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Updates on the use of Biological Membranes in the Healing of Skin Wounds in Animals

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ABSTRACT

In veterinary clinics, veterinarians are faced with several conditions that affect the skin, and among them are the wounds that are caused by burns, traumas, surgeries or infections. Wounds are a significant source of animal welfare problems and represent an inconvenience to animals and owners due to the multiple applications of their treatment. Therefore, it is necessary to develop new biocompatible materials capable of accelerating wound healing. In this context, biomaterials have arisen, and more precisely biological membranes, which is a polymeric device used for treating wounds and have been gaining relevance in the scientific community for their antimicrobial, anti-inflammatory and analgesic properties. They often do not require daily reapplications, thus representing a good alternative to topical formulations such as ointments, creams and sprays. This review aimed to address the use of biological membranes in skin wound healing, facilitating understanding by veterinarians and highlighting recent studies using this group of biomaterials in healing skin wounds in animals.

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Introduction

The market of animal wound care devices has seen growth in the last decade and is expected to grow at an annual rate of 6.7% between 2016 and 2021, amounting to US$1.134 billion until 2021. The great participation is attributed to adoption of these products in veterinary hospitals or clinics for wound healing, increased incidence of wounds in pets and the number of surgeries.

The study of cutaneous wounds and the ways to optimize their healing is primordial in veterinary clinics, because injuries to the skin occur frequently and are often difficult to solve (Amaral *et al*., 2016). The rapid healing of the damaged or lost skin area may represent an improvement in the patient's prognosis and for this purpose, biomaterials such as membranes have been widely used (Bellini *et al*., 2015).

The use of traditional formulations based on sprays, creams and ointments against wounds and infections presents disadvantages such as multiple applications and the need for prior cleaning of the lesion (which can be a painful process) (Abdel-Mohsen *et al*., 2016; Behera *et al*., 2017).

The traditional dressing that simply covered the wound was substituted by membranes that allow for controlling water loss and the entry of microorganisms, and often with bioactive molecules in the healing environment, replacing the damaged skin function and stimulating their healing (Santos *et al*., 2013, Bano *et al*., 2017).

In view of the previously expressed information and considering the growing medical and scientific importance of biological dressings, this review aims to address the role of biological membranes in skin healing, thus facilitating understanding by clinicians and highlighting recent studies on the use of this biomaterial in repairing cutaneous wounds in animals.

Skin Wound Healing

The skin acts as a barrier at the same time as an interface between the organism and the environment, helping it regulate the temperature and perception of the environment, and protect it from water loss, penetration of harmful substances and organisms (Ma *et al*., 2017). For this exposure, it is vulnerable to damage caused by microorganisms, chemical or me-

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chanical damage that can cause the rupture of this barrier.

A cutaneous wound is defined as a recent or old defect in skin tissue, with or without loss of basic function, formed by physical-chemical damage or the result of a pathological condition (Vyas and Vasconez, 2014). Wounds have great importance in medicine because of their high frequency, the morbidity they cause, the high risk of infections that occur most of the time, and because of the quantity and cost of treatment drugs (Borsari *et al*., 2014).

Inflamed or infected wounds can come from surgical interventions, trauma, abrasions or burns, and if not properly treated can trigger sepsis and culminate in death (Morgado *et al*., 2014; Marei *et al*., 2017). This is particularly problematic in veterinary medicine due to each species having their own peculiarities, and wounds in large animals usually heal more slowly, often presenting complicating factors such as the development of exuberant granulation tissue (Aghchelou *et al*., 2014).

Wound healing represents a natural morphogenic response involving inflammatory cells, immune cells and biochemical events of the organism to a trauma with the purpose of recovering the cellular structures and skin layers, restoring the anatomical and physiological function (Andrade, *et al*., 2011; Vyas and Vasconez, 2014).

Tissue healing is divided into 4 stages: hemostasis, which occurs soon after injury, triggering the release of platelet granules for clot formation, and inflammatory mediators that recruit polymorphonuclear cells triggering the inflammation phase; then the proliferative phase occurs with the multiplication of blood vessels, fibroblasts and collagen production, culminating in the formation of granulation tissue. Finally, the maturation phase in which granulation tissue remodeling occurs and possibly the replacement by equal or close tissue to the original tissue (Andrade *et al*., 2011; Marei *et al*., 2017). In order for the wound to heal satisfactorily, it is necessary to efficiently modulate the environment during healing stages, so that it does not deviate from the natural process, thereby controlling the interaction of inflammatory cells, the extracellular matrix and the cytokines (Bankoti *et al*., 2017).

In skin lesions, this environment can be offered by applying dressings, preventing infections and dehydration. They may be compatible with other topical therapeutic agents (Bankoti *et al*., 2017; Ma *et al*., 2017). To this end, a variety of wound dressings were developed based on synthetic or natural polymers such as chitosan, cellulose and collagen (Morgado *et al*., 2014; Ma *et al*., 2017).

Biological Membranes

Biological membranes are a group of biomaterials of a polymeric nature to cover wounds whose function is to assist in closing the wound, mechanically protecting it and often functionally replacing the skin temporarily or permanently. It is a good alternative when traditional treatment formulations are not available or when there are difficulties on the part of the owner, the injury or even the animal in daily reapplication of the dressing on the lesion (Ha *et al*., 2013).

As an alternative to the use of topical preparations for treating wounds, which require daily use, this treatment consists in covering the wound with membranes, thus replacing the function of the lost skin and protecting the wound from the loss of fluids and proteins; preventing the invasion of microorganisms and reducing exudate and mechanical stress, thus improving and stimulating repair (Abdel-Mohsen *et al*., 2016; Bano *et al*., 2017). There are also features that are important from the technical point of view, especially for veterinary field, as they have the capacity to be used in non-hospital conditions (Drewnowska *et al*., 2013).

In order to be effective and in addition to the good cost-benefit, the membranes must possess some biological and mechanical characteristics that adapt to the requirements of the organism, such as: biocompatibility (interaction with tissues without side effects); occlusive properties to prevent the entry of microorganisms and foreign bodies into the lesion; ability to adhere to the body even on uneven surfaces and prevent water loss (Campos *et al*., 2015). It should preferably be absorbable, but if it is not, it should be easily removable at the time of dressing change, and that the process be painless (Bano *et al*., 2017). With this property, membranes can provide an environment conducive to the physiological process of skin repair.

The properties of the membranes can be modified by changing the concentration of the cast solution, the ratio of non-solvent-solvent, pressure or temperature (Morgado *et al*., 2014). In addition, they can be impregnated with a wide range of bioactive compounds to facilitate and promote wound healing (Vyas and Vasconez, 2014), and this process is called membrane functionalization.

In this review, skin repair function will be emphasized. However, the use of biological membranes has already been referenced in the treatment of several pathological diseases such as perforation of the tympanic membrane (Zhang *et al*., 2017a), defects in the dura mater (Xu *et al*., 2014) and varicose ulcers (Cavalcanti *et al*., 2017) in animals and humans.

Membrane Classification: Membranes can be classified according to their origin as natural or synthetic, and as to the composition, for example carbohydrates (most used) or proteins (Ha *et al*., 2013). Synthetic biomaterials have numerous disadvantages such as cost of production and low biocompatibility (Ha *et al*., 2013), and therefore will not be addressed in this review. Despite the wide range of dressings available, progress in the wound dressing market depends on the growing interest in using natural biomedical products (Santos *et al*., 2013). The choice for natural membranes is mainly due to good biocompatibility, low immunogenicity, easy acquisition of renewable sources and material replication (Ha *et al*., 2013). Among the natural polymers, the main groups are those originating from carbohydrates whose main representative is chitosan, and proteins where collagen is the most used. In addition to the main cited examples, the number of reports on the use of protein extracted from silk, bacterial cellulose and latex has also increased.

Carbohydrates: Polysaccharides are a class of materials, which have been underutilized in the field of biomaterials in the past. However, recognition of the utility and potential of this class is increasing, and consequently the use of biomaterials based on polysaccharides (Pighinelli *et al*., 2016).

Chitosan (Cs)

Chitosan is a polymer derived from the alkaline deacetylation of chitin and this is the second most abundant biosynthesized material behind only cellulose (Behera *et al*., 2017; Muxika *et al*., 2017). Its main sources are crustaceans and mollusks, and it can also be removed from the cell wall of bacteria or fungi (Abdel-Mohsen *et al*., 2016; Marei *et al*., 2017). Its good solubilization rate allows for producing various pharmaceutical formulations such as films, powders, hydrogels, pastes or membranes (Muxika *et al*., 2017; Yuvaraja *et al*., 2017).

Because it is an inexpensive product and due to its peculiar characteristics, it has good antimicrobial, anti-inflammatory, analgesic and healing activity, especially in cutaneous wounds (Behera *et al*., 2017; Yuvaraja *et al*., 2017). Cs can induce analgesia, providing a fresh, pleasant and calming effect when applied to an open wound by blocking nerve endings. In addition, it is able to bind to erythrocytes, stimulating the secretion of Platelet-Derived Growth Factor and Transforming Growth Factor, thereby facilitating clot formation, and which is reason that it is used as a curative promoter of hemostasis in the United States and Europe (Oryan and Sahvieh, 2017).

Chitosan extracted from the fungus Schizophyllum commune was tested in dorsal skin wound healing of healthy mice and in diabetic mice in healthy treated mice, there were 30, 68 and 95% of wound contraction rates, reported after 5, 10 and 15 days, respectively, while untreated mice presented 18, 43 and 72% for the same period. In treated diabetics, there was a significant improvement ($p < 0.05$) in the repair rate of lesions in the treated group in relation to the control group (Abdel-Mohsen *et al*., 2016). Furthermore, the same authors tested the efficacy of this biomaterial against Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Bacillus subtilis, which was tested by disc diffusion, with better results in using the chitosan manufactured from the fungus than the control treatment (urea and hydroxide of sodium).

In 2017, two chitosan-based biomaterials were developed; one from chitin from shrimp shells (*Penaeus monodon*), and one from a locust (*Schistocerca gregaria*) for wound repair of created full thickness wound on back of mice. Therefore, these materials covered wounds produced in mice. Minimal healing was observed in the control group in the same period, which means that the quality of the healing process was very poor (Marei *et al*., 2017). However, when the authors compared the results of chitosan derived from locusts and shrimp, they observed that the insect showed better results, suggesting that the chitosan source may potentiate its medicinal properties.

The importance of combating or preventing wound infection during wound repair makes Cs an adequate dressing material due to its inherent antimicrobial activity, as well as many other advantages such as an analgesic effect and hemostatic activity (Muxika *et al*., 2017). However, it is not always effective in controlling bleeding or even killing bacteria.

This type of membrane may be added to ibuprofen, an agent capable of modulating the inflammatory response during the initial healing process (Celes *et al*., 2016). In an in vitro test using human dermal fibroblasts and surgically induced wounds in Wistar rats, a membrane composed of chitosan and PVA added with vesicles containing ibuprofen was found to have good adhesion and viability rates. In wound healing, a significantly faster closure was observed in the treated group than in the control group. In addition, a lower inflammatory reaction and an absence of scabs were observed in the treated wounds, and which presented total regression at the end of 21 days (Morgado *et al*., 2014).

Cellulose (CEL)

Cellulose is a long chain polymer composed of glucose monomers and is the most abundant component in nature (Barud *et al*., 2016). Often derived from plants, it can also be synthesized by bacteria, fungi and algae, in addition to being used in various medical devices (Lin *et al*., 2013). It exhibits great stability, low toxicity, porosity and elasticity; it also has water retention capacity and good adhesion to the lesion, thereby making it difficult to penetrate harmful agents and foreign bodies. Furthermore, it is non-allergenic, sterilizable and can be easily manipulated and applied with minimum changes (Barud *et al*., 2016; Pal *et al*., 2017).

Since the 1980s, bacterial cellulose (BC) -based membranes have been used as temporary dressings for treating cutaneous wounds mainly in burns, grafts and chronic ulcers in humans (Pitanguy *et al*., 1988) and pigs (Wouk *et al*., 1998). Thereafter the number of publications involving synthesis and clinical trials using this material has not only grown in cutaneous treatments, but also in other conditions. Lin *et al*. (2013) developed a study comparing the use of pure CEL membranes, CEL membrane immersed in solution containing 0.6% chitosan and a polyurethane-based hydrocolloid film on cutaneous wounds in Sprague Dawley rats. It was found that the wounds covered with bacterial cellulose membranes contracted more than on the covers with the film after 6 days; after 8 days the wounds covered by cellulose had already healed 85%, and the healing rate of the added chitosan membrane was higher, but not significant. The wound healing percentage in the hydrocolloid group was not reported. The authors attributed to these results to the ability of the two cellulose membranes to be easily removed from the lesion, whereas the hydrocolloid film was strongly adhered to the wound at the time of removal, causing damage during dressing exchange.

As already mentioned by Pal *et al*. (2017), it is necessary to add some antimicrobial agent in order to enhance the effect of cellulose membranes, as pure cellulose does not have this effect. BC can be easily manipulated to improve its properties or functionalities, resulting in several nanocomposites based on this material (Barud *et al*., 2016).

Pal *et al*. (2017) functionalized a cellulose-based membrane by adding silver nanoparticles. In the microbiological assay, this biomaterial presented a good response against Escherichia coli and good water retention, which led the authors to conclude that it is a good material to be used as a curative. However, they did not perform experiments on animals or even on cell cultures to test this potential efficacy.

Barud *et al*. (2013) associated the bacterial cellulose membrane with green propolis in the treatment of surgical wounds in mice. The healing effects of the membrane with and without green propolis, as well as the control wound were compared. It was observed that propolis-associated bacterial cellulose promoted a lower inflammatory reaction, faster healing, and biocompatibility with the animal in question, thus this material is considered good for use in healing cutaneous wounds.

Protein

Protein polymers are composed of amino acid chains and are typically modeled from structural proteins such as silk and collagen. These polypeptides can interact to form fiber networks and other three-dimensional structures with controlled properties.

Collagen (COL)

Collagen is a component in the extracellular matrix, and has been found to be useful as biomaterial in cell therapies and tissue engineering by providing a viable substrate for cell attachment and propagation (Vyas and Vasconez, 2014). The use of collagen as a biomaterial began in 1881. This discovery boosted numerous collagen innovations in soft tissue engineering and repair. Its main sources for biomedical applications are skin and tendons of bovine, skin, bladder mucosa or swine gut, rat tail and marine animals such as fish and mollusks (Drewnowska *et al*., 2013).

The greatest use of collagen is in producing dressings for wounds, vitreous implants and as carriers for drug administration. One of the interesting properties of collagen is its good moisturizing nature, so it is widely used in cosmetics production (Ramasamy and Shanmugam *et al* 2015). The membrane which has collagen either totally or partially in its formulation, presents good characteristics that facilitate the acceptance of the organism, since this material has the capacity to be resorbable, has good affinity with water, low antigenicity, good compatibility with cells and has the ability to promote tissue repair (Gokce *et al*., 2017).

Gokce *et al*. (2017) developed a collagen-based dermal matrix in which resveratrol microparticles were added and compared their healing power in diabetic rats with a pure resveratrol solution, a solution containing drug microcapsules and a membrane without drug addition. At the end of the experiment, they observed that all the treatments obtained good results; however, the healing time of the membrane with the microcapsules was significantly reduced ($p < 0.05$) when compared to the others. In addition, it reduced the amount of reactive oxygen species, leading the authors to conclude that the junction of the microparticles and membrane promotes a synergism that facilitates healing.

Ramasamy and Shanmugan (2015) developed a membrane based on association collagen and chitosan and tested them on albino male Wistar mice. The authors compared the results of using collagen membranes, chitosan, the association of the two (composite membrane) and also the control group (those that were not covered with any membrane). After 7 days of treatment the wound reduction rate was 96.25%, 33.75%, 65% and 55% in the groups that used composite membrane, the control, collagen membrane and chitosan membrane, respectively. Based on this, the authors support the idea that the association of the two substances in a topical application presents a viable option to aid in faster wound healing.

The use of cells has been described as having a promising future in wound repair and organ reconstruction. In this regard, researchers have studied the effects of the addition of a peptide (E7), which has a specific affinity for mesenchymal stem cells, to membranes composed of collagen in surgically manufactured wounds in pigs (Wang *et al*., 2014). From this study it was concluded by through a scanning electron microscopy that, in comparison to the membrane composed only of collagen, that with the stem cells (COL-E7), after 3 days of implantation in the lesion. It was able to recruit more cells, representing a greater adhesion to the site of the lesion and, consequently, an acceleration in the repair of the same, which was proven after 14, 21 and 28 days of treatment, when a significantly higher healing rate was observed between the group treated with the peptide than the group without the peptide.

Silk Fibroin (Fs)

The silk produced by the silkworm (*Bombyx mori*) mainly consists of two proteins, namely sericin and fibroin (Karahaliloğlu *et al*., 2015). Silk fibroin is a polymer that presents great potential for application as a biomaterial due to its biocompatibility, biodegradability, minimal inflammatory reaction, adequate resistance and elasticity, as well as high permeability for gases and water vapor, anti-hemorrhagic properties and is transparent (allowing visualization of the lesion site) (Inpanya *et al*., 2012; Zhang *et al*., 2017b). It can be used in various forms such as hydrogels, powders, sutures and membranes (Kundu *et al*., 2013).

In addition to presenting good results in wound healing in diabetic animals, fibroin helps to heal wounds from burns, as demonstrated by Ju *et al*. (2016). They assessed the healing power of induced burns on the skin of the dorsum in mice and were then covered by matrices of silk nanofibers, finding that there was reduced expression of interleukin (IL) -1 and 6, proinflammatory factors, a greater number of cells labeled for PCNA indicative of cell proliferation, and expression of IL-10 anti-inflammatory cytokine. There was an increase in the reepithelialization rate of the treated wounds relative to the control wound. After 14 days of treatment, the treated group had a similar morphology to that of normal skin and the wound area was completely regenerated without the presence of edema or granulation tissue.

Others

Latex

Rubber removed from the rubber tree (*Hevea brasiliensis*) has been used in implants for cutaneous or subcutaneous use (Andrade *et al*., 2011; Borges *et al*., 2014) since it has already been demonstrated that it is easy to handle and is low cost, and it has the capacity to accelerate the healing process. Moreover, it is not allergenic, it presents good cellular adherence and it promotes angiogenesis (Zimmermann *et al*., 2007; Borges *et al*., 2014). The first biocompatibility assay for this membrane was performed by implanting specimens in the subcutaneous of crossbred dogs, and the removal was done weekly to evaluate their interaction with the adjacent cells. In the early days, it was found that latex attracted a large amount of inflammatory cells, probably because it was a foreign body, but over the course of days there was a reduction of these cells. In addition, it was observed that as the inflammatory cells left the material vicinity, the subcutaneous cells adhered to it, and thus it can be concluded that latex was a good material to be used for repair of cutaneous wounds. In this same study, the therapeutic efficacy of dermal ulcers on rabbit ears was evaluated focusing on the presence of new vessel formation, epithelium and fibrosis. The lesion of the treated group was filled with organized tissue and new vessels, while the tissue in the control group was irregular with evident contraction of the edges and no signs of fibrosis were observed in any of the groups (Mrue *et al*., 2004).

Biocompatibility of three formulations (in natura, in natura plus sulfur and formic acid, and latex plus 0.1% polylysine) of latex membranes was investigated in dog wounds. The membranes were followed with the adjacent tissues being removed for histological analysis 45 days after implantation. It was verified that the membrane composed of sulfur and formic acid was the only one that did not present good compatibility because it is non-vulcanized latex. In vulcanization, the polymer matrix of the rubber is internally bound by strong disulfide bonds, thereby decreasing the effective contact of the rubber constituents with the medium. As a consequence, their contact including allergenic proteins are higher in this membrane, thereby causing the rejection and infection observed by the authors (Zimmermann *et al*., 2007).

In order to increase the properties of latex, Borges *et al*. (2014) functionalized the latex membrane using Salicaceae extract (*Casearia sylvestris Swartz*), a plant with known medicinal properties. After analysis of the material, it was found that it has good stability. Another functionalization of latex membrane was the addition of ciprofloxacin microcapsules, an antibiotic used in cases of severe infections. It presented as a promising alternative for treating diseases requiring long treatments and local applications (Murbach *et al*., 2014). However, until now there have been no reports of any of these membranes being used in the treatment of cutaneous wounds or any other type of treatment.

Conclusion

It is believed that with the growing understanding of animal welfare, there is the development of natural devices able to treat lesions quickly and comfortably for the reestablishment of innate repair mechanisms, and may involve the application of active biological agents with antimicrobial or anti-inflammatory properties. Therefore, it is important that the scientific community direct more efforts to improve the use of biomaterials, such as membranes. As such, this review aimed to inform readers and, more importantly, veterinarians about the existence of alternatives for the treatment of cutaneous wounds that are still little explored commercially and with that of arousing interest in new research using this biomaterial associated with other natural substances.

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