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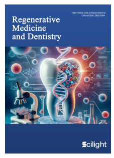

Review

Natural Materials in Regenerative Orthopaedics: A Historical Perspective

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How To Cite: Vasilev, O.; Campbell, D.; Jaarsma, R.L. Natural Materials in Regenerative Orthopaedics: A Historical Perspective. *Regenerative Medicine and Dentistry* **2025**, *2*(2), 7. https://doi.org/10.53941/rmd.2025.100007

Received: 18 March 2025
Revised: 31 March 2025
Accepted: 3 April 2025
Published: 16 April 2025

Abstract: The use of natural materials in regenerative orthopaedics has undergone significant evolution over many centuries. What began as the use of simple animal sinews and plant fibers for stabilizing fractures has now expanded into sophisticated biomaterials that are integral to modern regenerative medicine. Natural substances like collagen, silk fibroin, chitosan, and cellulose are now crucial in tissue engineering, providing innovative bone and cartilage regeneration solutions. Despite their promise, natural materials face challenges such as mechanical limitations, biodegradation rates, and immunogenicity. Additionally, advancements in 3D printing allow for the replacement of complex bone defects, particularly in trauma and tumour cases, but these remain non-biological solutions that lack permanent integration with host tissues. The emergence of hybrid materials—combining natural and synthetic components—offers new opportunities to enhance biomechanical properties and biocompatibility. Furthermore, emerging technologies such as gene editing and bioactive scaffolds are paving the way for more personalized and regenerative approaches. In this review paper, we will explore the historical progression of natural materials, their current applications, and the challenges that must be overcome to maximize their therapeutic potential in orthopaedic regenerative medicine. Ethical and sustainability considerations are also discussed. The review concludes with the authors' vision for the future of the field.

Keywords: natural materials; tissue regeneration; orthopaedics; 3D printing; bone; cartilage

1. Introduction

The field of regenerative orthopaedics is a dynamic and innovative branch of medicine aimed at restoring the structural and functional capabilities of the musculoskeletal system. This includes tissues such as bones, cartilage, tendons, and ligaments. Unlike traditional orthopaedic treatments that rely on mechanical fixation or prosthetics to replace damaged tissues with metals and plastics, regenerative orthopaedics seeks to leverage the body's intrinsic ability to heal itself, often augmented by advanced biomaterials and medical technologies [1]. This shift from replacement to regeneration represents an exciting potential transformation in medical science, driven by the increasing prevalence of musculoskeletal injuries and degenerative conditions [2]. Aging populations, sports-related trauma, and the global rise in lifestyle diseases, such as osteoporosis and arthritis, are increasing the demand for better solutions.

At the core of regenerative orthopaedics is the development and application of biomaterials. These materials, designed to support or enhance tissue regeneration, can be broadly categorized into synthetic, natural, and hybrid [3].

Synthetic biomaterials, such as polymers, ceramics, and metals, have historically dominated the field due to their mechanical strength, customizability, and ease of production. However, their lack of bioactivity limits their ability to integrate with living tissues, leading to long-term mechanical failures rather than true biological restoration. Unlike synthetics, natural biomaterials—derived from biological sources—exhibit bioactivity and biodegradability, providing a structural environment conducive to cell adhesion and growth. However, they are not without drawbacks; biologics may also trigger immune responses and carry a higher infection risk, as seen in past concerns like the HIV scare associated with tissue grafts.

The historical reliance on natural materials in medical treatments provides valuable context for their current resurgence in regenerative orthopaedics. Ancient civilizations utilized biological substances, such as animal sinews, plant fibers, and bones, for fracture stabilization and wound healing. While these early practices were rudimentary, they laid the groundwork for modern biomaterials by demonstrating the healing potential of natural substances [4]. Advances in biotechnology and materials science have enabled the development of bioengineered natural materials with enhanced properties tailored to specific clinical applications. For instance, collagen, a protein abundant in connective tissues, is widely used for its biocompatibility and ability to support cellular growth. Similarly, silk fibroin, chitosan, and cellulose have all gained attention for their mechanical strength, degradability, and versatility in applications ranging from bone grafts to drug delivery systems. To enhance their regenerative potential, these natural materials are often integrated into cutting-edge technologies such as 3D bioprinting and stem cell therapies, providing scaffolds that promote tissue regeneration while minimizing adverse reactions [5–7].

While natural biomaterials inherently support cellular interactions, their bioactivity can be both beneficial and detrimental. Unlike synthetic materials, which are biologically inert and do not elicit immune responses, natural materials interact with the body at a cellular level, which can either accelerate healing or trigger immune rejection. In orthopaedics, the goal is often to manipulate this biological response to favour tissue integration rather than merely dissolving over time, as seen with biodegradable plastics, or permanently replacing native tissue with metal implants. This paradigm shift has led to growing interest in hybrid biomaterials, which aim to combine the mechanical advantages of synthetics with the bioactivity of natural components [8].

The choice between natural and synthetic materials in regenerative orthopaedics is further complicated by ethical, environmental, and economic considerations. The extraction of natural materials, such as collagen from bovine tendons or chitosan from crustacean shells, raises concerns about sustainability, biodiversity, and animal welfare. Conversely, the production of synthetic materials often involves environmentally damaging processes, such as greenhouse gas emissions and chemical waste. These issues underscore the need for sustainable and ethically sourced biomaterials that align with both clinical and environmental priorities. Recent innovations in biomaterials research, including the development of plant-derived cellulose scaffolds and recombinant collagen produced through microbial fermentation, offer promising pathways to address these concerns while maintaining high standards of performance and safety [9–11].

The significance of natural materials in regenerative orthopaedics extends beyond their clinical utility, reflecting broader trends in biomimicry and sustainability. Biomimicry, which involves emulating nature's principles and processes to solve complex problems, has emerged as a guiding philosophy in regenerative medicine. By leveraging the structural, chemical, and functional properties of natural materials, researchers aim to create therapies that not only repair damaged tissues but also restore their biological integrity and functionality. However, a major limitation remains the extended time required for biological integration, compared to the immediate functional support offered by mechanical solutions like metal implants.

Additionally, the integration of 3D bioprinting has enabled the precise fabrication of scaffolds that mimic the complex architecture of native tissues, such as cancellous bone. When combined with stem cell therapies, these materials have shown the potential to accelerate tissue regeneration. Advances in gene editing, such as CRISPR-Cas9, are also being explored to enhance the regenerative capacity of natural materials, paving the way for personalized and precision medicine. These innovations underscore the transformative potential of natural materials in addressing unmet clinical needs in orthopaedics [12].

This review aims to explore the historical evolution, current applications, and future prospects of natural materials in regenerative orthopaedics. By examining their advantages, limitations, and interplay with synthetic materials, we seek to provide a comprehensive understanding of their role in advancing musculoskeletal healing. Through this discussion, we highlight the critical need for continued innovation in biomaterials to overcome existing challenges and unlock the full therapeutic potential of regenerative orthopaedics.

2. Historical Overview

2.1. Early Use of Natural Materials in Ancient Civilizations

The use of natural materials in regenerative orthopaedics dates back thousands of years, with ancient civilizations leveraging readily available biological and mineral resources to address skeletal injuries and diseases (Figure 1). These early efforts laid the foundation for modern biomaterials by demonstrating how natural substances could support bone repair and tissue regeneration. This section explores the pivotal role of natural materials in orthopaedic practices among ancient cultures, emphasizing their relevance to contemporary applications.

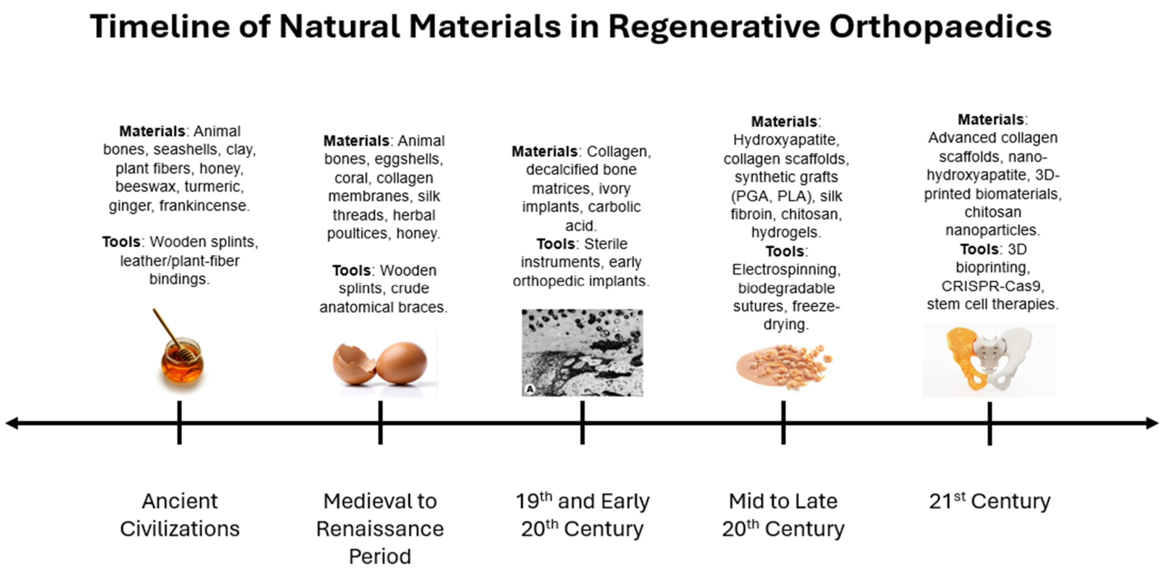

Figure 1. A timeline displaying the evolution of materials and tools in regenerative orthopaedics. The timeline is divided into five historical periods: Ancient Civilizations (represented by a honey jar icon for natural remedies like honey and beeswax), Medieval to Renaissance (a wooden splint icon for crude anatomical splint designs), 19th and Early 20th Century (a surgical scalpel icon for sterile instruments and ivory implants), 20th Century (a scaffold icon for synthetic grafts and hydroxyapatite), and 21st Century (a 3D bioprinter icon for advanced biomaterials and bioprinting technologies). The icons emphasize the progressive innovations in orthopaedics over time.

2.1.1. Early Bone Repair and Fracture Management

Bone fractures were among the most common orthopaedic injuries in ancient societies, and their treatment showcased remarkable ingenuity through the use of natural materials to promote healing and provide structural support. In ancient Egypt and Mesopotamia, practitioners utilized fragments of animal bones or seashells to stabilize fractures and fill bone defects. Chosen for their durability and structural compatibility with the human skeleton, these materials served as some of the earliest examples of bone grafting. Such techniques were not only practical but also visionary, as they directly influenced modern advancements like hydroxyapatite-based scaffolds and xenografts, which mimic the properties of human bone and remain critical in contemporary orthopaedics [1]. Additionally, clay and mud were moulded into splints or casts to immobilize broken limbs, a practice reflecting a sophisticated understanding of the importance of stabilizing fractures to promote proper healing. These casts were often reinforced with plant fibers, animal hides, or wooden supports which enhanced their effectiveness. Although simplistic by modern standards, these approaches demonstrate an intuitive grasp of biomechanical principles, and their influence can still be traced in the immobilization techniques used today. Together, these ancient practices reveal a profound legacy, connecting early human innovation with the highly advanced orthopaedic technologies of the present day [2].

2.1.2. Natural Remedies for Joint Pain and Inflammation

The treatment of joint conditions, such as arthritis, was a prominent aspect of ancient orthopaedic practices, with natural substances being skilfully utilized for their bioactive properties to reduce pain, swelling, and inflammation. In Ayurvedic medicine, herbal compresses and oils made from turmeric, ginger, and frankincense were applied directly to swollen joints. Turmeric contains curcumin, a potent anti-inflammatory compound, while ginger is rich in gingerol, known for its analgesic and anti-swelling effects. Frankincense, derived from Boswellia resin, was prized for its ability to inhibit inflammatory pathways, a concept that underpins its continued use in modern arthritis treatments. These poultices not only reduced inflammation but also improved mobility, offering patients a natural yet effective form of relief [3]. Meanwhile, in ancient Egypt, honey and beeswax were utilized as part of wound care regimens, valued for their antibacterial and healing properties. Honey's ability to draw moisture from wounds inhibited bacterial growth, while beeswax provided a protective barrier to prevent reinfection. These substances were frequently used in the treatment of open fractures and infected joints, serving to both preventing infection and promoting tissue regeneration. By combining bioactive plant compounds with antimicrobial agents, ancient practitioners demonstrated an advanced understanding of therapeutic techniques, many of which have informed the development of modern pharmacological and surgical approaches to managing joint disorders and injuries [9].

2.1.3. Prosthetics and Biocompatible Materials

Beyond fracture management, ancient civilizations demonstrated remarkable ingenuity by developing early prosthetics and orthotic devices using natural materials to restore mobility and functionality. In ancient Egypt, wooden prosthetics were crafted to replace lost toes or fingers, with leather straps providing a secure and adjustable fit. These materials were selected for their durability, lightweight nature, and biocompatibility, reflecting an early understanding of the need for replacements that were both functional and tolerable to the body. One notable example is the wooden prosthetic toe found on the foot of an Egyptian mummy, which displayed both craftsmanship and functionality, allowing the individual to walk more comfortably [4]. In South America, archaeological evidence reveals the use of gold and copper implants in cranial surgeries, likely to replace damaged bone or treat deformities. While these implants were primarily used in trepanation and not directly for orthopaedic purposes, they demonstrate an advanced understanding of metalwork and its potential application in structural repair. Gold and copper were chosen for their malleability, resistance to corrosion, and antimicrobial properties, which minimized infection risks. These pioneering efforts in prosthetics and implants underscore the resourcefulness of ancient medical practices and their foundational influence on modern orthopaedics, where materials like titanium and polymers are now used to create sophisticated prosthetic limbs and implants [1].

2.1.4. Cultural Contributions to Orthopaedics

The use of natural materials in orthopaedic care widely varied across cultures, reflecting differences in available resources and medical philosophies while demonstrating an intuitive grasp of biomechanics and healing. In traditional Chinese medicine, ancient physicians utilized animal tendons and silk to repair ligaments and tendons. These materials were prized for their exceptional tensile strength, flexibility, and biocompatibility, allowing them to mimic the properties of the body's own tissues. This practice not only facilitated effective soft tissue repair but also foreshadowed the modern use of biodegradable sutures, which serve a similar purpose in contemporary surgical procedures [5]. In Greco-Roman medicine, notable advancements in orthopaedic techniques were made by physicians such as Hippocrates and Galen, who emphasized the importance of understanding biomechanics in treating fractures and joint injuries. Greek and Roman practitioners employed plaster made from lime and gypsum to create rigid casts for immobilizing broken bones, ensuring proper alignment during the healing process. This innovation laid the groundwork for the development of Plaster of Paris, a material still widely used in orthopaedics today. These cultural contributions highlight the diverse approaches to orthopaedic care in the ancient world, many of which continue to inform and inspire modern medical practices [6].

2.1.5. Parallels with Modern Regenerative Orthopaedics

The natural materials employed by ancient civilizations were not chosen arbitrarily but reflected an understanding of their compatibility with the human body. This early knowledge is strikingly relevant to contemporary orthopaedics heavily reliant on materials biocompatibility and osteoconductivity. Materials like bone fragments, shells, and honey demonstrate early insights into biocompatibility and osteoconductivity, principles that underpin the development of modern scaffolds and bioactive coatings for implants. Furthermore, the use of locally sourced natural materials by ancient civilisation also aligns with the modern push for sustainable and eco-friendly approaches to biomaterial development [7].

The practices of ancient civilizations demonstrate the long-standing importance of natural materials in orthopaedics. By examining these early approaches, we gain a deeper appreciation for the principles that continue to drive innovation in regenerative medicine today. From fracture stabilization to joint repair, the ingenuity of ancient societies underscored the enduring potential of natural materials to support skeletal health and regeneration.

2.2. Medieval to Renaissance Periods

The Medieval to Renaissance periods marked a transitional era in medical practices. During this time, natural materials were first systematically explored for their potential in aiding tissue repair and skeletal reconstruction. While primitive compared to modern approaches, these early developments established important foundations for contemporary regenerative orthopaedics. The ingenuity of these methods demonstrated an emerging understanding of biology and biomechanics, with natural materials forming the core of experimental orthopaedic treatments.

2.2.1. Early Bone Repair: Pioneering Biocompatible Approaches

One of the primary challenges in orthopaedics during these periods was addressing fractures and skeletal deformities. Without advanced surgical tools or synthetic materials, physicians relied on accessible natural substances. Animal bones used as primitive grafts for fracture repair often included the use of carved animal bones (commonly sourced from cattle or sheep). These natural grafts were shaped to fit into defects, functioning as structural scaffolds to restore skeletal integrity. This concept, though limited in execution, mirrors modern allografts and xenografts, which aim to provide both mechanical support and biocompatibility [8]. Furthermore, small fragments of eggshells or corals were sometimes used as filler materials in cranial injuries or large fractures. Their calcium carbonate content made them early precursors to synthetic hydroxyapatite, which is now widely utilized for its osteoconductive properties [10].

2.2.2. Wound Care in Orthopaedics: Natural Antibacterial and Anti-Inflammatories

Managing open wounds and preventing infection were recognised as critical aspects of orthopaedic care. Natural materials were selected for their bioactive properties. These included honey and plant-based poultices. Honey was used extensively for treating wounds, including open fractures, due to its antimicrobial properties. It facilitated prevention of infection while accelerating tissue repair [11]. Similarly, poultices made from crushed herbs like comfrey and plantain were applied to reduce inflammation and promote healing [12]. Collagen-rich animal products were also utilised. For example, in some cases tissue repair was aided by wrapping injuries in collagen-rich membranes derived from animal intestines or skins. These rudimentary methods demonstrate early recognition of collagen's role in tissue regeneration [13].

2.2.3. Stabilization Techniques: From Natural Splints to Ligament Repair

Stabilizing injured bones and joints was a crucial aspect of ancient orthopaedic care, with natural materials playing a vital role in achieving immobilization and repair. Wooden splints made from sturdy materials such as oak or ash were commonly used to immobilize fractures and ensure proper alignment during healing. These splints were often bound with strips of leather or plant fibers, which improved their durability and provided a degree of comfort for the patient. This practice served as an early analog to modern orthopaedic braces, emphasizing the importance of stability in recovery. Additionally, silk threads and animal sinews were employed in basic suturing techniques to repair ligaments and tendons following injuries. Silk was prized for its smooth texture and tensile strength, while sinews offered natural elasticity and biocompatibility, making them effective for stabilizing soft tissues. These organic fibers paved the way for modern synthetic and biopolymer sutures, which have since been refined to improve strength, flexibility, and biodegradability. Together, these early techniques underscore the innovative use of natural resources in ancient orthopaedics and their lasting influence on contemporary practices in bone and joint stabilization [14–16].

2.2.4. The Renaissance: A Turning Point in Orthopaedics

The Renaissance brought about a profound shift in medical knowledge, driven by advances in anatomy and surgical techniques. This period saw an increased understanding of the body's structures and the potential applications of natural materials. A profound contribution were Leonardo da Vinci's studies on bones and mechanics. Da Vinci's anatomical drawings and studies of bone mechanics highlighted the relationship between form and function, influencing subsequent orthopaedic practices. His insights inspired the design of splints and braces tailored to the natural movement of joints [17]. In addition, surgeons like Ambroise Paré experimented with the transplantation of animal bone fragments to fill defects in human skeletons. Although crude, these attempts reflect the conceptual foundation for modern bone grafting procedures [18].

The practices of this era, while limited in precision and efficacy, were revolutionary for their time and had major implications for regenerative orthopaedics. They introduced ideas that resonate with modern regenerative orthopaedics. Medieval and Renaissance practitioners intuitively selected materials that the body could tolerate, such as bone, collagen, and calcium carbonate. This principle of biocompatibility continues to drive the development of natural and synthetic biomaterials for orthopaedic applications and beyond. Materials such as coral and eggshell hinted at bioactive and osteoconductive properties, which are now exploited in advanced bone substitutes. The use of collagen-rich membranes and animal-derived grafts paved the foundation of scaffolding technologies in tissue engineering, an approach that parallel current practice.

Collectively, although the Medieval to Renaissance periods lacked the technological capabilities of modern science, their contributions to orthopaedic care were transformative. The use of natural materials such as animal bones, collagen, and plant-based remedies not only addressed immediate medical needs but also established the groundwork for the principles of regenerative orthopaedics that shape the field today. By revisiting these historical practices, we gain valuable insights into the enduring importance of natural materials in regenerative orthopaedics.

2.3. 19th and Early 20th Century

The 19th and early 20th centuries marked a transformative era in orthopaedics, characterized by the integration of biological insights into material sciences and surgical techniques. This period saw a shift from the mere stabilization of fractures to a more advanced approach that sought to enhance tissue repair and regeneration. These developments were underpinned by advancements in materials science, a deeper understanding of biology, and pioneering surgical innovations.

2.3.1. The Introduction of Collagen for Tissue Regeneration

Collagen, a key structural protein in connective tissues, became a focal point for orthopaedic research during the 19th century. Derived from animal tendons, collagen was recognized for its biocompatibility and its role in promoting cell adhesion, a critical factor for tissue regeneration. Early experiments involved the use of decalcified bone matrices, rich in collagen, to encourage osteogenesis and soft tissue repair [19].

One of the most notable applications of collagen during this period was in bone grafting. Surgeons began using decalcified bone, which retained its collagen content, as a scaffold for new bone growth. This innovation addressed the challenges of treating large fractures and skeletal defects, providing a framework for osteoblasts to deposit new bone tissue. Although the molecular mechanisms of collagen's interaction with cells were not yet understood, its effectiveness in promoting healing was evident in clinical outcomes [1,20,21].

2.3.2. Pioneering Bone Grafting Techniques

Bone grafting emerged as a revolutionary procedure in the late 19th century, largely thanks to the work of the German surgeon Themistocles Glück. In 1891, Glück successfully used ivory implants to replace damaged joints, demonstrating the potential of grafting materials to integrate host tissues [22]. The use of ivory highlighted the importance of structural integrity and compatibility in grafting materials.

In parallel, decalcified bone grafts, which retained their organic components, gained popularity for their ability to promote osteogenesis. Early studies showed that these grafts served as a biological scaffold, allowing for the infiltration of blood vessels and bone-forming cells. This technique was particularly effective in repairing long bone fractures and spinal deformities, paving the way for more complex reconstructive procedures [23].

2.3.3. Antiseptic Techniques and Their Impact on Orthopaedics

The introduction of antiseptic techniques by Joseph Lister in the mid-19th century had a profound impact on orthopaedic surgery. Lister's use of carbolic acid to sterilize surgical instruments and wounds drastically reduced postoperative infections, which had been a significant barrier to the success of bone grafts and other regenerative procedures [24,25].

With the reduced risk of infection, surgeons were more willing to experiment with grafting techniques and implant materials. For instance, decalcified bone and collagen-based scaffolds could be used with greater confidence in their ability to integrate with host tissues without leading to sepsis. This period also saw the first attempts to use autografts—tissue grafts harvested from the patient's own body—further minimizing the risk of immune rejection and complications [26].

2.3.4. Emergence of Biocompatible Metals

While natural materials dominated early regenerative techniques, the late 19th and early 20th centuries witnessed the emergence of biocompatible metals as potential orthopaedic implants. Pioneers in the field like Lane and Glück experimented with metallic plates and screws to stabilize fractures, complementing the use of natural materials for tissue regeneration [27,28].

Although metals like steel and iron were not inherently regenerative, they provided the mechanical stability needed for natural materials, such as collagen or bone grafts, to function effectively. For example, a fractured femur might be stabilized using a steel plate, while a collagen-based scaffold facilitated tissue regeneration at the fracture site. This dual approach, combining mechanical and biological solutions, became a hallmark of orthopaedic innovation [29].

One of the most significant innovations of this era was the introduction of silk fibroin, a protein derived from the cocoons of silkworms. Silk fibroin gained popularity due to its exceptional mechanical properties, biocompatibility, and biodegradability. Its tensile strength rivalled that of steel, while its ability to degrade into non-toxic byproducts made it ideal for use in regenerative medicine [30]. Silk fibroin was extensively used as a scaffold material in tissue engineering. Its porous structure allowed for the infiltration of cells and nutrients, promoting the formation of new tissues. In orthopaedics, silk fibroin scaffolds were employed to repair cartilage and bone defects, demonstrating excellent outcomes in preclinical studies [31]. Additionally, silk fibroin was modified to incorporate bioactive molecules, such as growth factors and peptides, further enhancing its regenerative potential. These modifications allowed for the targeted delivery of therapeutic agents, facilitating faster and more effective tissue repair [32].

The mid-20th century also witnessed the rise of polymer blends, which combined natural and synthetic materials to create hybrid scaffolds with tailored properties. For instance, chitosan was blended with synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) to improve its mechanical strength and degradation rate [33]. These polymer blends were particularly effective in bone and cartilage repair, where the combination of natural and synthetic components provided the necessary balance between bioactivity and structural support. Blends of collagen and hydroxyapatite, for example, closely mimicked the composition of natural bone, making them ideal for use in orthopaedic implants [34].

Another key innovation during this period was the development of synthetic materials designed to mimic the properties of natural tissues. For example, researchers created synthetic hydrogels that replicated the viscoelastic properties of cartilage, enabling their use in joint repair and replacement [35]. These hydrogels were engineered to be injectable, allowing for minimally invasive procedures. Once injected, they could solidify in situ, conforming to the shape of the defect and providing immediate structural support. Hydrogels were also used as carriers for cells and growth factors, further enhancing their regenerative potential [36].

The introduction of biodegradable materials for sutures and implants was another milestone of this era. Polyglycolic acid (PGA) and polylactic acid (PLA), two biodegradable polymers that are made from naturally occurring compounds i.e., glycolic acid and lactic acid, respectively, were used to create sutures that dissolved over time, eliminating the need for removal surgeries [37]. These polymers were also used to fabricate screws, plates, and other implants for fracture fixation. Their ability to degrade into harmless byproducts, such as water and carbon dioxide, minimized long-term complications and paved the way for their widespread adoption [38].

Advancements in manufacturing techniques during this period, such as electrospinning and freeze-drying, played a critical role in the development of bioengineered materials. These techniques allowed for the creation of porous scaffolds with controlled architecture, enhancing their ability to support cell infiltration and tissue formation [39]. Electrospinning, in particular, was used to fabricate nanofibrous scaffolds that closely resembled the extracellular matrix (ECM) of native tissues. These scaffolds provided the structural and biochemical cues necessary for cell attachment and differentiation, making them highly effective in tissue engineering applications [40].

The clinical adoption of these bioengineered materials led to significant advancements in patient outcomes. For example, silk fibroin scaffolds were successfully used to repair meniscal tears, while chitosan-based dressings accelerated wound healing in trauma patients [41]. Similarly, cellulose-derived materials were used to fabricate artificial ligaments and tendons, demonstrating excellent mechanical performance and biocompatibility [42]. Biodegradable sutures and implants also became standard practice, reducing the need for secondary surgeries and improving recovery times. Due to their efficiency, these approaches are still used today.

2.3.5. Challenges and Future Directions

Despite these advancements, the use of bioengineered natural materials in the mid-20th century faced several challenges. One major limitation was the variability in material properties, which often depended on the source and processing methods. For instance, the mechanical strength of chitosan scaffolds varied significantly depending on the extraction technique and degree of deacetylation [43]. Additionally, the lack of advanced imaging and diagnostic tools (particularly in mid-20th century) limited the ability to monitor the integration of these materials with host tissues. This often led to unpredictable outcomes and highlighted the need for more reliable assessment methods [44]. The groundwork laid during this period set the stage for the modern era of regenerative medicine, where bioengineered materials continue to evolve with the advent of nanotechnology and tissue engineering. The principles established in the mid to late 20th century—such as the importance of biocompatibility, biodegradability, and functional mimicry—remain integral to the field.

2.4. 21st Century Advances in Natural Materials

The 21st century has ushered in a transformative era for natural biomaterials, marked by innovations that integrate biological sciences, engineering, and regenerative medicine. Specifically, materials like silk fibroin, collagen, and chitosan have remained central to orthopaedic applications, evolving alongside emerging technologies such as stem cell therapy, 3D printing, and nanotechnology. These latter advances have redefined how natural biomaterials are utilized, making treatments more efficient, customizable, and effective.

2.4.1. Silk Fibroin: Expanding Its Applications in Regenerative Orthopaedics

Silk fibroin has remained a standout natural material in regenerative medicine due to its remarkable tensile strength, flexibility, and biocompatibility. In the 21st century, its applications have broadened significantly, particularly in tendon and ligament repair. Researchers have developed silk fibroin scaffolds that mimic the hierarchical structure of tendons, enhancing their ability to promote cellular adhesion and proliferation [45].

Recent advancements have focused on enhancing silk fibroin's bioactivity through functionalization with growth factors and peptides. For instance, scaffolds impregnated with vascular endothelial growth factor (VEGF) have shown to improve vascularization in tendon repair [46]. Moreover, silk fibroin has been combined with other materials, such as hydroxyapatite, to create composite scaffolds with superior mechanical properties for bone regeneration [47].

3D printing has also revolutionized the use of silk fibroin in orthopaedics. Using additive manufacturing techniques, researchers have fabricated silk fibroin scaffolds with complex geometries tailored to patient-specific defects. These 3D-printed scaffolds have demonstrated excellent integration with native tissues in preclinical studies [48].

2.4.2. Collagen: The Gold Standard in Bone Grafting

Collagen continues to be a cornerstone material in bone grafting and tissue engineering due to its natural abundance and compatibility with the human extracellular matrix. In the 21st century, collagen-based materials have been refined for enhanced performance in regenerative applications.

Advances in crosslinking techniques have improved the mechanical stability and degradation rate of collagen scaffolds, addressing one of the primary limitations of earlier collagen-based materials [49]. These advancements have enabled the use of collagen in load-bearing applications, such as spinal fusion and large-scale bone defect repair.

Collagen has also been integrated with nanotechnology to create hybrid scaffolds with enhanced osteogenic properties. For example, collagen scaffolds infused with nanoparticles, such as bioactive glass or graphene oxide, have demonstrated superior bone-forming potential in preclinical studies [50].

Moreover, collagen-based hydrogels have gained traction as injectable biomaterials for minimally invasive procedures. These hydrogels are loaded with stem cells or growth factors to promote localized tissue regeneration, offering a less invasive alternative to traditional bone grafting [51].

2.4.3. Chitosan: A Versatile Material for Drug Delivery and Bone Regeneration

In the 21st century, chitosan has emerged as a highly versatile material, particularly valued for its applications in drug delivery and bone regeneration. Its ability to form hydrogels and nanoparticles has made it an ideal carrier for therapeutic agents, such as antibiotics, growth factors, and chemotherapeutics [52].

In orthopaedics, chitosan-based delivery systems have been used to achieve controlled release of bone morphogenetic proteins (BMPs), which has significantly improved bone regeneration outcomes [53]. These systems have proven especially useful in treating complex bone defects, where localized and sustained release of growth factors is crucial for successful healing.

Chitosan has also been widely used in 3D-printed scaffolds for bone regeneration. Its ability to blend with other biomaterials, such as calcium phosphate or collagen, has resulted in composite scaffolds with enhanced bioactivity and mechanical strength [54]. Furthermore, advancements in surface modification techniques have improved the integration of chitosan scaffolds with host tissues, making them a preferred choice for orthopaedic applications [55].

2.4.4. Stem Cell Technology: Transforming Natural Biomaterials

The integration of stem cell technology with natural biomaterials has been one of the most significant advancements in the 21st century. Stem cells, with their ability to differentiate into various cell types, have been combined with materials like collagen, silk fibroin, and chitosan to create bioengineered constructs with enhanced regenerative potential [56].

For example, collagen scaffolds seeded with mesenchymal stem cells (MSCs) have shown exceptional results in bone and cartilage repair. These constructs not only provide a structural framework for tissue formation but also deliver bioactive cues to promote cell differentiation and proliferation [57].

Silk fibroin has similarly been used as a carrier for stem cells in tendon and ligament regeneration. Its porous structure allows for efficient cell infiltration and nutrient exchange, creating an optimal environment for stem cell differentiation [58].

Chitosan-based hydrogels, loaded with stem cells, have also been employed for minimally invasive treatments of bone defects. These hydrogels are designed to solidify in situ, providing immediate structural support while promoting tissue regeneration [59].

2.4.5. 3D Printing: Revolutionizing the Fabrication of Biomaterials

3D printing has transformed the use of natural materials in regenerative medicine by enabling the fabrication of patient-specific scaffolds with unparalleled precision. Collagen, silk fibroin, and chitosan have been widely used in 3D-printed constructs for orthopaedic applications.

Collagen-based scaffolds fabricated using 3D bioprinting have shown great promise in cartilage repair. These scaffolds can replicate the intricate architecture of native cartilage, providing the necessary mechanical and biochemical cues for regeneration [60].

Similarly, 3D-printed silk fibroin scaffolds have been employed for bone regeneration, demonstrating excellent integration with host tissues and minimal inflammatory response [61]. Chitosan-based materials have also been used in 3D bioprinting to create scaffolds with customizable porosity and degradation rates, making them ideal for a wide range of orthopaedic applications [54].

2.4.6. Nanotechnology: Enhancing Natural Biomaterials

The integration of nanotechnology with natural materials has unlocked new possibilities in orthopaedic regeneration. Nanostructured materials, such as collagen nanofibers and chitosan nanoparticles, have demonstrated superior bioactivity and mechanical properties compared to their bulk counterparts [62].

For instance, collagen nanofibers have been used to fabricate scaffolds that closely mimic the nanoscale architecture of native bone tissue, enhancing cell attachment and differentiation [63]. Chitosan nanoparticles have been employed to deliver therapeutic agents, such as growth factors and antibiotics, directly to the site of injury, improving treatment outcomes [64].

Silk fibroin has also been incorporated into nanocomposites for advanced orthopaedic applications. These nanocomposites combine the mechanical strength of silk fibroin with the bioactivity of nanoparticles, creating multifunctional scaffolds for tissue engineering [65].

2.4.7. Future Directions and Challenges

While the 21st century has brought remarkable advancements in natural biomaterials, several challenges remain. Issues such as scalability, variability in material properties, and regulatory hurdles continue to limit the widespread adoption of these materials.

Nevertheless, ongoing research into biofunctionalization, advanced manufacturing techniques, and integration with emerging technologies promises to address these challenges. The continued evolution of natural materials, driven by interdisciplinary collaboration, is set to redefine the future of regenerative medicine.

3. Technological Advancements and Evolution

Regenerative orthopaedics has a rich history, evolving from early interventions in ancient civilizations to modern-day innovations that harness the latest technologies. This section traces the progression of techniques and materials used in musculoskeletal regeneration, from their historical roots to contemporary advancements and current clinical applications.

3.1. Historical Developments of Regenerative Orthopaedic Materials

In ancient civilizations, orthopaedic treatments primarily utilized natural materials such as bone, plant-based substances, and resins, which were crafted with rudimentary understanding of the body's healing processes. Early medical practitioners from cultures like the Egyptian, Greek, and Roman introduced basic techniques for bone-setting, employing splints and surgical interventions to manage fractures and musculoskeletal injuries [66]. Over time, these early practices paved the way for more scientifically informed approaches, incorporating evolving materials in response to an expanding understanding of anatomy and tissue regeneration.

3.2. Advancements in Biomaterials

In the 20th century, breakthroughs in biomaterials led to the development of more sophisticated and functional substances which have significantly impacted the field of regenerative orthopaedics. Materials like collagen scaffolds, hydroxyapatite-based implants, and synthetic bone grafts revolutionized the way musculoskeletal injuries were treated [67]. This period saw the creation of hydroxyapatite, a substance that mimics the mineral composition of natural bone and is critical in implantology [68].

The development of collagen as a key scaffold material marked a turning point, enabling more effective tissue regeneration strategies. This innovation laid the foundation for contemporary regenerative approaches, especially in applications requiring cartilage and bone repair [69].

3.3. The Advert of Stem Cell Research for Tissue Engineering

By the late 20th century, the advent of stem cell research revolutionized the field. Prior to this, chondral grafting had gained popularity since 1972 as a method for cartilage repair but was ultimately limited by the constraints of the collagen scaffold, leading to a decline in its use. The discovery that MSCs could be induced to differentiate into bone, cartilage, and muscle tissue sparked an era of biological regeneration [70]. Stem cell therapies, alongside advancements in tissue engineering, provided a biological solution to conditions where traditional surgical treatments had limitations. The use of autologous stem cells, particularly those harvested from bone marrow, became increasingly common in orthopaedics practices by the 1990s, presenting patients with an alternative to invasive surgeries [71].

3.4. Recent Technological Advancements and Their Clinical Applications

While historical developments laid the foundation, the last few decades have witnessed accelerated progress in regenerative orthopaedics, particularly due to advancements in biomaterials, stem cell therapies, nanotechnology, 3D printing, and robotics. These innovations are not just theoretical; they are actively reshaping clinical practices today, enabling more minimally invasive, personalized, and effective treatments. Notably, emerging technologies now mimic cellular and microstructural properties with unprecedented precision, pushing biomimicry to the next level and enhancing the integration of engineered tissues with native biology.

3.5. Biomaterials and Current Clinical Applications

Biomaterials, such as hydroxyapatite, collagen scaffolds, and biodegradable polymers have evolved significantly, now playing an even more pivotal role in musculoskeletal regeneration and repair. The clinical impact of these biomaterials cannot be overstated: they have led to the development of more durable and biocompatible implants, scaffolds, and grafts that support the body's natural regenerative processes. Key examples are listed below:

Hydroxyapatite-Coated Implants: In modern joint replacement surgeries, hydroxyapatite (HA)-coated implants are commonly used to promote osteointegration, i.e., the bonding between bone and implant. This advancement, particularly relevant in hip and knee replacements, has greatly improved the longevity of implants, reducing the risk of implant loosening and the need for revision surgeries. The use of HA-coated implants has significantly advanced in recent years, with clinical studies showing that osteointegration rates are much higher than with earlier implant technologies [72]. A key advantage of cementless fixation is the potential for biological fixation of metal to bone, unlike cemented prostheses, which can deteriorate over time. However, while this concept remains theoretically promising, current data does not conclusively support superior long-term outcomes. Despite this, the contemporary approach of integrating biologics with metal implants represents a pragmatic strategy in modern orthopaedics. These benefits are particularly crucial in an aging population where joint replacement procedures are becoming more common.

Collagen-Based Scaffolds for Cartilage Regeneration: The introduction of collagen-based scaffolds for cartilage regeneration, often used in autologous chondrocyte implantation (ACI), has proven to be one of the most successful techniques in regenerating damaged cartilage. These scaffolds provide a structure onto which new cartilage can grow, primarily addressing cartilage defects caused by trauma or conditions such as osteochondritis dissecans, rather than general wear-and-tear osteoarthritis. Recent advancements in these scaffolds have enabled better cellular integration and faster tissue regeneration, reduced recovery times and improving patient outcomes [73]. In modern practice, these scaffolds are often combined with stem cells to improve healing potential, allowing for a more functional repair of cartilage defects in the knee, hip, and shoulder joints.

Bone Grafting with Collagen and HA Composites: Spinal fusion surgeries, among other complex bone repair procedures, now frequently use composites of collagen and hydroxyapatite to improve bone graft healing. These materials support faster osteointegration, reducing healing time and improving success rates in high-risk surgeries [74]. This development is especially crucial for patients with severe bone fractures or spinal injuries, who may have previously faced long recovery times or complications related to graft failure.

3.6. Stem Cell Therapy and Its Applications

Stem cell therapy has undergone exponential growth in its applications within regenerative orthopaedics. The ability to use MSCs from a patient's own body (autologous cells) has drastically reduced risks associated with tissue rejection and immune reactions. While stem cells remain a key focus, bioengineering advancements now allow for the culture and replication of more differentiated cells, such as chondral cells, further refining regenerative strategies. These developments expand the potential for targeted tissue engineering, enhancing the healing of musculoskeletal tissues that are slow to regenerate, such as cartilage, bone, and tendons [75].

Osteoarthritis and Cartilage Regeneration: Stem cell-based treatments are increasingly being employed to treat osteoarthritis, particularly in patients who may be too young or too healthy for joint replacement surgery. Stem cells injected directly into affected joints help to regenerate damaged cartilage, slowing the progression of arthritis and often reducing the need for more invasive procedures [76]. The combination of mesenchymal stem cells with platelet-rich plasma (PRP) has shown promising results in improving cartilage repair and reducing inflammation, highlighting the shift towards regenerative therapies that are both biologically advanced and clinically effective [77].

Bone Fractures and Non-Union Fractures: Stem cells are also used to treat fracture non-unions, a relatively uncommon but significant issue in orthopaedics trauma. Research has shown that bone marrow-derived stem cells can significantly accelerate bone healing, especially in patients with fractures that fail to heal using traditional methods [78]. The ability to promote osteogenesis and osteointegration in complex fractures is a key advancement, allowing for faster recovery and reduced reliance on more invasive surgical options.

Ligament and Tendon Regeneration: Tendon and ligament injuries, which historically had limited treatment options, are now being addressed with stem cell therapies. MSCs can promote regeneration and repair of tendons and ligaments, and when combined with PRP, these therapies accelerate healing, offering an alternative to surgical repair. This approach is increasingly used in sports medicine, where tendon and ligament injuries are common, offering athletes faster recovery times and fewer complications [79].

3.7. Nanotechnology in Orthopaedic Treatments

Nanotechnology has emerged as one of the most outstanding, revolutionary advancements in orthopaedics regeneration. The ability to manipulate materials at the molecular level has allowed for the development of nanostructured materials, drug delivery systems, and scaffolds that are more effective and specific in their therapeutic applications. For example, nano-hydroxyapatite and other nanostructured coatings have been introduced to improve the osteointegration of implants. These nano-coatings mimic the natural surface of bone, enhancing the interaction between bone and implant. Recent studies have shown that nano-coatings not only improve implant fixation but also reduce infection rates, making them particularly useful in areas where infections have disastrous consequences, like spinal fusion surgeries and joint replacements [80]. On another hand, nanoparticles are now being used to deliver growth factors, anti-inflammatory drugs, and antibiotics directly to orthopaedics injury sites. This targeted drug delivery approach reduces systemic side effects, improves healing times, and ensures more efficient delivery of therapeutic agents. In fracture healing and joint repair, nanoparticles are used to accelerate tissue regeneration and prevent infections, further enhancing recovery rates [81].

3.8. 3D Bioprinting of Custom Implants and Tissues

The advent of 3D bioprinting represents a milestone in orthopaedic regenerative medicine (Figure 2). This technology allows for the creation of patient-specific implants and tissues, enabling personalized treatment strategies. For instance, 3D-printed implants are revolutionizing joint replacements and bone grafting by allowing surgeons to create customized solutions that perfectly fit an individual's anatomy. Custom implants have been particularly noteworthy in addressing traumatic defects and tumours, where precision-engineered solutions are essential. Pioneering work by Colton and colleagues, originally developed for UK war veterans, laid the foundation for these advancements. The integration of computer-assisted design, robotics, and high-resolution imaging has further enhanced precision in manufacturing and surgical execution. The ability to print patient-specific bone scaffolds ensures a better match, reducing the likelihood of implant failure and the need for revision surgeries [82]. Additionally, 3D bioprinting is being used to create cartilage and ligament tissues for regenerative purposes. Researchers are now working on printing complex tissues that can be implanted into joints to repair cartilage damage, a promising development for patients suffering from degenerative diseases such as osteoarthritis [83].

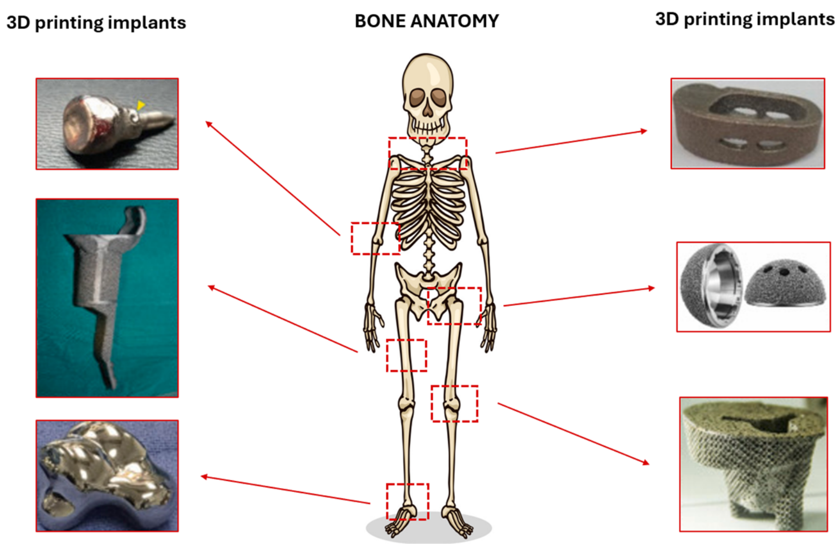

Figure 2. A diagram illustrating the use of 3D-printed implants in orthopaedic applications, overlaid on a skeletal diagram to indicate their anatomical placement. On the left, examples include a 3D-printed femoral implant, a tibial prosthesis, and a custom-designed joint surface. On the right, images show a porous spinal cage, an acetabular cup for hip replacement, and a lattice-structured knee joint component. The red arrows and outlined regions on the skeleton highlight the specific anatomical locations where these implants are utilized, emphasizing the precision and adaptability of 3D printing in producing patient-specific solutions for orthopaedic surgeries [84].

In summary, the technology associated with regenerative orthopaedics has evolved significantly over the centuries, from early treatments in ancient civilizations to cutting-edge technologies that enable us to heal and regenerate musculoskeletal tissues. Today, innovations such as advanced biomaterials, stem cell therapies, nanotechnology, and 3D printing are reshaping the landscape of musculoskeletal care, offering more effective, personalized, and sustainable treatment options for patients worldwide. As research and technology continue to advance, the future of regenerative orthopaedics promises even greater possibilities, improving the quality of life for patients and enabling a return to active, pain-free living.

4. Challenges and Limitations

Natural materials have long been at the forefront of regenerative orthopaedics, offering a range of advantages such as biocompatibility, biodegradability, and a natural ability to integrate with human tissue. However, despite their promising applications, these materials also come with significant practical and technological limitations that hinder their widespread use. This section will explore the key challenges and limitations of natural materials in regenerative orthopaedics applications, including issues related to mechanical strength, biodegradation, sourcing, and immunogenicity, comparing different materials such as collagen, silk fibroin, chitosan, and alginate.

4.1. Mechanical Strength and Load-Bearing Capacity

One of the primary limitations of natural materials in orthopaedic applications is their insufficient mechanical strength, particularly in load-bearing scenarios (Figure 3). The mechanical properties of natural materials like collagen and silk fibroin are often not suitable for the demands of musculoskeletal tissue engineering, especially in areas such as joint replacement or bone repair, where strength is crucial for long-term functionality.

Collagen, a protein commonly used in scaffolds for tissue regeneration, has relatively low tensile strength compared to synthetic polymers and metals used in traditional orthopaedic implants. Additionally, collagen degrades over months, leading to a loss of structural integrity before native tissue can fully replace it. This deterioration limits its long-term mechanical viability, especially in load-bearing applications. To address this, researchers have explored hybrid approaches that combine collagen with more durable materials, such as hydroxyapatite or synthetic polymers, to provide temporary structural support while allowing gradual tissue integration [83]. Even with these modifications, collagen-based materials still face challenges in high-stress applications like bone grafts or spinal fusion, where they may deform under prolonged mechanical loads, emphasizing the need for optimized hybrid scaffolds that balance strength and bio integration.

In contrast, silk fibroin, derived from silk, has superior mechanical properties compared to collagen, offering greater tensile strength and stability. However, while silk fibroin shows promise in soft tissue applications, it still falls short in load-bearing applications due to its lower compressive strength compared to human bone. This limitation is especially relevant in orthopaedic applications such as bone scaffolding, where materials must endure constant mechanical stress without failure [85]. The need to strengthen silk fibroin through cross-linking or hybridization with other materials adds complexity to its use and can lead to increased costs and fabrication challenges.

Chitosan, a polysaccharide derived from the shells of crustaceans, also faces challenges related to mechanical strength. While it is biocompatible and biodegradable, its mechanical properties are generally weaker than those of synthetic materials like polylactic acid (PLA) and polyglycolic acid (PGA), which are often used in load-bearing applications in orthopaedics [86]. Chitosan's fragility limits its use in applications requiring substantial load bearing, and like collagen, it often requires reinforcement with other materials to be effective.

Alginate, another polysaccharide derived from seaweed, is frequently used in soft tissue engineering due to its ability to form hydrogels that mimic the extracellular matrix. Alginates are used as a void fillers and antibiotic delivery agents but their mechanical properties are also a limiting factor when it comes to bone regeneration. The material is too soft to provide sufficient mechanical support for bone repairs, and while it is often used in combination with other materials to enhance its properties, the underlying weakness remains a significant limitation [87].

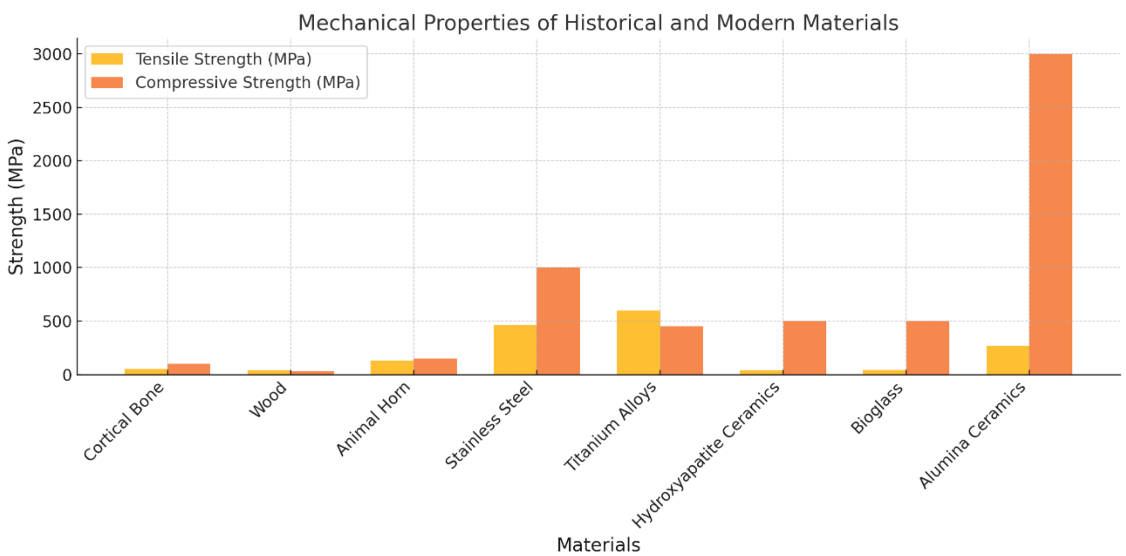

Figure 3. A bar chart comparing the tensile and compressive strengths of selected historical materials (e.g., cortical bone, wood, animal horn) and modern materials (e.g., stainless steel, titanium alloys, hydroxyapatite ceramics, bio glass, and alumina ceramics). The chart highlights the significant improvements in strength for modern materials [70,71].

4.2. Biodegradation Rates and Longevity

Another significant challenge with natural materials is their variable and often unpredictable biodegradation rates, which can affect their long-term efficacy in regenerative applications. The rate of degradation must be carefully matched to the tissue regeneration process to avoid premature material breakdown or excessive persistence, both of which can lead to complications.

Collagen, for example, is known for its rapid degradation rate in vivo. While this can be beneficial in some applications, such as wound healing, it poses a problem in orthopaedic applications where the material needs to remain intact long enough to support tissue regeneration. In bone and cartilage regeneration, collagen degradation often outpaces tissue growth, leading to inadequate support for the healing process [72]. This mismatch can result in implant failure or the need for additional surgeries, significantly impacting patient outcomes.

On the other hand, silk fibroin has a much slower degradation rate, which can be both an advantage and a disadvantage. In some cases, the prolonged persistence of silk fibroin can lead to inflammation or foreign body reactions as the body struggles to break down the material [85]. While the slower degradation of silk fibroin can be advantageous for certain applications, such as tendon and ligament repair, where prolonged support is necessary, its longevity can present issues in other contexts, particularly when the material interferes with natural tissue remodelling.

Chitosan and alginate are both biodegradables, but their rates of degradation vary depending on the formulation and the environment. Chitosan's degradation rate is influenced by factors such as pH, temperature, and the degree of deacetylation, which can result in inconsistent degradation profiles across different applications [86]. Alginate degradation also varies based on its cross-linking density, and although it is generally considered to degrade at an acceptable rate in soft tissue applications, its slower degradation in bone scaffolding applications can hinder the process of natural bone remodelling [88].

4.3. Sourcing and Availability

Sourcing natural materials for use in regenerative orthopaedics presents its own set of challenges. The availability and consistency of these materials can be unpredictable, and the process of harvesting them can have environmental and economic implications.

Collagen, derived primarily from animal sources, is widely available but can be costly and subject to variability. The quality of collagen extracted from different animals (bovine, porcine, or marine) can vary significantly, leading to inconsistent performance when used in medical applications [72]. Additionally, ethical concerns surrounding the sourcing of animal-derived collagen have led to increased interest in alternative sources, such as recombinant collagen or plant-based substitutes. However, these alternatives are still in the experimental stages, and their efficacy in orthopaedics applications is yet to be fully proven.

Silk fibroin is harvested from silkworms, making it more sustainable than collagen in some respects. However, silk fibroin production can be labour-intensive and costly, limiting its accessibility for widespread clinical use. Additionally, the purification and processing of silk fibroin can be complex, requiring specialized facilities and equipment [85]. This makes silk fibroin less readily available for mass production compared to synthetic alternatives, limiting its use in large-scale orthopaedics treatments.

Chitosan and alginate, sourced from marine organisms, face similar challenges in terms of sustainability. Overfishing and habitat destruction can threaten the supply of these materials, raising concerns about their long-term availability. Moreover, while chitosan is generally considered to be more abundant and affordable than silk fibroin, its extraction process still requires significant resources and can lead to environmental impacts, particularly if the raw materials are sourced from endangered species [86].

4.4. Immunogenicity and Compatibility

Immunogenicity is another major concern with natural materials, particularly those derived from animals. The risk of immune reactions can complicate the use of these materials in human patients, especially in the case of materials that may not be adequately purified or processed.

Collagen, being derived from animals, poses a risk of immunogenicity. While collagen-based materials are generally well-tolerated by the human body, there is still a potential for allergic reactions, especially when the material is not adequately purified. The use of animal-derived collagen also raises concerns about disease transmission, although stringent processing protocols have been developed to mitigate these risks [89].

Silk fibroin, despite its advantages in mechanical properties and biodegradability, also faces potential immunogenic issues. Although silk fibroin is generally considered biocompatible, its immune response can vary depending on the specific processing techniques used. Some studies have indicated that silk fibroin may elicit a mild inflammatory response, particularly in high concentrations [75]. However, the overall immunogenicity of silk fibroin is generally lower than that of other natural materials, making it a favourable option for many orthopaedics applications.

Chitosan has been shown to exhibit low immunogenicity in vivo, and it is often considered a safer alternative to animal-derived materials. However, some studies have suggested that high concentrations of chitosan can cause mild irritation or inflammation at the site of implantation [86]. Alginate, too, is generally well-tolerated and shows minimal immunogenicity, though its use in bone regeneration is still limited by its mechanical and degradation properties.

The practical limitations of natural materials in regenerative orthopaedics are diverse and complex. While these materials offer promising potential for tissue regeneration, their use is hindered by issues such as insufficient mechanical strength, unpredictable biodegradation rates, sourcing challenges, and potential immunogenicity. The need for enhanced material properties, more consistent sourcing, and improved biocompatibility remains central to advancing the field. Despite these challenges, continued research into hybrid materials, processing techniques, and innovative biomaterials will likely lead to significant improvements in the performance and applicability of natural materials in regenerative orthopaedics.

5. Ethical Considerations

Natural materials in regenerative orthopaedics are highly valued for their biocompatibility and ability to support tissue repair and healing. Materials like collagen, silk fibroin, and chitosan have gained widespread use due to their structural similarity to human tissues and their capacity to promote cellular growth and regeneration. However, the ethical implications of their sourcing—particularly when derived from animals—pose significant challenges to researchers, clinicians, and patients alike [90,91].

One major concern is animal welfare. Extracting materials such as collagen or silk often involves processes that may harm or kill animals. This raises ethical questions about the balance between scientific advancement and the humane treatment of animals. Moreover, cultural sensitivity plays a crucial role, as some patient groups may object to using animal-derived products based on religious or personal beliefs, limiting the acceptance of such treatments across diverse populations [90,91].

Environmental sustainability is another critical factor. The sourcing of materials like chitosan, obtained from crustacean shells, and alginate, derived from algae, has ecological repercussions. Overharvesting can disrupt ecosystems, threaten marine biodiversity, and jeopardize the long-term availability of these resources. This highlights the need for sustainable extraction practices and the exploration of alternative sources, such as plant-based or synthetic analogs, to mitigate environmental harm [92,93].

Addressing these ethical and environmental challenges is crucial for guiding the future direction of regenerative orthopaedics. Developing transparent sourcing protocols, prioritizing sustainability, and considering cultural contexts can help advance innovation while ensuring these treatments align with ethical standards. Such measures can foster greater acceptance of natural materials in medical applications, promoting both scientific progress and social responsibility [90,91].

Additionally, the environmental footprint of harvesting natural materials needs to be compared with that of synthetic alternatives. While synthetic materials may not directly deplete biological resources, their production can lead to pollution, plastic waste, and long-term environmental damage. Thus, the ethical debate becomes a balancing act between the ecological footprint of natural material extraction and the potential harm posed by synthetic alternatives [94].

One of the core ethical concerns regarding the use of natural materials in regenerative orthopaedics is the potential for adverse immune reactions or disease transmission. Collagen, silk fibroin, and other natural materials have the advantage of being biocompatible, mimicking human tissues. However, there are inherent risks in using these materials in medical treatments, particularly when sourced from animals or marine life [95]. The use of animal-derived collagen, for example, can elicit immune responses in some patients, leading to complications such as inflammation, infection, or rejection of the material. These potential reactions raise significant ethical concerns, particularly because patients may not fully understand the risks associated with animal-derived materials. The possibility of disease transmission, particularly prions or zoonotic diseases, remains a critical issue, adding another layer of ethical complexity to the use of natural materials in orthopaedics [96].

When compared to synthetic materials, natural materials can sometimes offer a less predictable response. The question of whether synthetic alternatives, which are often designed to be inert and hypoallergenic, present fewer risks is central to the ongoing ethical debate.

5.1. Cultural and Religious Considerations

Natural materials derived from animals may also present ethical dilemmas in the context of cultural and religious beliefs. Many cultures and religions have specific dietary and lifestyle restrictions, such as prohibitions on consuming certain animals or using animal-derived products. For example, Islamic and Jewish laws prohibit the consumption of pork, and Hindu beliefs restrict the use of cow-derived products [97].The use of animal-derived collagen and other materials may conflict with these beliefs, raising ethical issues about the imposition of such materials in medical treatments. While synthetic alternatives may not have the same cultural or religious concerns, the use of natural materials may inadvertently marginalize individuals who adhere to specific cultural or religious practices [98].

In contrast, synthetic materials generally avoid such issues, providing a more culturally neutral solution to material sourcing. However, the ethics of using synthetic materials may revolve around other considerations, such as their environmental impact or long-term sustainability [99].

5.2. Access and Equity in Healthcare

Ethical considerations regarding equity in healthcare access also come into play when discussing natural materials in regenerative orthopaedics. The cost of acquiring and processing natural materials can be higher than for synthetic alternatives, making treatments using these materials less accessible to lower-income populations [100]. For instance, the extraction and processing of natural materials, particularly from animals or marine organisms, can involve complex procedures that increase production costs. For example, collagen derived from animals may be more expensive due to the need for intensive animal farming, whereas synthetic collagen or other biomaterials might be more affordable and easier to mass-produce. This disparity in cost can create ethical concerns around healthcare accessibility, particularly in low-resource settings [82].

Furthermore, the availability of natural materials is often limited by geographic factors, which can further restrict access to regenerative treatments. While synthetic materials may be produced and distributed globally, natural materials are subject to supply chain issues, regulatory constraints, and environmental factors that limit their widespread use.

5.3. Comparison with Synthetic Materials

The ethical considerations associated with natural materials must be weighed against those related to synthetic materials. Synthetic materials, such as polymers and composites, offer several advantages, including consistency, reproducibility, and lower costs. However, they also introduce their own set of ethical challenges.

- *Advantages of Synthetic Materials:* Synthetic materials avoid many of the ethical concerns associated with animal-derived products, such as animal welfare and cultural restrictions. Additionally, they are often more affordable and accessible due to their ease of production and scalability. However, synthetic materials are not without their own environmental and ethical concerns, including their biodegradability, recycling challenges, and pollution [83].
- *Disadvantages of Synthetic Materials:* Synthetic materials often lack the natural biocompatibility of animal-derived or plant-based materials. They can sometimes provoke immune responses, leading to complications that would not be as prevalent with natural alternatives. Furthermore, the production of synthetic biomaterials can involve the use of non-renewable resources and contribute to environmental degradation, raising ethical questions regarding their long-term sustainability [99].

As the field of regenerative orthopaedics evolves, innovations in material science are poised to address some of the ethical challenges associated with natural materials. Emerging technologies, such as lab-grown tissues and plant-based alternatives, hold promise for mitigating the ethical concerns of animal-derived materials. Advances in tissue engineering may allow for the creation of lab-grown materials that mimic natural tissues without the ethical issues related to animal sourcing. These materials could potentially be derived from human cells, reducing the risk of immunogenicity and disease transmission while offering a sustainable, ethically sound alternative to traditional biomaterials [101].

Ethical considerations regarding the use of natural materials in regenerative orthopaedics are multifaceted, involving animal welfare, environmental sustainability, cultural sensitivity, and patient safety. While natural materials offer unique advantages in terms of biocompatibility and healing potential, they also raise significant ethical concerns related to sourcing, sustainability, and equity in healthcare access. A notable example is the use of porcine collagen in dental grafts, which highlights concerns about animal welfare and the sourcing of materials. These ethical challenges require careful consideration by medical professionals, researchers, and policymakers as they work to balance innovation with responsibility in the development and use of natural biomaterials in regenerative medicine.

6. Future Directions and Potential for Regenerative Medicine

Regenerative orthopaedics is at a crucial juncture, with new technologies and materials rapidly advancing our ability to repair, regenerate, and replace damaged musculoskeletal tissues. While the use of natural materials in regenerative orthopaedics has shown promise, the future holds even more potential with the incorporation of advanced techniques such as hybrid materials, stem cell therapies, gene editing, and 3D printing. These innovations, which are being developed and refined with each passing year, are pushing the boundaries of what is possible in tissue regeneration. By focusing on these future advancements and their potential applications, we gain a clearer picture of how regenerative orthopaedics may evolve over the next few decades.

6.1. Hybrid Materials: A Fusion of Natural and Synthetic Components

Hybrid materials, which combine natural and synthetic components, represent one of the most exciting areas of future development in regenerative orthopaedics. These materials aim to overcome the limitations of purely natural or synthetic materials by capitalizing on the strengths of both. The potential for hybrid materials to enhance the regenerative properties of orthopaedic treatments lies in their ability to provide mechanical strength, biological compatibility, and controlled biodegradability, all tailored to the unique needs of individual patients.

Among the standout natural materials, silk fibroin and recombinant collagen have shown particular promise. Silk fibroin, due to its exceptional mechanical properties and biocompatibility, is being explored for use in bone and cartilage regeneration. Recombinant collagen, produced through biotechnology, offers a renewable and customizable alternative to collagen sourced from animals, with potential applications in creating scaffolds for tissue engineering. These materials exemplify the future of regenerative orthopaedics, combining the best of nature with cutting-edge technology.

One of the key challenges in using natural materials for orthopaedic applications is their insufficient mechanical strength, particularly when used in load-bearing tissues such as bones and joints. However, combining natural materials, such as collagen, with synthetic polymers, such as polycaprolactone (PCL) or polylactic acid (PLA), can overcome these weaknesses. Hybrid scaffolds that incorporate both types of materials not only provide improved mechanical strength but also promote tissue regeneration and cell growth. The future potential for these materials lies in their ability to match the biomechanical properties of native tissues while maintaining the biological signalling required for tissue repair [102]. With ongoing research and development, hybrid materials could become a staple in bone grafts, cartilage regeneration, and tendon repair.

Hybrid materials can also be customized to meet the specific requirements of various orthopaedic applications. For example, in bone regeneration, hybrid materials can be designed to provide both structural support and promote osteointegration, the process by which new bone cells adhere to the surface of the scaffold. In cartilage repair, hybrid materials can be fine-tuned to support chondrocyte (cartilage cell) growth and encourage the regeneration of functional cartilage tissue. As these materials continue to evolve, their ability to be tailored for different orthopaedic tissues will become even more precise, improving their clinical success rates and reducing complications [103].

6.2. Stem Cell Therapies: Enhancing the Body's Natural Healing Abilities

Stem cell therapies are one of the most promising areas in regenerative medicine, offering the potential to regenerate damaged tissues from within the body. By harnessing the body's own regenerative capabilities, stem cells can differentiate into various tissue types, including bone, cartilage, and muscle, providing a natural means of healing. Stem cell-based therapies in orthopaedics are already in clinical trials for a range of conditions, including osteoarthritis, tendon injuries, and bone fractures. However, the future potential of stem cell therapies goes far beyond current applications.

One of the most exciting future applications of stem cell therapy in orthopaedics is the ability to regenerate large segments of damaged or degenerated tissues. For example, in patients with osteoarthritis, MSCs can be used to regenerate cartilage, reducing the need for joint replacement surgeries. As research progresses, stem cell therapies could allow for the regeneration of entire joints, offering a more permanent solution to joint degeneration [90]. Furthermore, stem cells could be combined with hybrid biomaterials to create scaffolds that provide both structural support and promote stem cell growth and differentiation, enhancing tissue regeneration.

Advances in stem cell research could lead to personalized treatments tailored to the individual patient. Using autologous stem cells (cells derived from the patient's own body) can reduce the risk of immune rejection, making stem cell therapies more effective and safer. Moreover, new techniques such as gene editing could be used to enhance the regenerative capabilities of stem cells, further improving their therapeutic potential [91]. This personalized approach to treatment could revolutionize orthopaedics by offering highly specific solutions for each patient's unique condition.

6.3. Gene Editing: Precision Medicine and the Future of Regenerative Orthopaedics

Gene editing technologies, particularly CRISPR-Cas9, hold immense promise in the field of regenerative orthopaedics. By allowing scientists to directly modify the genetic makeup of cells, gene editing can be used to enhance the regenerative potential of tissues, improve stem cell function, and even correct genetic defects that contribute to musculoskeletal diseases. The future of orthopaedics may involve precise, individualized gene therapies that promote tissue repair and regeneration at the genetic level.

Gene editing can be used to optimize the differentiation of stem cells into specific tissue types, such as bone or cartilage. By introducing specific genes that promote the formation of these tissues, researchers can create stem cells that are better suited for regeneration. For example, gene editing could be used to enhance the production of bone morphogenetic proteins (BMPs), which are critical for bone growth and healing. This could significantly improve the outcomes of stem cell-based therapies, especially in challenging cases such as large bone defects or advanced osteoarthritis [104].

Gene editing also has the potential to treat musculoskeletal disorders at their genetic root. For example, gene therapies could be developed to correct mutations in the genes responsible for conditions like osteogenesis imperfecta (brittle bone disease) or Duchenne muscular dystrophy. By directly editing the genes associated with these disorders, gene editing offers a potential cure, moving beyond symptom management to the eradication of the disease itself [92]. This precision approach could revolutionize the treatment of genetic musculoskeletal conditions, providing more effective and lasting solutions.

6.4. 3D Printing: Revolutionizing Personalized Orthopaedic Solutions

3D printing, or additive manufacturing, is set to transform regenerative orthopaedics by enabling the creation of highly customized implants and scaffolds. This technology allows for the precise fabrication of materials with complex geometries that perfectly match the patient's unique anatomical structure. In orthopaedics, 3D printing can be used to create personalized implants for joint replacements, bone grafts, and even custom scaffolds for tissue regeneration. The potential for 3D printing to create personalized solutions is vast, and ongoing advancements are pushing the boundaries of what is possible.

One of the most exciting applications of 3D printing in regenerative orthopaedics is the creation of patient-specific implants. By using medical imaging techniques like CT scans and MRIs, clinicians can design and print implants that are perfectly matched to the patient's anatomy. This precision not only improves the fit and function of implants but also reduces the risk of complications, such as implant failure or misalignment. For patients undergoing joint replacement or fracture repair, 3D-printed implants offer a more tailored and effective solution compared to traditional off-the-shelf implants [93,105].

Another groundbreaking potential of 3D printing lies in bioprinting, which involves printing human cells along with biomaterials to create functional tissues. While this technology is still in its early stages, it holds the promise of printing tissues like bone, cartilage, and skin for use in orthopaedic treatments. In the future, bioprinting could be used to create fully functional tissues for transplantation, eliminating the need for donor tissue or synthetic implants altogether [106]. As research in this area progresses, the ability to print complex tissues could significantly improve the outcomes of regenerative orthopaedic treatments.

The future of regenerative orthopaedics is rich with potential, driven by innovations in hybrid materials, stem cell therapies, gene editing, and 3D printing. These advancements hold the promise of transforming orthopaedic medicine, offering personalized, precise, and effective solutions for a wide range of musculoskeletal injuries and diseases. As research and development continue, the boundaries of what is possible in tissue regeneration will continue to expand, providing new hope for patients and improving the quality of life for those suffering from chronic conditions. The integration of these technologies will undoubtedly shape the future of orthopaedics, offering more durable, biologically integrated, and individualized treatments for patients around the world.

7. Conclusions

Natural materials have played a foundational role in the development of orthopaedics, with their use in healing and stabilizing musculoskeletal injuries tracing all the way back to ancient civilizations. From the application of bone and plant-based materials for fracture stabilization to the early attempts at tissue regeneration, natural substances have been integral in shaping orthopaedic practices. These materials were the first tools available to heal fractures, restore mobility, and aid in tissue repair long before modern advancements in synthetic biomaterials. Today, natural materials continue to play a critical role in regenerative orthopaedics, especially in tissue engineering and regenerative medicine, where they offer a bio-compatible foundation for the healing process.

Despite their lasting significance, natural materials face several inherent challenges that have limited their use in clinical orthopaedics. These challenges include insufficient mechanical strength for load-bearing applications, unpredictable biodegradation rates, and the risk of immunogenic reactions when these materials are introduced into the body. Ethical concerns around sourcing, particularly with animal-derived materials, also persist as a point of contention in their widespread application. However, the promise of natural materials in advancing musculoskeletal healing is undeniable, with ongoing research focusing on overcoming these limitations.

The future of regenerative orthopaedics lies in the further development of bioengineered natural materials, which seek to address current shortcomings while maintaining the benefits of biocompatibility and functionality. Hybrid materials, combining the advantageous properties of both natural and synthetic materials, are already being explored to create scaffolds with improved mechanical properties, controlled biodegradation, and enhanced tissue regeneration. Advances in 3D printing technology and stem cell-based therapies also promise to unlock new potential in creating personalized, patient-specific treatments that are tailored to individual anatomical and functional needs.

Looking ahead, the role of natural materials in regenerative orthopaedics is poised for significant growth. As bioengineering techniques advance, these materials are expected to become even more vital in developing therapies that regenerate bone, cartilage, and other tissues while simultaneously restoring function and improving the quality of life for patients. With ongoing innovations, natural materials could ultimately lead to groundbreaking treatments that surpass the limitations faced by current synthetic alternatives, allowing for more effective, long-lasting solutions in the management of orthopaedic disorders.

Natural materials, having been used in regenerative orthopaedics for thousands of years, continue to hold vast promise for the future. By overcoming the current challenges and building on their historical applications, these materials could play an even more significant role in the development of advanced regenerative therapies, offering transformative benefits for patients suffering from musculoskeletal injuries and disorders. The continued exploration and innovation in the field of natural materials in orthopaedics will likely be pivotal in shaping the future of musculoskeletal care, with potential breakthroughs that could revolutionize treatment strategies and enhance patient outcomes.

Author Contributions

O.V.: conceptualization, writing—original draft preparation and editing, visualization; R.L.J.: writing—reviewing and editing; D.C.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Novel data were not generated.

Conflicts of Interest

The authors declare no conflict of interest.

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