

Nanofiber Dressings; A Quantum Leap in the World of Wound Healing

Nanofiber Örtüler; Yara İyileştirme Dünyasında Kuantum Sıçrama

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ABSTRACT

The skin is periodically exposed to many external factors that affect it. Sometimes, these external influences can cause wounds and serious damage. In this case, the skin begins the processes of restoration, rebuilding and healing of damaged tissues, but it may face many challenges that may hinder or slow down the healing process. In order to reduce the external factors that affect the healing process of the wound and to speed up the healing process, the use of wound dressings has become the best way in treatment of wounds. Recent studies indicate that using nanofibers is the best among the other types of wound dressings and promises great healing effects and maximum wound protection. This is due to the similarity of the nanofibers structure to that of the Extra Cellular Matrix (ECM), and the structure of nanofibers providing high surface area and high porosity. Also, different types of medicines and plant extracts can be loaded in nanofibers. In addition, the electrospinning method used to manufacture nanofibers is an inexpensive and versatile method. The aim of this review article is to give brief information on the nanofibers as wound dressing biomaterials and their advantages over traditional dressings. Recently loading the nanofibers with various plant extracts to take advantage of plant extracts' significant healing, antioxidant, antibacterial and anti-inflammatory properties is subject of many studies. Also, some recent studies on this topic were discussed in this review.

Keywords: Nanofiber, electrospinning, wound dressings, plant extracts

ÖZET

Cilt periyodik olarak kendisini etkileyen birçok dış faktöre maruz kalır. Bazen bu dış etkiler yaralara ve ciddi hasarlara neden olabilir. Bu durumda cilt, hasarlı dokuların restorasyonu, yeniden yapılanması ve iyileşmesi süreçlerine başlar ancak iyileşme sürecini engelleyebilecek veya yavaşlatabilecek birçok zorlukla karşı karşıya kalabilir. Yaranın iyileşme sürecini etkileyen dış etkenleri azaltmak ve iyileşme sürecini hızlandırmak için yara örtüsü kullanımı yaraların tedavisinde en iyi yol haline gelmiştir. Son zamanlarda yapılan araştırmalar, nanofiber kullanımının diğer yara örtüleri arasında en iyisi olduğunu ve büyük iyileşme etkileri ve maksimum yara koruması vaat ettiğini göstermektedir. Bu, nanoliflerin yapısının Ekstra Hücrel Matris (ECM) ile benzerliğinden ve nanoliflerin yüksek yüzey alanı ve yüksek gözeneklilik sağlayan yapısından kaynaklanmaktadır. Ayrıca nanoliflere farklı türde ilaçlar ve bitki özleri yüklenebilir. Ayrıca, nanolifleri üretmek için kullanılan elektro-eğirme yöntemi, ucuz ve çok yönlü bir yöntemdir. Bu derleme makalesinin amacı, yara örtüsü biyomateryalleri olarak nanolifler ve onların geleneksel örtülere göre avantajları hakkında kısa bilgi vermektir. Bitki ekstraktlarının önemli iyileştirici, antioksidan, antibakteriyel ve antiinflamatuvar özelliklerinden yararlanmak için nanoliflere çeşitli bitki ekstraktları yüklemek son zamanlarda birçok çalışmaya konu olmaktadır. Ayrıca, bu derlemede bu konuyla ilgili bazı yeni çalışmalar tartışılmıştır.

INTRODUCTION

Wounds of all kinds and forms need extreme care in order to heal faster and not be exposed to various bacterial and fungal attacks that cause chronic infections.

With the passage of time, different types of wound dressings have been developed. In ancient times, honey, spider webs, vinegar and wine were used to sterilize and heal wounds. In the twentieth century, modern types of wound dressings appeared, starting with traditional forms such as gauze, lint and plasters. Gauze dressings are made of non-woven and woven fibers of cotton, polyester and rayon. It can keep the wound away from harmful external influences and absorb wound exudates. But it also has many drawbacks as it needs frequent change to protect healthy tissues from maceration. Also, gauze tend to become adherent to the wound when moistened, which makes the removing process very painful (1,2).

In general, wounds need a moist environment to heal, and this is what traditional dressings can't provide, which prolongs the healing time of the wound (3).

To overcome these drawbacks, modern dressings have been developed based on advanced technologies that provide protection for the wound and promote the healing process.

There are many types of modern dressings, such as hydrogels, hydrocolloids, alginates, foams and nanofiber films. Each type has its own characteristics, and all of them are mainly made of synthetic or natural polymers (3). Hydrogels are widely used because of their good properties, such as hydrophilic nature and good flexibility, but on the other hand, there are many disadvantages that make nanofibers superior to them. Hydrogels have poor mechanical stability at swollen state, need frequent changing, and it causes maceration of healthy tissues and foul smell in the case of high exudate wounds (2,4). While the nanofibers manufactured by electrospinning method combine the amazing properties of biomaterials at the nanoscale level with the ideal structure resembling the native skin extra cellular matrix (ECM). Also, the nanofiber dressing doesn't need frequent change. These unique properties of nanofibers are not available in hydrogel dressings and other types (5,6).

Usually, bacterial infections are the main reason that hinders the healing process of the wound and causes serious complications, for this reason, wound dressings containing antibiotics are the most requested. However, excessive use of antibiotics may lead to the emergence of antibiotic-resistant bacteria. To avoid this problem, researchers directed to develop wound dressings containing plant extracts with antibacterial activity instead of antibiotics (7).

Since ancient times, plant extracts containing many bioactive compounds such as alkaloids, polyphenols and glycosides have been used to heal wounds, remove scars, stop bleeding and solve various skin problems (8).

The effectiveness of these bioactive compounds has been proven as antibacterial, antioxidant, astringents, antifungals, epithelization stimulators, analgesics, anti-inflammatory and many other properties. Also, these natural plant extracts have fewer side effects than synthetic compounds, which makes them ideal wound dressing material ingredients (9).

From all that was mentioned above, it can be concluded that the electrospun nanofiber dressings loaded with plant extracts meet all the provisions to be an ideal wound dressing that is environmentally friendly and harmless to the body.

PROPERTIES OF NANOFIBER MATS

Nanofiber dressings are characterized by small pore size and high porosity, which provides excellent protection to the affected area, prevents the entry of pathogens, and provide good gas exchange. Moreover, nanofiber dressings have a high specific surface area, and its structure is closely similar to the structure of natural extra cellular matrix (ECM), which stimulates proliferation, cell adhesion, migration and differentiation (5). In addition, the nanofiber dressing doesn't need frequent change like other dressings, as it can carry high amounts of drugs and provide a sustained release for it. Thus, it saves time, effort and cost (6).

Nanofibers can be made from natural polymers such as collagen, hyaluronic acid and chitosan or synthetic biopolymers such as poly(vinyl alcohol) (PVA), and Poly(ϵ -caprolactone) (PCL), or a mixture of them (10).

As an important point to mention, almost all polymers that are used to manufacture nanofibers are biocompatible, biodegradable and non-toxic to the human body. Also, nanofiber dressings maintain the moisture of the affected area and can effectively absorb wound exudates (11).

ELECTROSPINNING METHOD

electrospinning is a pioneering technology in the world of nanofibers industry. Although there are many methods to produce nanofibers, the electrospinning method receives the most attention because it is a versatile, simple and cheap method, and various types of polymers can be spun with it. By this method, fibers are manufactured with diameters ranging from 2 nm to several micrometers and lengths up to few kilometers using electrostatic forces from polymer solutions or melts (12,13).

The electrospinning method produces nanofibers with properties that other methods can't provide, such as high specific surface area, high porosity, gas permeability, structural similarity to extra cellular matrix (ECM), and adjustable fiber diameter and morphology (14). It is also the only procedure for large-scale production of continuous nanofibers in industry (15).

The electrospinning setup includes a syringe containing the polymer solution, a syringe pump, a spinneret (needle with blunt tip), a collector and high voltage power supply. When a high voltage is applied to the polymer solution then electrostatic forces are formed that oppose the surface tension forces of the polymer solution and this leads to elongation of the hemispherical surface of the solution at the tip of the needle to form a conical shape known as Taylor cone. When the high voltage continues to be applied and reaches the critical value, then the fluid will be ejected from the needle tip. Before the fluid jet reaches the collector, the solvent is evaporated. As a result, thin polymeric non-woven fibers are formed and distributed randomly on the collector (16,17).

There are different electrospinning parameters that determine the morphology and nature of the resulting nanofibers such as applied voltage, distance between tip and collector, flow rate, polymer concentration, solution conductivity and solvent volatility (16). Therefore, these parameters must be determined before starting to produce nanofibers to obtain the desired characteristics.

NANOFIBERS WITH PLANT EXTRACTS

Based on all the practical experiences of using plants to treat wounds and solve various skin problems in folk medicine, nanofibers containing various plant extracts have been developed to obtain the maximum benefit from combining the amazing properties of plant extracts with the advanced technology of nanofibers.

The following table includes several studies in which nanofibers containing different plants were produced for wound healing.

Table 1. Recent studies on developing nanofibers with plant extracts

Polymer name	Plant name	Method name	The results	References
polycaprolactone	<i>Inula graveolens (L.)</i>	electrospinning	The inula graveolens (L.) extract has been successfully combined with the PCL nanofiber, and it can be used to heal wounds	(18)
PCL and collagen	<i>melilotus officinalis</i>	electrospinning	After applying the resulting nanofiber to the wounds of diabetic rats, the effectiveness of these nanofibers in stimulating and accelerating the healing process was proven	(19)
Chitosan and polyethylene oxide	<i>calendula officinalis</i>	electrospinning	The nanofibers were successfully synthesized. in vitro tests on fibroblast cells showed that the resulting nanofibers enhanced proliferation, growth and attachment of the cells. In vivo tests on rat wounds showed that CS/PEO/CO dressing has excellent wound healing ability.	(20)
polyacrylonitrile	Moringa leaf extract	electrospinning	In vivo tests on rats proved the effectiveness of the prepared nanofiber in wound healing.	(21)
PVA	<i>Salvia officinalis folium, Thymus vulgaris, And Hyperici herba</i>	electrospinning	These plant extracts have been successfully loaded into PVA nanofibers and have wound healing, antibacterial and antifungal properties.	(14)
PCL/gelatin	<i>Melia dubia</i> leaf extract	electrospinning	In vitro tests have shown that the produced nanofibers have antibacterial activity and enhance the proliferation and attachment of fibroblasts cells and can be used as a good wound healing dressing.	(22)
Cellulose acetate	<i>Bixa orellana L.</i>	electrospinning	All the tests conducted on the prepared nanofiber proved that it is capable of healing and repairing wounds	(23)
PVA	Momordica charantia	electrospinning	PVA/MC nanofibers had antibacterial properties and could be used as an advanced wound dressing.	(24)
Chitosan and polyethylene oxide	Aloe vera	electrospinning	These nanofibers have been successfully manufactured and can be used to heal wounds.	(25)

CHALLENGES AND FUTURE PROSPECTS

Despite the remarkable progress in nanofiber fabrication field, there are still some challenges that must be overcome in order to produce the ideal nanofiber dressings that meet the needs of the huge pharmaceutical market. Some of these challenges are related to electrospinning method. The slow production speed of this method, the use of biotoxic solvents, most of electrospinning parameters

must be determined according to the type of selected polymer and the fact that the production of nanofibers is affected by humidity, all together hinder large scale production (15).

As for the nanofibers, the main challenge is to start the clinical testing stage to determine the effectiveness of these dressings. So far, all the developed nanofibers are still tested on animals only because clinical tests are very expensive and require large funds (26).

The future smart nanofiber dressing should contain sensors that provide accurate reading of pH, humidity, temperature and amount of exudate, as well as showing when to change the dressing and stimulating the release of therapeutic agents only if infection occurs (27). If nanofiber dressings can be manufactured with these specifications in the future, it will facilitate the work of the medical staff and provide a comfortable healing process without complications.

Also, one of the remarkable developments that should be mentioned in the field of nanofiber fabrication is that portable electrospinning devices have been developed for personal use. Long et al. designed a battery-operated portable handled electrospinning apparatus (BOEA) relies on the use of two AAA batteries and one high-voltage converter instead of using the typical high voltage power supply. This device weighs about 120 g, has a small volume and low cost. Also, it can spin nanofibers directly onto the skin in a few minutes anywhere and anytime (28).

Research is still going on to develop new types of electrospinning devices, and soon great achievements will be made in this field.

CONCLUSION

Nature is very rich in different types of plants whose amazing healing properties haven't been discovered yet.

Therefore, efforts must be intensified to discover new plants and identify their bioactive compounds to use them in the treatment of wounds together with nanofiber dressings.

Previous researches have proven the effectiveness of this combination (nanofibers with plant extracts) in healing wounds within a shorter time and without harsh side effects that may harm humans and the environment.

In general, electrospun nanofibers are the best wound dressings that have been developed at the present time and will be promising for the treatment of difficult-to-heal wounds in the future.

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