue engineering. This technology combines an engineered scaffold, or 3-dimensional structure with living cells. These scaffolds can be constructed of various materials and made into different shaped depending on the desired application [14]. Many

naturally occurring scaffolds can be used as biomaterials for tissue engineering purposes, and one of the typical examples is hydroxyapatite which is obtained from coral or animal bone. Proteins are one of the important candidates for tissue engineering. They provide cell support for anchorage and adherence through cellular growth and development [148, 149]. Currently available proteins for application in tissue engineering include fibrin, collagen, zein, silk fibroin, keratin, casein, and albumin. A more speculative application is the use of biopolymers as scaffolding in the formation of new cartilage in the body. With the advantage of biocompatibility, biopolymers are likely to be used in many more novel orthopaedic applications [67].

**6.4. Medical Fibres and Biotextiles.** The application of fibres and biotextiles as components for implantable devices is widespread and covers all aspects of medicine and healthcare. They are used as drapes and protective apparel such as protective surgical gowns, operating room curtains, masks, and shoe covers. Textiles can also be used as topical and percutaneous applications in areas like bandages, wound coverings, and nappies. Lastly, three key applications of biotextiles in general surgery are sutures, haemostatic devices, and hernia repair meshes. Catgut is a natural collagen-based suture material obtained from ovine intestine, which is cross-linked and cut into narrow strips, and it is one of the first bioabsorbable fibres used in surgery. Silk and collagen are two natural fibres that have been widely used in medicine and multiple applications. Silk is inexpensive and is considered to be the gold standard in suture-handling characteristics. Collagen sutures are primarily used in microsurgery or ophthalmic surgery. Cotton was and still is commonly employed for bandages, surgical sponges, curtains, and surgical apparel, and in surgical gowns [14].

Antimicrobial textiles help to reduce effectively the ill effects associated with microbial growth on textile material. The use of natural products such as chitosan and natural dyes for antimicrobial textile materials has been reported. Plant products comprise the major segment of natural antimicrobial agents; sericin, natural dyes, tannins, and aloe vera among others. Aloe vera also possesses antifungal and antibacterial properties, which can be exploited for medical textile applications, such as wound dressing, suture, and bioactive textiles. The major challenges in application of natural products for textile application are that most of these biomaterials are complex mixtures of several compounds, and also the composition varies in different species of the same plant. The activity and composition also vary depending on their geographical location, age, and method of extraction. The availability of these products in bulk quantities, their extraction, isolation, and purification to get standardized products are other challenges in their applications [143].

## 7. Conclusion

Natural products have found many applications in the field of pharmaceuticals and medicine; healthcare and nutritional supplements; agrochemicals among others. The paper looks

at the recent research in natural biomaterials towards applications in various biomedical fields. The purpose of this paper is to highlight information available on the various forms of natural products for biomaterials as well as to highlight the applications of natural biomaterials. The properties, demand, and economic importance of different natural biomaterials are discussed. Three major areas of intervention of natural biomaterials were discussed. It is advocated that future work should be focussed on the methods of reducing the major disadvantages like poor immunogenic response, variability, and the technological processing techniques. The poor immunogenic response is attributed to the presence of antigenic determinants which can be reduced by either chemical modification or standardized natural material sourcing. There is a need to develop a well-tested production and processing route for producing the biomaterials from the natural products as this will reduce the effects of variability among others.

In this paper, an attempt has been made to increase the understanding of the utilization of natural products in the biomedical field. This will attract the attention of specialists in the study of natural products and biomaterials.

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