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A review on biomaterials on wound healing

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Abstract
Skin injury and wound healing are complex biological and compatible processes that involved in the activation of inter-cellular pathways, co-ordination of tissue integrity and homeostasis. The wound can be categorized into acute and chronic depending upon the nature and depth of injury. The important part of the wound healing is wound care dressing. Wide varieties of dressing materials are available to intensify the activity of wound healing. Numerous plants are reported to posses wound healing property. The consummate wound dressing biomaterial act as a three-dimensional template which can mimic extracellular matrix, be biologically stable, flexible and can remove the wound exudate by providing the moist environment to the wound site. It protects the wound from the external hazards and act as a bed. Now-a-days polymer-based biomaterial attracts the researcher for biomedical applications. This article presents a review of variety of polymer-based biomaterials, characteristic features, history, divisions, chemical structures and its formulations used in pharmaceuticals.

Keywords: biopolymer, biomaterials, skin injury, extracellular matrix, hyaluronic acid

1. Introduction

Wound healing is enhanced by the plant products rich in active principles such as terpenes and alkaloides [1] and biomolecules [2]. The process of wound healing is broadly categorized into inflammatory phase, proliferative phase and finally the remodeling phase which ultimately determines the strength and appearance of healed tissue [3]. Likewise the wound dressing material also must have some conditions and should exhibit repose of application and proper adherence left for bacterial proliferation [4] (Quinn *et al.*,1985.). An important aim in providing topical wound care is to select a suitable wound dressing that should manage exudates and maintain a moist wound surface [5]. Wound healing is a dynamic or active or powerful process of regenerating dermal and epidermal tissue and the performance requires a dressing that injured part to as near its normal condition as possible. Healing thus is an complicated process initiated in response to an injury that restores the function and integrity of damaged tissue [6]. In recent past considerable research was done in the field of dermal substitution and wound healing. Nowadays both artificial and natural materials have been used for reconstitution of dermis [7]. An ideal wound healing material should be non cytotoxic, harmless, maintain cell viability and should induce migration, and proliferation of epithelial cells fibroblasts and endothelial cells as well as extracellular matrix components required for wound repairing process [8]. The several natural products or biomaterials promote the process of wound healing [9]. A thorough literature work is carried out on the preparation of biomaterials on wound healing. The skin gives the primary protection against infection by acting as a physical barrier. When this barrier is damaged by pathogens, there is a direct route to infiltrate the body, potentially resulting in infection [10].

Biomaterial

Most popular and often cited definition of the biomaterial is, as a nonviable material that intends to interact with physiological environment [11]. While the biomaterial definition was reframed as a non - drug substances which is suitable for inclusions in systems which augment or replace the function of bodily tissues or organs [12]. Any non-drug materials that can be used to treat, enhance or replace any tissue, organ or function in an organism is derived as biomaterial [13].

Haemostasis, is the process of wound healing follows a progression of events including inflammation, generation of new tissue, and remodelling of the nascent tissue; these phases occur over timescales that range from hours to many months. Biomaterials can be used to augment the natural repair process at all stages of wound repair, depending on the aspect of the repair process that is looking to be modulated. Ideally, biomaterials are designed/chosen according to the underlying biological process that is being targeted – there is no determined set of biomaterials that are ideal for one aspect of the wound healing process. This diversity and complexity in options for biomaterials mirrors the complexity of the biology underlying the process of wound repair.

2. Reports of plants as biomaterials involved in wound Healing

In tissue engineering, the collagen scaffolds such as skin, cartilage, bone and nerve are employed as a support for cell mobility infiltration, proliferation and differentiation [14, 15, 16]. The wound healing potential of plants like *Aloe vera* [17], *Allium cepa* Linn [18] was reported recently. Noorgahan *et al.* [19] prepared the wound dressing material based on physiologically clotted fibrin [PF] and its craft copolymers. Choudhary *et al.* [20] reported the wound healing activity of ethanolic extract of *Terminalia bellirica* Roxb fruit on excision and incision wound models. For dermal wound healing Gomathi *et al.* [21], used quercetin incorporated collagenous matrix and tested in rat. In the treatment of skin and epithelium wound, the extracts of polysaccharide containing plants were widely employed [22]. Trombetta *et al.*

[23] 2006 studied about the plants which contain polysaccharides and its wide use for the treatment of skin and epithelial wounds and of mucus membrane irritation. Senthil Kumar *et al.* [24] reported that the *Triphala* extract was incorporated in collagen sponge and its effectiveness was evaluated in healing of infected dermal wounds. Due to the anti ulcer and wound healing activities the extract of *Opuntia ficus-indica* cladodes were used in folk medicine. The phytochemical studies in *Piper hayneanum* revealed that presence of phytochemical compounds which had antimicrobial activity and wound healing property [25]. Varatharajan *et al.* [26] reported that soya protein and sago starch made composite film used as a wound dressinng material healed the wound faster. Composites of chitosan, *Calendula officinalis* and Aloe vera had efficacy as wound dressing for diabetic foot sore [27]. For burn wound care the *Fagonia sp.* extract loaded Chitosan topical gel accelerates the re-epithelialization of skin wound with proper healing process after burn [28].

3. History of biomaterial usage

As early as the first century AD, the physicians were belonged to Greece and India, were using natural biomaterials while performing plastic surgery to repair mutilations from battle and punishment [29]. The new interest in natural biomaterials could really be considered as revival. Historians have marked use of sutures made from animal sinew to ancient Egypt, while some say they were even used even earlier [29]. In ancient Phoenicia, the loose teeth were bound together with gold wires, trying artificial teeth to neighboring teeth [30]. In the early 1900's, to stabilizing bone fractures, the bone plates were successfully implemented to accelerate their healing [30]. At a time of circa 2650 BC when disease were still thought to be of mystical origin, the Egyptian high priest and physician Imhotep developed on evidence based guide for treating wounds that includes using bioactive substances such as honey and copper. Many of the details are entered in the form of written evidences on the Edwin Smith Papyrus, an ancient text that dates to circa 1600 BC [31]. For the hip replacement surgery, the ivory was used in Germany in 1891 AD. Even the ivory was inexpensive cost, it is used for its biomechanical bonding qualities, which make its well suited to work with human body tissue [32]. The biomedical materials, was first used by ancient Egyptians who employed coconut shells to repair injured skulls; wood and ivory as false teeth and these dated as far back as 3000 BC [32]. Theoretically any material may be natural or man-made can serve as a biomaterial as long as it serves the stated medical and surgical purposes. The mankind develops the main strategies to promote wound healing in ancient times onwards [33]. The honey and metal ions are the key bioactive constituents in some of our most advanced wound dressing for more than4500 years [34].

4. Characteristics of biomaterials

Naturally derived biomaterials are act as the facilitators to enhance the wound healing activity and regeneration. In the field of modern medicine, biomaterial research is the most important one. Biomaterials are employed in organ implants, wound healings, drug delivery, and so forth. Biomaterials are biodegradable, biocompatible, and nontoxic [35]. A functionalizable free hydroxyl group of biomaterials allow facile modification with biomolecules, which can lead as versatile biomaterials that afford controlled interaction with cells and tissues.

The key factor for the usage of biomaterial is due to its biocompatibility, bio-functionality, and availability to a lesser extent. Biomaterials are specially designed with a range of properties that are capable of either promoting or inhibiting specific host cell and tissue responses [36]. The choice of biomaterial depends on the type of procedure being performed, the condition of the patients and the surgeons preference. The prime reason for the usage of biomaterials to provide a remedy for surgical problems [36]. Biomaterials are biologically derived materials employed for their structural rather than biological properties. For example collagen is an ingredient of cosmetics and carbohydrates are being used as lubricants for biomedical applications and as bulking agents in the food industry [13]. The development of biomaterial is not a new area. It encompasses elements of medicine, biology, chemistry, tissue-engineering, and material science. An ideal biomaterial is described as, non- immunogenic biocompatible and biodegradable which can be functionalized with bioactive proteins and chemicals. One of the most important essential properties of biomaterial is biodegradability [37].

5. Division of biomaterials

Biomaterials are classified into four groups, namely; polymers, metals, ceramics and natural materials. Composite materials are comprised of two or more different classes of materials and they indicated as the fifth class of biomaterials [38]. By 2020, the utilization of natural biomaterials and nutraceuticals, Ireland will have the leading capacity.

6. Natural Polymer as Biomaterials

Several natural polymers are widely used as biomaterials which imparting 3-D Structures and their immense biocompatible and biodegradable properties. Natural polymers are widely applied in regenerative medicine, implantable materials, controlled release carriers or scaffolds for tissue engineering. The natural polymers are cellulose, chitin, chitosan, and gelatin which is used as drug delivery carriers, they are degraded into biologically accepted compounds, which leave the incorporated medications behind [39]. Good compatibility [40], biodegradable in nature and do not require any surgery for removal of polymers [41]. Biological dressings like fibrin glue, gelatin sheets, chitosan films and collagen are famous for acceleration of wound healing. These polymers show better results when used in combination such as fibrin-gelatin, fibrin-chitosan, than used alone [42].

6.1. Collagen

Collagen is mostly found in connective tissues and it is biodegradable and biocompatible one. Collagen was used to provide co-reaction of contour deformities and the first medical application of collagen was reported in human by [43]. Joseph Lister who founded the modern surgery, informed that the advantages of a biodegradable suture termed "cat gut" a collagen rich biomaterial. He prepared the catgut from small intestine of sheep [44]. Collagen is the most abundant of animal proteins and it is non-toxic to exogenous application which is endowed with high tensile strength. The use of collagen only began in 1881 as a modern biomaterial [45]. Bovine collagen was employed as suture and haemostatic agents after years. In 1980. Zyderm 1 was released, which a suspension form, containing sterilized bovine collagen that was used for injecting under the dermis in wounds. Now a days collagen is used for numerous biomedical applications [46, 47]. Glucose oxidase is incorporated with collagen matrix to promote the sustained delivery of growth factors, antibiotics, natural compounds and antimicrobial agents like silver at the wound site [48, 49]. The application of collagen suspension includesr dermal injection, topical haemostatic agents, wound dressing materials, collagen suture and catguts, collagen gels for predontal reconstruction, collagen sponges for the haemostasis and coating of joints, collagen rich pig skin wound dressing materials [50, 51]. When collagen matrix is applied on the wound bed the drastic changes occur within 10-14 days and improved wound is observed in the case of chronic wounds like diabetic foot ulcer or chronic venous leg ulcer. Collagen dressings absorb the wound fluid and establish moist environment around the wound, when in contact. The dressing are semi-permeable to oxygen and water. The hydrophyllic nature of collagen helps to retain the fluid and pick up cells containing phagocytosed microorganisms. It play a vital role in inducing clotting and forming matured scar at the wound site. It speeds up the re-epithelization of skin by combined with dermal cells, growth factors and cytokines derived from the patient. To deliver the therapeutic drug on the wound surface the collagen dressings are also designed as vehicles [49]. Neurotensin loaded collagen dressings act as wound healing accelerators that induce the activity of fibroblasts and granulation tissue to accumulate at the wound site leading to the production of sufficient organized collagen matrix [52]. Collagen is a suitable polymer to fabricate and design a wide variety of wound dressing materials because it has resemblance with structure and composition of skin. Collagen is the main protein present in extracellular matrix and it is abundantly found in mammals. It forms 70-80% of the dry skin weight and it has a tough triple stranded helical structure [53]. The cellular functions like cell shape, proliferation, differentiation and cell migration is regulated by collagen and it gives structural support to the body [48, 53]. The cellular and molecular cascades of wound healing is stimulated by collagen and it helps in the development of new tissue and wound debridement. To achieve as non-antigenic material, collagen dressings are further purified which are mostly derived from bovine, porcine or avian sources [54]. Collagen hydrogels have potential application in treating cutaneous wound infections and collagen sponges are widely used into treat deep cuts. Fibroblast and keratinocytes incorporated collagen scaffolds are used in skin grafting. It is also cross-linked with alginate and produced as a wound dressing materials [49, 54].

6.2. Gelatin

Gelatin is obtained through the controlled denaturing of collagen protein. Gelatin is widely used as a wound dressing in medicine, and also has been used as scaffolds for tissue engineering and as an adhesive, absorbent pad for surgical use [55, 56]. Gelatin film is entirely effective for wound closure purpose by exhibiting re-epithelization of the epidermis and repair of ECM in dermis. The deep partial thickness wounds are cured by gelatin sheaths. The limitation of gelatin is its mechanical properties. Different alginate dressings are studied which is unsuitable for healing a dry wound with hard necrotic tissues because, they dehydrate the wound easily resulting in delayed wound healing activity at wound site [57, 58]. Gelatin/poly ethylene glycol composites serve as a wound healing material with low cytotoxicity [59].

Recent research proposed that gelatin is definitely an effective biomaterial for wound dressing and it has a positive biological response to facilitate cell adhesion and proliferation [57]. Gelatin has a low antigenicity and is in-expensive unlike collagen [52]. Diabetic and venous stasis ulcers and trauma, the gelatin is preferred to be used as a blending agent with other polymers [52, 54].

6.4. Alginate

Mostly the alginate dressings are porous and without adhesive property. Zinc and silver loaded alginate dressings possess antibacterial properties [57]. Alginate can trigger the activity of macrophage and the level of cytokine at the wound site. Besides, Simvastatin loaded alginate dressing is non-toxic that serves as an excellent dressing which is prepared by solvent casting method and act as template to protect the wound and support the growth of fibroblast on it [58]. To produce the alginate sheaths, the alginates are cross-linked with polymers like gelatin, heparin and poly vinyl alcohol which directly controls the degradation of alginate. Besides calcium alginate and collagen alginate act as high absorbent fibre dressings and give a moist environment at the wound site.

Alginate loaded with growth factors like stromal derived factor-1 improves the wound healing activity [62]. Alginate is a non-toxic, mucoadhesive and pH sensitive and it is a linear unbranched polysaccharide which is composed of (1-4)-linked β-D-mannuronic acid and α-glucuronic acid residues. Alginate forms a reversible hydrogel which act as a 3-D platform form for cell transplantation and new skin formation [63].

6.5. Chitosan

To increase the stability of chitosan, this is cross-linked with natural polymers like collagen and gelatin. Chitosan silk fibroin composites form excellent bandage for skin tissue regeneration. Chitosan-nano-silver films possess antibacterial properties and chitosan films along with anti-oxidants are used extensively in dermal wound healing. By controlling the loss of physiological fluid, such film forms the dense layers which enhance the functional property of the dermis [48, 54]. To improve the mechanical strength, chitosan has been blended with PEG to achieve hydrogel [64]. It can be easily modified in to films, gels, scaffolds and sponges which easily applied to wound site as healing material. It enhances the synthesis of collagen and promotes fibroblast growth on it [65]. Extensive in vivo experiments on wistar albino rats for chitosan based dressing materials showed effective and progressive wound healing and its efficiency compared to normal cotton gauze [66]. Chitosan provides haemostatic and antibacterial properties and its unique property to heal wound makes it a suitable polymer for the fabrication of wound dressing materials. Generally chitosan is used as in pure form and also it is treated with cross linkers. The pure form of chitosan unsuccessful to provides mechanical support to the cells at the burn or wounded region. Crosslinking of chitosan increases the mechanical properties and it is provided the layered structure for skin tissue engineering [67]. Deacetylization of chitin gives the chitosan which is derived from crustaceans like shrimps and crabs, the exoskeleton of insects, invertebrates and cell wall of fungi. Chitosan is a poly N-acetyl-glucosaminoglycan and is the deacetylated form of chitin. It exhibits antibacterial properties and it is highly biocompatible, biodegradable, non-toxic and non-immunogenic [68]. It can be easily modified in to films, gels, scaffolds and sponges which easily applied to wound site as healing material. It enhances the synthesis of collagen and promotes fibroblast growth on it [68]. When chitosan blended with PEG, chitosan accelerates fibroblast proliferation by suppressing infiltration of inflammatory cells whereas PEG enhances epithelial [69].

6.6. Hyaluronic acid (Ha)

It can enhance the process of angiogenesis and decreases the intensity of chronic wound to acute wound [71]. Hyaluronic acid forms a three dimensional matrix when it combines with other polymers which structurally and biologically equivalent to the skin. HA, incorporated with silver-sulfadiazine in polyurithane foam, is broadly employed in wound healing applications [70]. Hyaluronic acid is a linear polysaccharide, and it is consist of N- acetyl-D-glucosamine and glucuronic acid. It is highly used for treatment of severe burns and wounds. Thiolated carboxy methyl hyaluronic acid based biomaterial enhance wound healing rate in rats. It can be synthesized in the form of gel, sheath, mesh and film. This polymer showed great pledge in animal and clinical studies of skin and tissue engineering [71]. Hyaluronic acid forms a three dimensional matrix when it combines with other polymers which structurally and biologically equivalent to the skin. HA, incorporated with silver-sulfadiazine in polyurithane foam, is broadly employed in wound healing applications [71]. (Anjum *et al.*, 2016). HA is a natural biopolymer that consists of D-glucuronic acid and 2-acetamido-2-deoxy-D-glucose.It is generally found in mammal's bone, tissues and synovial fluids [72, 73]. HA plays an important role in healing of various types of wounds by interacts with proteins, proteoglycans, growth factors and tissue components called biomolecules [74]. The interaction of hyaluronic acid plays an vital role in acceleration of tissue repair and wound healing. It protect the injured area against microorganisms due to their bacteriostatic activity [75].

7. Pharmaceutical formulations using biomaterials

Many pharmaceutical formulations have been recently developed as dressing material for wound and burn treatment.

7.1. FILMS/Membranes

Collagen films have been employed primarily as a barrier in wound healing and tissue engineering. Films of ~0.1 to 0.5mm thickness can be prepared from collagen solutions and air-dried in the manner similar to ophthalmological shields [76]. A blend of collagen and another polymer such as an atelo-collagen matrix, added on the surface of polyurethane films enhance the attachment and proliferation of fibroblasts, support their growth and promote the long term survival [77]. Films are ideal dressing material and it is commercially available. It is a homogenous polymeric network structure which are used to treat the damaged area and it is generally protect the wound and burn area against the external factors [78, 79]. The polymers used in the preparation of films include hyaluronic acid [80, 81], Chitosan and its derivatives [82]. Colloidal materials like carboxy methyl cellulose, alginates and elstomers or adhesives fabricated extensively in the form of films or sheets and importantly used for the treatment of light exuding wounds like minor burns, traumatic soures and injuries [83].

7.2. Gels/Hydrogels

Gels are viscous semi-solid preparations produced by dispersion of organic or inorganic substances that have bigger size than colloidal particles in a liquid phase. By a combination of one or more hydrophillic polymer, the hydrogels are formed which is a semi-solid systems. Gels/hydrogels are used frequently among all the dressing material in the treatment of wounds and burns. As they are capable of absorbing much more water than their weight, and reducing potential irritation when in contact with tissue and other similar structures. It permits oxygen penetration and keeps the moisture at the application site or wound site [84, 85]. Natural polymers are mostly preferred in the preparation of hydrogels. Chitosan and hyaluronan hydrogels are described as an ideal wound dressing material [60, 61]. The synthetic polymers are blended with natural polymers due to its poor adherence property, and to form composites, then it is applied for wound treatment.

7.3. Composites

Composite is an elastic outer layer with high mechanical strength which is developed for wound treatment. Composites are resistance to the effects of environment and provide moisture by preventing the evaporation. The unique property of collagen, chitosan and silver nanoparticles makes biocomposite sheets, which is one of the unique and ideal material for the production of moist healing wound dressings. Biodegradable and biocompatible property of biocomposite sheets has various pharmaceutical and biomedical applications such as drug delivery system and cells encapsulation [86]. Various clinical studies have been conducted of chitin nanofibrils/chitosan glycolate composites [87], salmon milt DNA/salmon collagen composites [88] etc. Composites of chitin and chitosan were found to be very promising in the treatment of wounds [87]. Chitosan and gelatin composite films may show improvement in wound healing property. Percentage of wound contraction was more for wounds treated with gentamycin loaded chitosan-gelatin composite film than chitosan film alone in wound healing activity [89].

7.4. Particulate Systems

The high advantages of particulate system are that, when applied to wound site they easily provide water vapour and oxygen permeability of the wound. Due to their multiparticulate structures they have high contact surfaces and high bioadhesiveness. The particulate system also controlled the drug release in the wound area and increases the speed of wound healing [90] (Kawaguchi, 2000; Date & Patravale, 2004.) In recent researches on micro/nano particulate system in wound and burn treatment, the usage of nitric acid nanoparticles [91], poly (ethylene-co-vinyl alcohol) nanofibre [92], fucoidan microparticles [93], collagen sponges [94], and liposomes containing epidermal growth factor [95] have examined. The biomaterial prepared with natural polymers incorporated with silver nanoparticles made as wound dressing material. It is non-toxic, biodegradable and biocompatible and it enhance the wound healing activity by providing a moist environment [96]. The extraction of silver nanoparticles from the *Hibiscus rosa-sinensis* will influence the regulation of fibrogenic cytkines and to enhance wound healing by accelerating re-epithelization and differentiation of fibroblasts [96].

8. Conclusion

In this review we have covered the biomaterials and its characteristics. In the past two decades, what are the plants itself used as the source of biomaterials are also knowledge about biomaterials and its types, healing mechanism, characteristics and division in biomaterials leads to design and develop the biomaterials successfully in future. However we have discussed here about natural polymers used as biomaterials and the presence of different pharmaceutical formulations as a dressing materials. It is plausible that this will pave the way forward in future developments for more advanced methods that will tackle the problems of synthesis of biomaterials and its application in wound healing process.

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