Review Article

Role of hyaluronic acid based hydrogel in management of wound healing effect

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Abstract

Hyaluronic acid (HA) is a natural polymer of the body capable of reaching high molecular weights leading to a excess of properties. HA is a high molecular weight biopolysaccharides, it is a natural linear dipolysaccharides consists of β -(1,4)-linked D-glucuronic acid and β -(1,3) N-acetyl-D-glucosamine units. HA is naturally degraded by hyaluronidases, reactive oxygen species, and by endothelial cells of the lymphatic vessels. HA plays an important role in regulating cell differentiation, migration, angiogenesis and inflammation responses. HA has been widely researched and applied in dermatology. It has shown to be effective as dermal fillers, anti-wrinkle agents, and in tissue regeneration. Serving as volumetric fillers, HA can treat superficial depressions thus improving skin quality. Hydrogels have several unique characteristic properties, including their similarity to tissue extracellular matrix (ECM), support for cell proliferation and migration, controlled release of drugs or growth factors, minimal mechanical irritation to surrounding tissue, and nutrient diffusion, that support the viability and proliferation of cells. Since HA is rich in carboxyl and hydroxyl groups, it can form a hydrogel under mild conditions like chemical modification, crosslinking or photo-crosslinking. HA's utilization in wound healing is an extremely intriguing area of research for the future. Most notably, HA is an effective alternative to mainstay treatment since it is a natural polymer of the body, thus having limited adverse reactions. Hyaluronic acid is a promising candidate for the tissue engineering field because of its unique physicochemical and biological properties. Thus, this review provides compilation of selective studies have been investigated to develop biocompatibility of hyaluronic acid based hydrogel for effective wound healing applications.

Keywords: Hyaluronic acid, hydrogel, wound healing, dermatology, drug delivery

Introduction

Hyaluronic acid (HA) is an unbranched biopolysaccharides having high molecular weight. It is a natural linear dipolysaccharides consists of β -(1,4)-linked D-glucuronic acid and β -(1,3) N-acetyl-D-glucosamine units (Figure 1). It is a polyanionic polymer with unique physicochemical properties and distinctive biological functions. A is presented in the human body specifically in neural and epithelial tissues. Thus, HA was chosen as a good polymer due to its biological, endogenous and

natural origin. Recently HA is known for its widespread biomedical applications such as ophthalmic surgery, arthritis treatment, polymeric scaffolds for wound healing, tissue engineering, cartilage repair, and drug delivery, and it has been used also as components for implant or scaffold materials. HA is naturally degraded by hyaluronidases, reactive oxygen species, and by endothelial cells of the lymphatic vessels. Hyaluronidases and reactive oxygen species degrade about 30% of HA while 70% is degraded

Figure 1. Chemical structure of Hyaluronic acid

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systemically by the lymph vessels. The activity of HA is somewhat depending on its molecular weight such as HA's with a molecular weight of >1000 kDa have anti-apoptotic activity whereas HA fragments with a mass of <200 kDa have a strong pro-inflammatory stimuli's. HA was first extracted by Karl Meyer and John Palmers in 1934 from bovine vitreous, and is now derived from additional sources such as rooster combs, shark skin, and many microorganisms (Fahmy et al., 2015). Hyaluronic acid or hyaluronan (HA) was named because of its transparent appearance in water and the probable presence of hexuronic acid as one of the components. HA is a linear polysaccharide without branches and is one of the most important components of extracellular matrix. Researches demonstrated that HA plays an important role in regulating cell differentiation, migration, angiogenesis and inflammation responses. The versatility of HA is closely related to its unique properties, and HA with its different states or molecular weights can exhibit diverse features. Therefore, to understand the application of HA, it's very must essential that we should have idea about the basic physical, chemical and biological properties of HA (Zhu et al., 2017).

Properties of hyaluronic acid

HA is an unbranched non-sulphated glycosaminoglycan composed of repeating disaccharides. Since HA is rich in carboxyl and hydroxyl groups, it can form a hydrogel under mild conditions like chemical modification, crosslinking or photo-crosslinking. The mechanical strength, physical and chemical properties of the materials depend on the degree of the modification and crosslinking (Tan and Marry, 2010). The physical properties of HA include its compressive stress, compressive modulus, storage and loss modulus, porosity, swelling rate, degradation rate and density (Collins and Birkinshaw, 2013). In physiological pH, HA is predominantly negatively charged and highly hydrophilic. The intramolecular hydrogen bonding minimizes free rotation, thus leading to a rigid conformation of polar and non-polar moieties. As the molecular weight increases the viscosity and viscoelasticity progressively increases. Due to its HMW the physico-chemical properties allow HA to modulate tissue hydration and osmotic balance creating a hydrated and stable extracellular matrix (ECM).

Physical properties of hyaluronic acid

The high hydrophilicity of HA is the physical basis for its wide presence in the human body. The molecular chains of HA are intertwined in solution and it occurs even when the concentration is very low. This phenomenon can be observed in HA solution as low as 1 mg/mL, which is one of the reasons to the unique rheological characteristics of HA (Zhu et al., 2017). In human bodies, especially soft tissues, HA has high viscosity even in diluted solutions this is because of high molecular

weights of HA. Moreover, the mutual macromolecular crowding in human body contributes to the higher viscosity (Cowman et al., 2015). With macromere concentrations from 2 to 20 wt.%, networks exhibited volumetric swelling ratios ranging from ~42 to 8, compressive moduli ranging from ~2 to over 100 kPa, and degradation times ranging from less than 1 day up to almost 38 days in the presence of 100 U/mL of hyaluronidase. Although higher molecular weight or crosslinking degree can result in improved compressive modulus that is essential in the tissue engineering of cartilage or bone, the viability of seed cells would be compromised (Burdick et al., 2005). In most instances HA exhibited a highly porous morphology, so that the cells can permeate easily into the scaffold. Under most circumstances, the HA macromere is degraded by hyaluronidase. However, it can also be degraded by reducing substances or at acidic pH values after modification (Cui et al., 2015).

Chemical properties of hyaluronic acid

HA has been used as excellent moisturizer in cosmetic dermatology due to chemical properties such as consistency, biocompatibility, hydrophilicity, limited immunogenicity and unique viscoelasticity because of these properties it is used in skin-care products as well as a potential biomaterial in tissue engineering. However, HA has greater and rapid absorption in human body without nay modification, which makes it unqualified in tissue engineering. To solve this problem, chemical modification is indispensable. Many biomaterials do not have a lot of chemically modified sites, while HA can be chemically modified with its hydroxyl, carboxyl and N-acetyl amino ends. The chemical modification of HA can be roughly divided into two types: esterification and crosslinking. The esterification is carried out to link HA with certain hydrophobic groups, reducing the poly anion properties of HA. Under certain conditions, the carboxyl group of HA can undergo esterification reaction to produce HYAFF, an esterified derivative of HA (Zhu et al., 2017). In this reaction, many different alcohols, such as fatty alcohols and aryl fatty alcohols can be bound to HA molecule sin order to improve the chemical properties of HA and its stability as a tissue engineering scaffold, as well as to extend its maintenance in the human body. The HA cross-linking is carried out to convert it from solid state to hydrogel state under mild conditions and to prolong its maintaining time in the human body (Segura et al., 2005). Besides the crosslinked HA also increases the mechanical strength remarkably as compared to the noncrosslinked one, which makes it more suitable for tissue engineering applications.

The cross-linking reaction of HA can be divided into complete or incomplete one. The complete cross-linking reaction causes the HA molecules to be covalently attached to the continuous polymer network so that HA is no longer soluble in the water. While the incomplete reaction prompts part of the covalent binding reactions of HA molecules, resulting in partial solubility after the reaction. 1-ethyl-3-(3dimethylaminopropyl) carbodiimide, divinyl sulfone, glutaraldehyde, butanedioldiglycidyl ether are the most common crosslinking agents (Zhu et al., 2017).

Biological property of hyaluronic acid

HA is synthesized by HA synthesis (HAS) on the cell membrane and it is the only glycosaminoglycan that is not synthesized in the Golgosome. There are three different HAS in mammals, HAS1, HAS2 and HAS3. The three enzymes are located on different chromosomes, producing HA with different molecular weights. The expression of HAS isoenzymes varies under different status of morphogenesis and pathology. For example, HA in infants is of abundant quantity, however, in the process of growing up it is gradually replaced by collagen fibers and proteolycins which accounts for the fact that mature tissue can withstand greater mechanical force. It is almost certain that most kinds of vertebrate cells synthesize HA at some point in their natural history. When fibroblasts, mesothelial or certain other kinds of cell are plated out in tissue culture, they surround themselves in a few hours with a transparent gel-like HA which can protect themselves against damage by immune cells, impedes virus infection and may be important in mitosis (Zhu et al., 2017).

Therapeutic uses of hyaluronic acid

HA was first used to control bone and cartilage healing. Likewise, in 1960 the use of HA as a viscous material for vitreous of the eye was evaluated. This became the framework of the concept of “matrix engineering” for improving and controlling the regenerative and development processes of both the circulatory and musculoskeletal systems. HA has been widely used in many fields, in particular medical, pharmaceutical, food, and cosmetics first commercial usage of HA was in 1980 as an ophthalmic viscosurgical device solution under the trademark of Healon®. Since then, HA has been applied to the fields of ophthalmology, rheumatology, and dermatology. Dermatology is a field of medicine focused on alleviating skin disease as well as to improve cosmetics (Greene and Sidle, 2015). HA has been widely researched and applied in dermatology. It has shown to be effective as dermal fillers, anti-wrinkle agents, and in tissue regeneration. Serving as volumetric fillers, HA can treat superficial depressions thus improving skin quality. Dermal fillers serve as one of the most common and useful treatments for wrinkles and folds and appeal to the growing population keen to

reverse the “signs of aging”. HA-based fillers appear to be ideal due to their low immunogenic potential and relatively long-lasting effect. A multicentre randomized double-blind study examined the safety and effectiveness of a HA dermal filler for nasolabial folds (NLFs) (Monheit et al., 2018). Nasolabial folds are the result of deep fat loss and muscle contour loss in the midface resulting in wrinkles and folds. The study compared VYC-17.5L, a non-animal HA gel with a control HA dermal filler. Patients were included if they were ≥ 18 years with two fully visible NLFs with a severity score of two (mild) or three (severe) based on a NLF Severity Score. Subjects were treated with both VYC and control, injecting VYC on one side and the control on the other side. Outcomes were assessed on the NLF Severity Scale, pre/post photographs, as well as patient satisfaction. 123 patients were treated and were followed up after six months. Treatment was given as single injections with a median volume of 1.7 mL. Patients reported injection site reactions of firmness, swelling, tenderness to touch, lumps/bumps, but were resolved within 60 days. Overall, the adverse events were mild to moderate with no serious events reported. Improvement of severity scores were seen in both groups, however patients were more pleased with the results from the VYC injection. The study indicated that the efficacy of VYC was non-inferior to HA control (Monheit et al., 2018).

As HA's anti-inflammatory properties were applied in OA, it is also tested in skin wound healing. Wound healing involves the control of inflammation, cell migration, and new tissue remodelling (Huang et al., 2019). HMW-HA exhibits anti-inflammatory, anti-bacterial, and even anti-oxidant properties since it is degraded by reactive oxygen species and free radicals (Huang et al., 2019). LMW-HA on the other hand demonstrates pro-inflammatory and immunostimulatory behaviours (Gao et al., 2019). The wound healing properties of HA are an intriguing area that has yet to be fully explored. HA has become a hotspot in the fields of scaffold materials in tissue engineering because of its ubiquitously distribution in vertebrate tissues, good biocompatibility and non-toxic degradation products (Zhu et al., 2017).

Hydrogel

Hydrogels are characterised by having several unique properties, including their similarity to tissue extracellular matrix (ECM), support for cell proliferation and migration, controlled release of drugs or growth factors, minimal mechanical irritation to surrounding tissue, and nutrient diffusion, that support the viability and proliferation of cells (Sureerat et al., 2017). In the field of tissue engineering

injectable hydrogels are promising materials, as they can target defects in very deep tissues with minimal invasiveness and better abandon edge adjustment (Sivashanmugam et al., 2015). Hyaluronic acid (HA) and sodium hyaluronate are widely used to prepare biomaterials for tissue engineering because they give highly reproducible and affordable biomaterials.

HA exhibits interesting viscoelastic properties, excellent biocompatibility, and biodegradability. These properties of HA-derived hydrogels make them ideal biomaterials for tissue engineering. Injectable hydrogels based on HA are prepared using various physical and chemical crosslinking methods (Sureerat et al., 2017). Several chemical modifications are carried out for enhancing, modulating, or controlling the therapeutic action of HA, are used to develop new products. These modifications are performed at different sites on HA and produce different results in terms of modification effectiveness and chain length damage (Prestwich et al., 1998). Physical crosslink hydrogels, or “smart materials,” so-called because they respond to changes in temperature, pH, or ionic strength, have been extensively examined due to their simple application, and the low toxicity of the crosslinking agents to tissues (Kim et al., 2011).

Wounds treatment and problems encountered

Skin is the largest organ of the human body and plays crucial roles in maintaining body temperature, preventing microorganisms' intrusion, and supplying sensory information about the external environment. Damage to the integrity of the skin caused by genetic disorders, acute trauma, chronic wounds, or surgical procedures may result in significant disability or even death. Full-thickness defects or wounds greater than ~1cm in diameter need a skin graft to prevent serious scar formation which will lead to impaired morbidity and cosmetic deformities (Shevchenko et al., 2010). Chronic skin wounds are a serious problem that is reaching epidemic proportions; they are estimated to affect 20–60 million people worldwide by 2026 (Lucília et al., 2019). As compared to acute wounds, which heal after a certain period of time, chronic skin wounds heal slowly (in 8 weeks or more) or not at all. Chronic wounds can lead to long term hospitalization, which entails a high burden on the health care system due to medical costs associated with wound care products, surgery, and physician and nursing resources. Medical assistance does not prevent serious complications such as foot amputation, morbidity, and mortality, as no efficient therapies have been developed. In fact, the 5-year mortality rate of chronic skin wounds is comparable to or worse than that of some common types of cancer, including prostate, breast, and colon cancers (Armstrong et al., 2007). The etiology of chronic skin wounds is variable, and although not completely understood, it has allowed classification into ulcers of pressure and of

venous/arterial or diabetic origin. Venous and pressure ulcers commonly affect elderly people, and their prevalence is due to an increase in the elderly population, who are likely to develop chronic venous disease and venous hypertension (venous ulcers) or to be bedridden (pressure ulcers) (Lucília et al., 2019). Diabetes and associated comorbidities that result from hyperglycaemia, such as obesity, peripheral vascular disease, atherosclerotic disease, and peripheral neuropathy, have been associated with diabetic foot ulcerations and arterial ulcers (Lucília et al., 2019). A detailed investigation of the pathophysiology of chronic skin wounds reveals that different cellular and molecular mechanisms are impaired in wound healing. Wound healing should occur following a coordinated sequence of phases (hemostasis, inflammation, proliferation, and remodeling), but in chronic skin wounds the process halts at the inflammatory phase. Patients with vascular impairment have less blood flow to the site of injury, resulting in an impaired immune response and great vulnerability to infection. Nevertheless, the inability of the immune cells to eradicate infection contributes to a persistent state of inflammation that is believed to be what prevents wound healing from progressing to the proliferative phase (Lucília et al., 2019). Other factors are also known to contribute to the poor healing of chronic wounds. Blood circulation is destabilized in chronic skin wounds not only because of inadequate blood supply to pressure and venous/arterial ulcers but also because of impaired angiogenesis arising from the decrease in angiogenic molecules (Armstrong et al., 2019; Barrientos et al., 2008). Re-epithelialization is weakened, possibly because of the decreased proliferation and keratinocytes. The integrity of the migration of extracellular matrix (ECM) is likewise affected by excessive degradation associated to the unbalanced ratio of metalloproteinases (MMPs) and tissue inhibitor metalloproteinases (TIMPs). Neuropathy in patients with diabetes also affects the release of neuropeptides and neurotrophic factors known to regulate important mechanisms in wound healing (Lucília et al., 2019). In order to restore full-thickness cutaneous wound and to promote the wound healing, many kinds of skin substitutes have been tried to develop, like autografts, allografts, xenografts, and tissue-engineered skin products etc. Some of them are commercially available for clinical application (Mihail et al., 2016). However, there existed some considerable problems in wound treatment, for example, limited supply, high manufacturing costs, inflammation, disease risks, and poor quality of wound healing. These disadvantages request more advanced

alternatives of skin grafts for the clinical purpose (Yu et al., 2015). Thus, it is necessary to explore a wound dressing with excellent properties to regenerate skin and to restore skin's functions (Selvaraj et al., 2015). The wound healing is a complex, continuous and dynamic process with three phases, namely inflammation, proliferation and maturation or remodelling. The proliferation phase is mainly responsible for the wound closure. The movements like reepithelialization and angiogenesis would take place in this phase. While, the remodelling phase is an attempt to recover the normal tissue structure and functions. These healing activities are regulated by a complex signaling network involving numerous growth factors, cytokines and chemokines (Barrientos et al., 2008). Particularly, transforming growth factor β 1 (TGF- β 1) is a common cytokine to initiate the wound healing progresses like inflammation, angiogenesis, re-epithelialization, and connective tissue regeneration. It is closely involved in the remodeling phase with the function of stimulating the collagen synthesis from fibroblasts. TGF- β 1 up-regulates the angiogenic growth factor, vascular endothelial growth factor (VEGF), potentially inhibits metalloproteinases (MMPs) such as MMP-1, MMP-2 and MMP-9, and promotes the synthesis of tissue inhibitor of

metalloproteinase 1 (TIMP1), which would inhibit collagen decomposition (Lei et al., 2018). The smooth muscle α -actin (α -SMA) isoform is critical for both cell motility and contractility, and plays an important role in myofibroblast function (Rockey et al., 2013). So, α -SMA, secreted by myofibroblasts, is an important factor to promote cell migration and contraction which are significant components in wound healing and, vascular endothelial growth factor (VEGF), a key regulator of normal and abnormal angiogenesis, is related to tissue repairing in animals and human (Lei et al., 2018). VEGF will promote endothelial cell proliferation and migration, vascular permeability, as well as the adhesion of leukocytes, aiming to enhance the angiogenesis (Soyer et al., 2011; Nissen et al., 1998). On the other side, VEGF promotes the epithelialization and collagen deposition during wound repairing (Bao et al., 2009). However, long-term and much excess VEGF will generate excessive collagen deposition, resulting in serious scar formation. Notably, inhibition of VEGF by neutralizing antibodies results in a decrease in the migration of fibroblasts and a delay in wound healing (Lee et al., 2009) while treatment with recombinant VEGF, or

Table 1. Some hyaluronic acid-based hydrogel strategies for the healing of skin wounds

Drug substances/Cell type	Hydrogel	Outcome/Results	Wound model	References
Hyaluronic acid	Hyaluronic acid (HA) -based hydrogels with polysaccharides	The wound was healed while the defect was contracted with the time since the shape altered from the original square to the X pattern scar.	Full thickness in rabbits	Lei et al 2018
VEGF (20 μ g), IL-10 (2 μ g)	PEG and hyaluronic acid	Enhanced re-epithelialization, vessel formation; led to less occlusion and death of blood vessels and fewer epidermal rete ridges	Excision wound on healthy horse	Wise et al., 2018
ASCs	PEG and hyaluronic acid	Accelerated wound closure; enhanced re-epithelialization and neodermis and vessel formation; inhibited inflammatory mediators	Diabetic mice	Greiser et al., 2018
hASCs	Gellan gum and hyaluronic acid	Faster transition from the inflammatory to the proliferative phase, thicker and more mature epidermis, enhanced neoinnervation, and increased ECM formation	Diabetic mice	da Silva et al., 2017
hAFSS	Heparin conjugated hyaluronic acid	Improved wound closure, re-epithelialization, vascularization, and ECM production	Full thickness wound in mice	Laverdet et al., 2015.
VEGF plasmid (250 μ g)	Hyaluronic acid-MMP	Enhanced granulation tissue formation	Diabetic wound in mice	Tokatlian et al., 2015
hASCs	Gellan gum and hyaluronic acid	Increased epidermal thickness; enhanced ECM formation	full-thickness excision wound	Cerqueira et al., 2014
Thiolated carboxymethyl - HA	Thiolated carboxymethyl - HA (CMHA-S)	Suitable formation of healthy granulation tissue, fractional wound closure was observed	Excision wound in rats	Guanghui et al., 2011

Abbreviations: hASCs: human adipose stem cells; VEGF: Vascular endothelial growth factor; ASCs: adipose stem cells; MMPs: Matrix metalloproteinases; ECM: Extracellular matrix

overexpression of VEGF accelerates wound (Lei et al., 2018).

Wounds treatment using hydrogel based on hyaluronic acid

Hyaluronan (HA) has been shown to interact with signaling cascades that influence cell migration, proliferation, and gene expression. Further, HA is a ligand of CD44, whose receptor expression has also been found to correlate with reepithelialisation. The suggested connection for the presence of increased HA in the wound bed and enhanced re-epithelialization has led to the development of a range of HA-containing biomaterials as wound dressings (Guanghui et al., 2011). In wound treatment, the wound dressing materials with superior properties is typically used to facilitate wound healing, in which hydrogels with high water content, flexible mechanical property, and good biocompatibility is considered as a promising candidate for practical application (Li et al., 2018; Yi et al., 2018; Li et al., 2019). Firstly, by providing a porous structure and suitable swelling ratio, hydrogel matrix can allow for oxygen presence, remove wound exudates, maintain a moist wound bed to promote wound healing (Kaoru et al., 2010; Rakhshaei and Namazi, 2017). Secondly, the antibacterial property of traditional dressing is endowed by antibiotics capsulated in the hydrogel matrix (Li et al., 2016). However, the hydrogels with inherent antimicrobial property has received widespread interest among biomaterial researchers (Gonzálezhenríquez et al., 2017; Kumar et al., 2018; Zhao et al., 2017). Thirdly, unlike traditional wound dressing (gauze and cotton wool), biodegraded hydrogel dressings are easy peel off and spontaneous degradation, which avoid pain and secondary trauma during dressing changes (Yang et al., 2018). Inspired by the concept of moist wound healing, numerous novel hydrogels were designed and it played an important role in the treatment of various wounds (Blacklow et al., 2019; Wang et al., 2019). The majority of hydrogels were prepared by natural polymer materials (e.g., alginate, carboxymethylcellulose, dextran, gelatin, collagen, and hyaluronic acid) and synthetic polymer materials (e.g., methoxy polyethylene glycol, poly (vinyl alcohol), peptide and polyamidoamine), because of their excellent biocompatibility and biodegradability (Travan et al., 2016). Hyaluronic acid (HA), the main component of the extracellular membrane (ECM), can increase cell-matrix interaction and initiate signal transduction essential for cell survival and function, which has been widely used in the biomedical material field because of its easily peeling properties, excellent biocompatibility and high-water retention ability (Yang et al., 2018). Some examples of Hyaluronic acid-based hydrogel strategies for the healing of skin wounds are given in table 1.

Conclusion

Hydrogels are found to be promising formulation for treatment for necrotic and sloughy wounds. Due to higher content of water, hydrogels are responsible for their unique ability to immediately

cool a wound surface, providing a soothing effect, and promote autolytic debridement. Hydrogels containing bioactive agents used in the different healing stages have great potential to improve wound healing, but standardized protocols are required to better understand that which bioactive agent at what amount and rate should be released for quality healing. Polysaccharide-based hydrogels possess no. of unique characteristics such as high-water retention capacity, biocompatibility, biodegradability, and nontoxicity, which increases the use of hydrogel in biomedical interface applications. Polysaccharide-based hydrogels possess numerous advantages in specific medical applications as a result of their changeable structure and networked morphology, which could facilitate a number of functions such as controlling their diffusion, environmental sensitivity, and gas exchange between the wound and outside.

Tissue engineering is one of the most reliable methods in wound healing. HA is one of the most suitable natural materials in hydrogel scaffolds. HA has good tissue compatibility because of having same water content as in human tissue. In addition, high molecular weight HA has a certain anti-inflammatory effect, and low molecular weight HA oligomers have been shown to promote angiogenesis. At present, HA as a scaffold material, connecting molecules, carrier of drugs and other small molecules has been widely used in tissue engineering. But the use of HA is affected method of crosslinking. Several methods are available to create various types of hydrogel based on HA. HA-based hydrogels are developed to improve properties, such as mechanical properties, biodegradation, antimicrobial activity, and cell biocompatibility, for their use in certain applications, including conjugation of bioactive molecules for controlled release, or wound healing. Hyaluronic acid-based hydrogels accelerate the healing process as well as exhibit excellent reepithelialization, greater granulation tissue thickness, higher density of collagen deposition, a smaller number of bacteria and endotoxin level, and balanced inflammatory infiltration. Stem cell based hyaluronic acid-based hydrogels were found to be promising role in treatment of diabetic wound healing. HA based hydrogels are also used to develop antimicrobial hydrogel wound dressings for wound healing application, especially for open and infected traumas due to the good bioactivity and inherent antibacterial property.

Conflict of interest

None

References

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