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Cellulose and Lignin-Derived Scaffold and Their Biological Application in Tissue Engineering, Drug Delivery, and Wound Healing: A Review

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Abstract

The goal of tissue engineering is to repair and regenerate diseased and damaged tissues and organs with functional and biocompatible materials that mimic native and original tissues which leads to maintaining and improvement of tissue function. Lignin and cellulose are the most abundant polymers in nature and have many applications in industry. Moreover, recently the physicochemical behaviors of lignin and cellulose, including biocompatibility, biodegradability, and mechanical properties, have been used in diverse biological applications ranging from drug delivery to tissue engineering. To assess these aims, this review gives an overview and comprehensive knowledge and highlights the origin and applications of lignin and cellulose-derived scaffolds in different tissue engineering and other biological applications. Finally, the challenges for future development using lignin and cellulose are also included. Plant-based tissue engineering is a promising technology for progressing areas in biomedicine, regenerative medicine, and nanomedicine, with much research focused on the development of newer material scaffolds with individual specific features to make functional and biocompatible tissues and organs for medical applications.

Keywords: Cellulose, Drug Delivery, Lignin, Scaffold, Tissue Engineering

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Introduction

Tissue engineering for the first time in 1993, was defined as “an interdisciplinary and modern science”. The goal of tissue engineering is to repair and regenerate diseased and damaged tissues and organs with functional and biocompatible materials that mimic native and original tissues which leads to maintaining and improvement of tissue function (1, 2). Generally, tissue engineering aims to prepare a “scaffold” or three-dimensional environment cells to repair damaged tissues (3). Tissue engineering is made up of three vital components that work together to produce a successful structure, i. A biological scaffold that temporarily mimics extracellular matrix (ECM), provides a 3D structure for cell proliferation, differentiation, and attachment, ii. A set of relevant cells (differentiated cells and stem cells), and iii. Suitable signals include chemical mediators (vitamins, hormones, growth factors, amino acids, and cytokines), and physicochemical and mechanical factors (4, 5).

Tissue engineering has continued to evolve as an exciting and multidisciplinary field aiming to develop biological substitutes to restore, replace or regenerate defective tissues (6). Cells, scaffolds, and growth-stimulating signals are generally referred to as the tissue engineering triad, the key components of engineered tissues. Scaffolds, typically made of polymeric biomaterials, provide the structural support for cell attachment and subsequent tissue development. However, researchers often encounter a variety of choices when selecting scaffolds for tissue engineering (7, 8).

Scaffolds are produced from diver’s biomaterials and manufactured using various techniques and used in tissue engineering to regenerate different tissues and organs in the body (1). Regardless of tissue types, there are some important criteria to determine the suitability of used scaffold in tissue engineering such as: a. Biocompatibility: the used tissue construct or scaffold must produce a negligible immune reaction in order to prevent a severe inflammatory response that would reduce repair or reject the scaffold (9). b. Biodegradability: The scaffold or tissue must be biodegradable to allow cells to develop their ECM. The by-products of this process should also be non-toxic and able to exit the body without affecting other organs and cells (6, 10). c. Mechanical properties: The suitable scaffold must have mechanical properties similar to the anatomical site implanted in and, it should be strong enough to allow handling during implantation. d. Scaffold architecture: Scaffolds must have an interconnected pore construct and high porosity to allow adequate diffusion and penetration of nutrients to cells within the structure

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and the extra-cellular matrix formed by these cells. Moreover, a porous interconnected construct is needed to allow the disposal of waste and by-products of scaffold degradation out of the scaffold without affecting other tissue and cells (11).

Annually, approximately 50 million animals are killed in research (12). Animal testing is extensively used for in vitro analysis of organ engineering and pharmacologic materials for regenerative medicine or transplantation (8, 13). Moreover, the source of animal-derived scaffolds are often limited, unstable, or sometimes contaminated with human pathogens. However, plant-based systems require less energy and chemicals and are also not contaminated with human pathogens (14, 15). In theory, cost-effective and stable production of plant-based scaffolds are feasible and appropriate for use in the biological application (14).

In recent decades, many studies have started to use plant-based scaffolds to provide biomechanical and structural scaffolds for regeneration of mammalian cells, thus providing a way to use plant material to produce large tissue grafts. Plant materials and tissues have significant properties that make them very appropriate for use as scaffolds, including high biocompatibility and biodegradability, vast surface area, inexpensiveness, preexisting vascular networks, appropriate mechanical features, suitable pore size and large porosity (16). Plant scaffolds are easily produced and manipulated in large volumes due to their inexpensiveness and renewability. Nevertheless, these materials must be analyzed in animal models, and further studies are needed. Moreover, some studies have suggested the toxicity of these structures (17). Despite all these issues, nowadays many studies are being conducted on the application of plant-based scaffolds in tissue engineering, mentioned below.

Cellulose and lignin have many applications in industry, including use in the production of biofuel, adsorbents, fillers, dispersants, additives, and surfactants (18, 19). Moreover, recently, these biomaterials have been considered by researchers. These researchers reported that the intrinsic properties and discovery of the new physicochemical and biological behavior of cellulose and lignin and using them in various applications ranging from tissue engineering, food science, drug delivery, materials science, skin products, biofuel, energy and catalysis (20-22). Therefore, the quantity of studies conducted on the biological use of cellulose and lignin is expanding rapidly (22, 23). Recently, due to the significant properties of plant-based scaffold including biocompatibility, reactivity, biodegradability, and other biological and physicochemical properties, the use of cellulose and lignin in biological applications including tissue engineering, wound healing and drug delivery are gaining considerable interest (19, 22, 24) (Fig.1).

Cellulose and lignin are widely studied and used for tissue engineering due to high biodegradability, biocompatibility, and non-cytotoxicity (25, 26). The highly organized structure of cellulose and lignin can endure biodegradation in the absence of lytic enzymes. Due to their biocompatibility, water absorption and retention capacity, chemo-mechanical properties, and optical translucency, these biomaterials can play a significant role in the cell and tissue replacement and mimic the natural microenvironment of the human body, hence supporting cell and tissue regeneration (27).

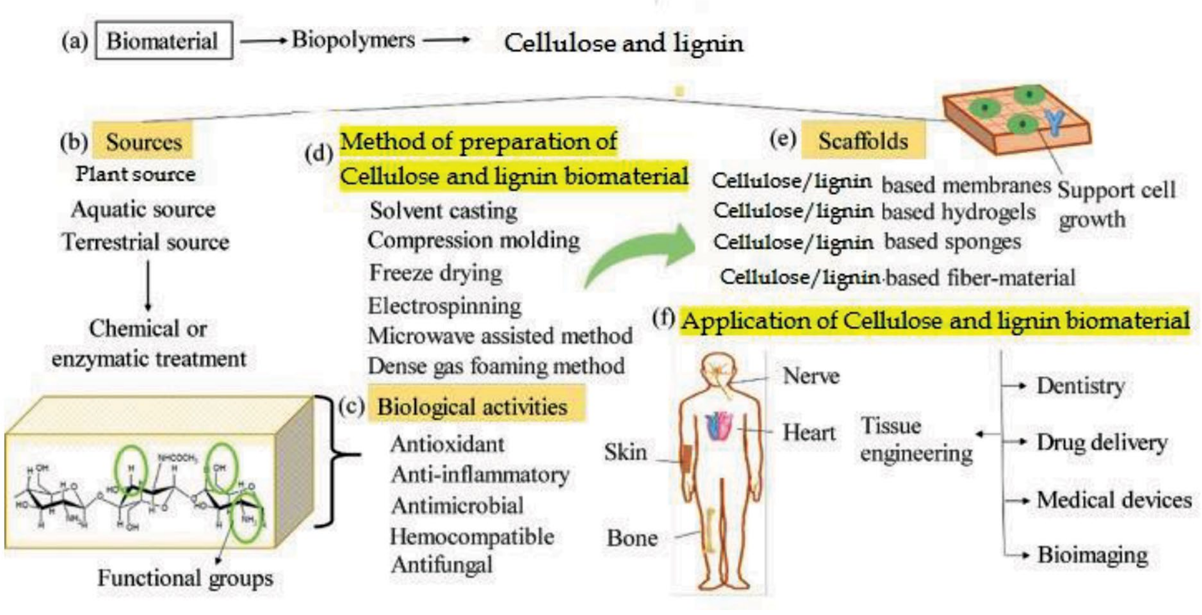

Fig.1: A detailed scheme of sources, preparation methods, biological activities, different types of cellulose and lignin derived scaffold, and applications of cellulose and lignin in tissue engineering (28).

This study presents an extensive insight into the advances, challenges, and future vision in plant-derived scaffolds: lignin, cellulose, and composite scaffolds, with an overview of applications in tissue engineering, drug delivery systems, and wound dressing. Despite having a high potential for applications in different fields, extensive use of lignin and cellulose is largely limited to industrial applications, and less used for medical and biological purposes. Due to this effort, this review demonstrates the recent advance and insight into the biomedical application of plant-based scaffolds.

Cellulose-derived scaffolds

Cellulose is the most prevalent polysaccharide in nature. It can be extracted from numerous sources. For example, the cell walls of plants, many species of algae and bacteria, although tunicates, that are the only animals containing cellulose led researchers to discover new applications for cellulose (1, 5, 8, 29). Due to its shapes and dimensions, and physical features, cellulose exists in the diverse morphological forms of fiber, nanofibril, and nanocrystalline (29, 30). These different types of cellulosic particles are based on the inherent variability between the sources of materials or due to the conditions of processing and biosynthesis that determine the dimension and geometry of cellulose particles. These various cellulosic particles, as scaffolds, make materials of diverse properties and microstructures needed for different biological applications (30, 31).

Lignin-derived scaffolds

Lignin is the second most abundant molecule in nature and exists in the cell walls of vascular plants (32). Lignin is a cross-linked polymer composed of phenylpropanes and monolignols in different proportions among various plant species. Annually, more than 80 million tons of lignin derivate products are produced from the pulp industry; however, only less than 3% of this amount has been used for commercial application of adhesives, surfactants, and dispersants for rubbers and plastics (32, 33). Recent reports showed that lignin has high thermal stability, durability, good biocompatibility, antibacterial, and the potential of protecting cells from oxidative stress, making it potentially appropriate for biomedical applications (21, 22). Moreover, lignin due to its phenolic hydroxyl groups, which have a significant ability to eliminate free radicals can act as an antioxidant (22, 34).

Because of the low viscosity and brittle of lignin, it can hardly be used to make fibrous membranes. To overcome this limitation, lignin polymers can be conjugated with different polymers, including isopropyl acrylamide, polyethylene glycol (PEG), lactic acid, cellulose, and polypropylene (35). These copolymers can be readily introduced into hydrogels, fibrous membranes, and nanoparticles for biomedical usages, such as drug delivery, wound healing, and tissue engineering (36).

Application of cellulose and lignin-derived scaffold in tissue engineering

Tissue engineering is an area of restorative medicine that originated from the field of biomaterials development. In general, tissue engineering improves, repairs, and maintains the function of damaged organs or tissues by combining biologically active molecules, scaffolds and cells (37, 38). For example, in the treatment of burn wounds, several treatment strategies have been considered, which usually use crushed and whole skin grafts (16, 39). Although this treatment option is available, grafting carries the risk of organ or tissue rejection and transmission of infection. Moreover, it requires additional surgical processes making it difficult to find healthy donor tissue. But tissue engineering provides a hopeful outlook for patients with chronic and severe injuries (40). A tissue or organ can be engineered using cells (stem cells are made of tissue), scaffold (material that prepares support for cells proliferation and growth), or mediators (such as bioactive molecules including cytokines or growth factors which lead to assemble the cells in the proper shape and functioning). For instance, in clinical practices, the use of human tissues or cells is strictly controlled by different regulatory laws, while the use of scaffolding is free of such rules and conditions (41).

Many bio-polymers, such as laminin, lignin, cellulose, chitosan, fibronectin, polyethylene glycol, collagen, polyurethane, and polycaprolactone are widely reported as the biomaterial for scaffolding preparation (8). Regardless of the type of tissue, several factors including biodegradability, biocompatibility, scaffold architecture, mechanical features, and construction technology are critical when designing the scaffold suitable for application in tissue engineering (16). In engineered tissues, the scaffolds imitate the ECM in natural tissues. Some important methods for processing the scaffold are listed below: embedding cell-seeded acellularized allograft or xenograft ECM, implantation of cell-seeded pre-made porous scaffolds, injecting cell-encapsulated self-assembled hydrogels and insert multilayer cell sheets with the secreted ECM (6, 16). Moreover, self-assembly methods such as Langmuir-the Blodgett approach for electro-spinning and preparation have been used for vascular and bone tissue scaffold assembly (6).

Huge groups of biomaterials, including ceramics, and synthetic and natural polymers are used for the preparation of tissue engineering scaffolds (42). Natural polymers such as plant carbohydrates or animal proteins, despite biocompatibility and chemical signals, can act as key elements in shaping cell behavior. In this regard, their efficiency is limited due to rapid biodegradability and poor mechanical properties (16). However, these disadvantages can be overcome by combining natural biopolymers with biocompatible synthetic polymers or by crosslinking methods with suitable cross-linkers, which may create an appropriate framework for applications of tissue engineering (42) Plants-based biopolymers consisted of plant proteins and polysaccharides including gluten, cellulose, lignin, and pectin which are routinely surveyed for biological applications (16, 43).

The synthetic, autologous, and animal-derived grafts currently applied as scaffolds for tissue engineering have limitations due to their scarcity, expensive nature, and low biocompatibility (44).

Application in Bone tissue

High mineralization and biocompatibility are critical for the scaffold formation in the restoration and treatment of the damaged bone (45). Solubility, high safety, renewability, and high biocompatibility are the reasons for using plant-based scaffolds such as cellulose and lignin in bone tissue engineering. Due to significant mechanical and biological strengths, including biodegradability and biocompatibility, cellulose and lignin have been intensively investigated for tissue engineering and treatment of damaged organs as safe and natural materials (46). The configuration of the 3D porous structure of cellulose and lignin scaffolds using freeze-drying assay and applying nontoxic solvent such as glycerol for the modification and preparation of reactant confirmed adhesion to this compound. By using these methods, the average tissue pore size was reduced, which significantly improved the compressive structure of the bone (47). In total, the results of studies conducted on the biological activity of the cellulose and lignin scaffolds have shown drug release, degradability, and biocompatible characteristics of these materials (48).

Application in skin tissue

The skin is the biggest organ of the body and is the first defensive line of the body against external factors such as toxic and mutagenic substances or microbial pathogens. Any injury to the skin following any chemical, electrical or thermal stimulant leads to skin complications and in unfavorable cases may lead to chronic and non-healing injuries (28, 49). Existing treatment methods and skin grafting assays show improper and delayed healing. Nowadays, tissue engineering provides a hopeful solution because it mimics natural systems in morphology, thus promoting an effective recovery process. This assay allows 3D cell proliferation and growth, as well as supports the production of growth factors required for cell differentiation and proper migration of skin cells (50). Cellulose and lignin-derived scaffolds are proper for tissue engineering as biodegradable, biocompatible, and non-toxic, and they can be configured to develop multipurpose structures with a natural matrix-like morphology (51).

The high potential of cellulose and lignin-derived membranous scaffolds is extremely surveyed to find their tissue engineering capabilities. For example, a study was conducted on a lignin film made of titanium dioxide nanoparticles having functional and structural regenerative properties (28). The membrane scaffold has good crystallinity and mechanical and flexible specifications. Furthermore, these membranes showed antimicrobial activities against diverse microbial pathogens. Application of lignin scaffold on mouse fibroblast showed fast growth, decreased apoptosis, and oxidative stress (26). Moreover, protein expression analysis showed, that fibroblast-associated biomarkers are involved in cell survival and growth at the membrane surface (52). The addition of glycerol caused long-term stability to the scaffold while an antimicrobial substance acted against microbial growth. The *in vitro* dermal fibroblast culture method showed increased proliferation of cells on the scaffold. The results showed that prepared lignin and cellulose scaffold can be used as an antimicrobial coating system to treat skin damage (53).

In vitro analysis of the scaffold showed suitable physicochemical and antibacterial properties against tested microbes which are shown to have an inhibitory ability against both gram-positive and gram-negative bacteria. Furthermore, lignin and cellulose scaffolds lead to effective modulation of cell proliferation. Therefore, plant-derived scaffold membranes have wound-healing and antimicrobial properties (16, 21). Hence, the biocompatibility analysis approved the tested scaffold, with no side effects on normal dermal fibroblast cells, and also, induced the growth and adherence of the cultured cells (54). Although, biocompatible cellulose and lignin-based scaffold membranes were prepared. The laboratory evidence revealed that cellulose and lignin-based scaffold materials can acts as suitable and effective modulators of the healing cells and. because of their antibacterial ability they can be a hopeful candidate for membrane production for skin tissue engineering (25).

Application in muscle tissue

Cellulose and lignin-derived scaffolds used in muscle tissue engineering are safe, cost-beneficial, and eco-friendly auxiliaries and solvents, which lead to the enhancement of biological mechanical, biodegradation and biocompatibility properties of muscle tissue (16, 17, 44). Muscle tissue engineering is the use of scaffolds and cells for the treatment and healing of damaged muscles with urgent elements to develop functional scaffolds such as natural muscles being able to contract. Proper methods such as plant-based plant-based techniques are required to produce scaffolds which are natural compounds or biomaterials, such as ECM, to produce muscle organs and tissues (55). Mimicking the fibrous conductivity and structure of the ECM for the electrical distribution of cardiac and skeletal myocytes should be sufficient for various muscle bio-actuators and scaffolds. Myocytes have electroactivity specifications and can respond to electrical signals. Hence, to simulate myocardial-based materials, we must contain ECM like nanofibrous structures and conductivity to allow electrical transmission (56). It is urgent to have flexible and electrically conductive safe materials to produce the elastic scaffolds and arrangement of the cell distribution while scaffolding treatment. To overcome these problems, various new degradable and conductive lignin-derived biopolymers with elastomeric properties were produced by the mentioned method have a high capability for the regeneration or treatment of elastic tissues for cardiac muscle, skeletal muscle, and nerve (57).

Application in neural tissue

Neural tissue engineering is an assay to eliminate fibrosis and inflammation after the implantation of material into the nervous tissue and system. The emergence of neural tissue engineering due to the difficulty of producing neural cells and tissues, after a neural injury is necessary (58). Schwann cell myelination is critical for nerve cells and the preparation of tissues and materials that can be produced from Schwann cells as tissues. Application of cellulose and lignin-derived scaffolds to regenerate Schwann cells myelin gene expression and neurotrophin secretion are examples of tissue engineering in nervous tissue engineering. Results of studies on inducing neurotrophin secretion from Schwann cells showed that electroactive and biodegradable cellulose and lignin-derived scaffolds had great potential for nervous tissue engineering (16, 58). A safe and biocompatible system for Schwann cells generating, is an example of the healing of peripheral nerve injuries. For instance, the application of cellulose and lignin-derived scaffolds for repairing the damaged sciatic nerves in rats showed that the produced scaffold can repair the sciatic nerve lining to preserve the nerve, restore axons, myelination and conduction in the target muscle (58).

Other applications of cellulose and lignin-derived scaffold

Wound healing

Wound dressings are permeable barriers to moisture and oxygen, which are not only crucial to the healing processes, but also protect the wound against further damage such as the risk of infection (59). Lignin and cellulose biopolymers, because of their remarkable properties, have been applied in wound dressings. They cover the skin around the wound, provide proper moisture in the wound, prevent the formation of microbial biofilms, remove dead spaces, cleanse the injured tissues, eliminate pain, and tissues and control bad odors (60, 61). Biopolymer hydrogel dressings are widely used due to their potential to hold closeness and moisture to the ECM, leading to wound healing induction. Nowadays, cellulose and lignin nanoparticles have been investigated to be used as suitable materials for wound healing, due to their high surface-to-volume ratio that can increase cell proliferation, migration, and attachment. The application of cellulose and lignin nanoparticles in wound treatment and healing was recently reported in several studies (61, 62). Cellulose and lignin nanoparticles, in combination with antimicrobial agents (tetracycline and mupirocin) were used to produce bioactive wound dressing to inhibit the colonization of bacteria, especially *Staphylococcus aureus* and *Escherichia coli* (62). The controlled release of drugs in wound dressings permitted the healing process in burn victims to be completed within 10-16 days (61).

Medical implants

Medical implants are designed and conducted to replace an injured structure or organ inside the body to be able to perform the normal function of that organ for example, hip replacement. Traditionally, materials such as synthetic polymers, ceramics, and metals have been applied for medical implants. Although these materials work suitably as implants, they immunogenic and inflammatory (63). Biopolymers such as cellulose and lignin have the capability to solve these issues as they are non-immunogenic, biocompatible, and biodegradable. Cellulose and lignin nanoparticles have shown hopeful results for medical implants and non-biodegradable implants with appropriate shapes and mechanical properties. Cellulose and lignin have antimicrobial properties and could be applied as antimicrobial coatings on other implants, such as catheters, which leads to a decrease in the colonization of bacteria on these devices. As a result, it reduces infections caused by this equipment. Moreover, hemicellulose-based hydrogels were recovered from pulping of eucalyptus and N-isopropyl acrylamide obtained via UV photo-crosslinking showed a hopeful result for application as a safe and suitable material for medical usage (25, 63).

Drug delivery

Drug delivery systems are applied to obtain a higher dosage of a drug or other compound in a particular diseased site. Application of biopolymers such as cellulose and lignin in drug delivery systems have higher biocompatibility, biodegradability, and lower immunogenicity in comparison with synthetic peers. Biopolymers, such as lignin and cellulose can be easily converted into suspensions that act as vehicles for the delivery of drug molecules (64, 65). Lignin has been applied as a matrix producer for continuous drug delivery and as a film for the rapid release of low-soluble drugs. Moreover, in the study conducted on the controlled release of drugs to achieve wound healing dressings made of cellulose and lignin nanoparticles, the drug delivery potential of these materials have been reported. In total, this material shows good results in drug delivery and wound healing applications (64, 66).

Conclusion

Tissue engineering is a promising technology for progressing areas in biomedicine, regenerative medicine, and nano medicine, with much research focused on the development of newer material scaffolds with individual specific features to make functional and biocompatible tissues and organs for medical applications. It appears that cellulose and lignin-derived scaffolds are new-generation biomolecules that have eco-efficiency, cost-effectiveness, biodegradable and low immunogenicity properties which can be efficient in tissue engineering and other medical applications. In addition, creating complex vascular-like structural scaffolds is critical for transforming cell culture from simple assemblies to functional tissues. Sourcing cellulose and lignin from plant tissues can reduce the cost and simplify the scaffold producing process. Despite all the above advantages in using cellulose and lignin-derived scaffold, due to lack of clinical trials results, the application of these biomaterials in various applications is limited. To overcome the barrier among the research and applications of the sustainable valorization of these material, more studies are required to be carried out in the future due to elucidate their construct, reaction mechanisms and interactions with body microbiota.

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Authors' Contributions

R.Ch., M.R.R., B.H., L.R.; Contributed to the study conception and design, material preparation, data collection and analysis performed by R.Ch. and L.R. The first draft of the manuscript was written by R.Ch., M.R.R. B.H.; Commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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