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*Review*

# Development of films from natural sources for infections during wound healing

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**Abstract:** The skin is the largest organ in the human body, and due to its barrier function, it is susceptible to multiple injuries. The appearance of infections during the wound healing process is a complication that represents a formidable hospital challenge. The presence of opportunistic bacteria with sophisticated resistance mechanisms is difficult to eradicate and compromises patients' lives. Therefore, the search for new efficacious treatments from natural sources that prevent and counteract infections, in addition to promoting the healing process, has increased in recent years. In this respect, films with the capability to protect wounds and release drugs are the presentation that predominates commercially in the hospital environment. Those films can offer several mechanical advantages such as physical protection to prevent opportunistic bacteria's entry, regulation of gas exchange, and capture of exudate through a swelling process. Wound dressings are generally curative materials easily adaptable to different anatomical regions, with high strength and elasticity, and some are even bioabsorbable. Additionally, the components of the films can actively participate in promoting the healing process. Even more, the film can be made up of carriers with other active participants to prevent and eradicate infections. Therefore, the extensive versatility, practicality, and usefulness of films from natural sources to address infectious processes during wound healing are relevant and recurrent themes. This work presents an analysis of the state-of-the-art of films with natural products focused on preventing and eradicating infections in wound healing.

***Key words:*** Skin; Wound; Infection; Wound dressing; Polymeric film.

## Introduction

Skin wounds are a consequence of multiple frequent accidents involving friction, cuts, burns, or chronic conditions such as diabetes and blood circulation problems (1). The skin is one of the largest and most exposed organs in our body; consequently, it is plausible to suffer some skin injury of unpredictable degrees throughout life. Thus, due to the impact on the quality of life of patients, in the hospital economic system, and the complicated process involving at a cellular and molecular level, the treatment of wounds requires special attention (2). Although the evolutionary process gives our body the capacity for self-repair, serious injuries can set the patient's life at risk (3). Likewise, microorganisms' presence is always a latent risk because they can colonize the wound bed in an uncontrolled course; moreover, clinical factors such as bacterial resistance and the lack of effective antibiotics represent additional troubles (4). Concerning this, an infection process can delay the closing wound, turn towards a pathological scar, or even cause septic shock, compromising the patient's life. Some of the leading opportunistic microorganisms include *S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. coli*, *Klebsiella* sp., and *Propionibacterium acnes* (4). Wound dressings are materials that have the function of protecting the wound and promote the healing process. Although most of these remain solely on the surface, mechanical protection can offer a) moist environment, b) allow vapor exchange from wounded tissue and environment, c) maintain temperature, and d) protection against opportunistic bacteria (Figure 1)

(5). The above factors would allow enhancement of epidermal migration, promotion of angiogenesis, and connective tissue synthesis. Even today, the most basic management consists of gauzes impregnated with petroleum jelly as a primary treatment with frequently favorable results in the quality of tissues. Wound dressings include foams, hydrogels, gauze, and films. Films are one of the forms of wound dressing that predominate commercially due to their mechanical resistance, ease of application, versatility in sizes, and because they offer uniform protection. Films differ from membranes in thickness; films are usually about 100 µm thick or less (6). Films can be occlusive (seal the wound) or semi-occlusive (with microscopic pores to allow the transmission of gases); these can include a single layer or different layers of different compositions. Traditionally, films are made of non-biodegradable polymeric materials to take advantage of the broad domain in handling known materials. Subsequently, the use of materials with more outstanding biocompatibility was preferred. Therefore, the use of natural products to obtain films is highly attractive, and the latest strategies include highly biocompatible and biodegradable polymers. Natural products can participate in the main composition of the film, or they can be an additional excipient to promote wound closure and prevent infection. Furthermore, they can also contain other active components.

This mini-review focuses on describing and analyzing polymeric films obtained from natural products to prevent infections in the wound approach. It highlights the importance of infection prevention and addresses the manufacturing of films with natural products from a technological perspective.

## Wound healing

In economic terms, wound treatment represents a very high cost in most countries. For example, in the United States, nonhealing wounds account for approximately $50 billion (1). Without considering the physical and emotional impact of poor wound management on the patient's quality of life.

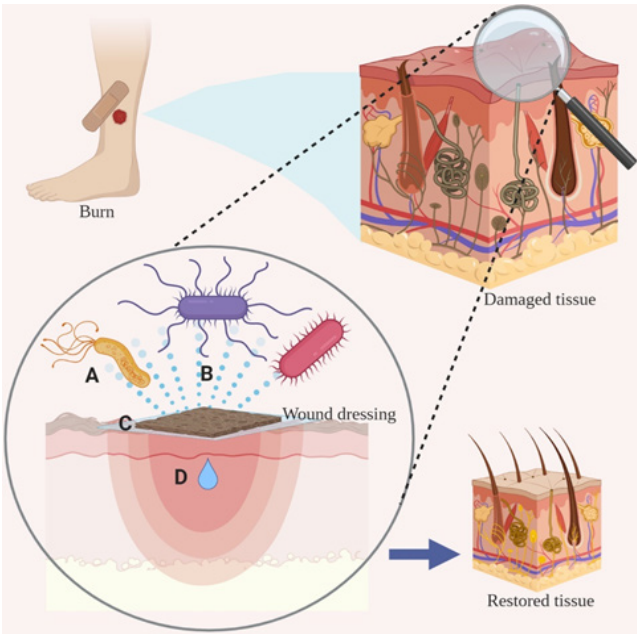


**Figure 1.** Role of films as wound dressings in wound care. A) preventing the entry of opportunistic bacteria, B) regulation of vapor transmission, C) capture of exudates, and D) maintenance of interior humidity.

The speed and quality of response on the battlefield depend on the patient's health and nutritional level. The first response to a wound is the formation of the fibrin clot. This bandage is a kind of plug that prevents possible bleeding and is accompanied by a cell battery of neutrophils as the first line of defense against microorganisms (7). Subsequently, in the inflammation stage, the cavalry of monocytes rises that will be transformed into macrophages, in addition to the archers constituted by Langerhans cells, dermal dendritic cells, and T cells. All united to defend our body against the loss of our main barrier, the skin. Interestingly, as in the epic battles of our history, the best defense is not always enough, and a more significant number of soldiers does not guarantee better protection. One of the drawbacks of the adaptive response in the inflammatory stage is an exacerbated reaction. At the end of the battle, in the splendor of tranquility, the angiogenesis process begins when the inflammatory phase ends. The angiogenesis stage involves the formation and growth of blood vessels with the arrival of nutrients and the restoration of cellular components (8). In particular, proliferation and migration of fibroblasts occur through the fibrin scaffold in the clot, enriching the restoration of the extracellular matrix with the synthesis and deposition of collagen. Later the re-epithelialization process appears with greater intensity, deriving cell lines from stem cells from the basement membrane, and differentiation of terminally differentiated epidermal cells. In parallel, the reconstruction of skin appendages arises. Finally, in the remodeling-maturation stage, the abundant presence of macrophages ceases, and there is a predominance of collagen I instead of collagen III. Formally, it is a stage that can last several years of slow and silent advance, but delicate, that affects in the quality of mechanical response of the skin (3,9,10).

## Infections: the main silent problem

The presence of normal flora in the skin promotes homeostasis that counteracts the possible invasion of pathogenic microorganisms (Figure 2). Microorganisms colonizing the skin include *Staphylococcus epidermidis*, *Corynebacterium*, *Propionibacterium*, *Brevibacterium*, *Micrococcus*, *Malassezia* spp., *Demodex folliculorum*, and *Demodex brevis* (11). While the presence of viruses is not well defined yet in regulating the homeostasis of the skin. Variations in the anatomical region influence the shape and chemical composition of the skin surface, and therefore, the predominant microbiome. However, *Staphylococcus* and *Corynebacterium* spp. are the most abundant organisms in the different anatomical regions.

Nevertheless, a break in the skin barrier may lead to antibiotic-resistant commensal organisms such as *Staphylococcus epidermidis* to colonize the wound and cause infections that can be fatal. The issue of wound infections is a global public health problem, and statistics of impact on patients are not entirely accurate due to the constant change in the biochemistry of antibiotic-resistant microorganisms. Undoubtedly, it represents a significant challenge in the hospital setting due to the lack

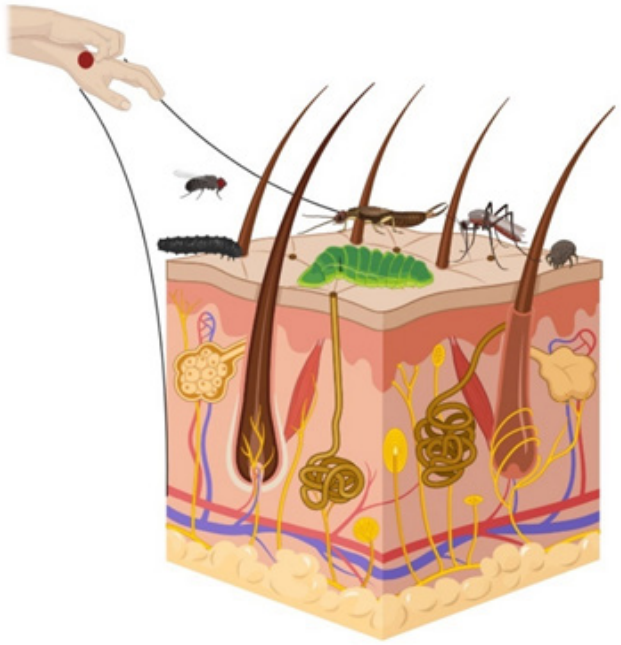

**Figure 2.** The microbiome of the skin helps the expression of T cells that maintains protection against pathogenic microorganisms and possible skin infections.

of effective antibiotics, and more than half of critically ill patients die for this reason. It is even well known that one of the problems of a prolonged stay in high-attendance hospitals is colonization by highly resistant and pathogenic microorganisms. Gram-positive microorganisms (e.g., *Staphylococcus aureus*) predominate in the initial stages of wounds, while Gram-negative species (e.g., *Escherichia coli* and *Pseudomonas* spp.) with a greater internalization capacity in the different layers of the skin are preponderating in advanced stages. Other species involved in chronic wounds are *Streptococcus pyogenes*, *Klebsiella* spp., *Propionibacterium acnes*, and *Acinetobacter baumannii* (4).

## Films as wound dressings: the last dance?

### *Generalities*

Films are described as thin sheets (approximately 50 to 100 µm thick), formed by one or several polymers as matrix-forming materials, plasticizers, active ingredients, residual solvents (e.g., water or ethanol), and additional excipients such as stabilizers, disintegrants, and preservatives (12). The application of films for drug delivery offers several advantages (13): the ability to cover large areas of anatomical regions, high bioadhesion if desirable, swelling capacity, transparency, uniform surface, microneedle adhesion, and control of the porosity of the materials. Its versatility comes from the wide range of natural and synthetic polymers available and the ease of industrial scaling for their manufacture. One of the key agents in its formulation are plasticizers; these are low molecular weight chemical structures with the ability to intercalate between polymer chains to increase their displacement and allow greater mechanical strength and flexibility (Figure 3) (14,15). The application of films on the wound bed permits the control of infections during the healing processes through the gradual release of antibiotics; furthermore, films constitute a physical barrier to prevent the entry of other pathogenic microorganisms (16).

### *Types*

Most antibiotic-releasing films are of the hydrophilic type with rapid dissolution when applied to an anatomical region in the presence of physiological fluids. Furthermore, the presence of hydrophilic plasticizers increases the dissolution rate. Hydrophobic films (the opposite strategy) are less frequent, but their slow dissolution rate is attractive for prolonged-release systems. In films containing antibiotics or molecules against microorganisms, the second option is convenient because it allows a long time of action. In terms of architecture, films can combine two polymers as components of the matrix or constitute two or more layers of the same or different composition. With this strategy, an antibiotic can be incorporated into one layer, a different one in the second layer to the outside, consecutively. The sealing and bonding of the layers will depend on the type of polymer; it can be manufactured by consecutive deposition or by pressing.

### *Manufacturing methods*

The manufacturing method that predominates in the literature for obtaining films to counteract the presence of microorganisms in wounds is by solvent casting (12). This method involves the formation of the matrix polymer, plasticizer, and antibiotic solution. It is then poured into a container of a variable nature such as glass, Teflon, silicone, stainless steel, or aluminum. The composition of the mold, shape, and size is crucial to obtain an easily removable film of homogeneous thickness and with appropriate dimensions for wound protection. Pouring into the mold is the critical first step because it will depend on the viscosity of the solution; a high viscosity will complicate pouring and possibly will lead to the appearance of bubbles that will later form semi-pores in the membrane. Although highly viscous hydrogels require less drying time, low-viscosity solutions will be

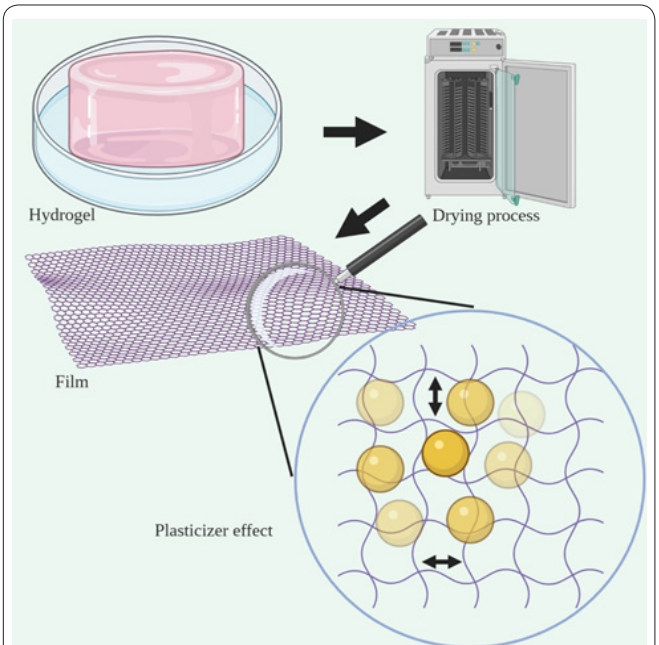


**Figure 3.** Intrachain interactions of the plasticizer increase the movement of the polymer chains with an improvement in strength and elasticity.

easy to mold and may not bubble. We suggest an intermediate stage considering a balance of time and energy consumption (17). The second crucial step is the drying to convert the semi-solid to a solid. The type of drying will depend on the solvent to be removed (e.g., water, ethanol, acetone, among others) and the matrix polymer. High rates of drying speed can lead to the appearance of bubbles and possible precipitation of excipients (e.g., antibiotics). Depending on the type of furnace, if the energy transfer is not homogeneous, the drying and formation of the membrane will not either, causing more significant drying on the edges. Leveling the oven is essential to ensure a homogeneous thickness. Finally, the ability of the plasticizer will also be demonstrated in the ease of film release in the mold. If the plasticizer is not enough, a low proportion of talc or glycerin can promote the release.

## Films from natural sources for wound infection control

The matrix-forming polymer must have adequate mechanical properties to facilitate the handling of medical personnel and remain in the wounds for a few days (5). The discovery of new natural origin components is attractive because it allows exploring new mechanical properties that are sometimes not possible to offer with traditional synthetic polymers (18). The impact on the new mechanical properties also modifies and makes it possible to control the release conditions of the active principles. Matrix-forming natural excipients include polymers from plants, animals, fungi, or bacteria (19). The first two options provided abundant sources of biomaterials, but the new sustainable trends will drive the predominance of materials from fungi or bacteria. Additionally, most polymers of natural origin have hydrophilicity in common, while most active ingredients are lipophilic.

Natural polymers for the fabrication of films can include pectin, tamarind seed polysaccharide, fenugreek gum, zein, gelatin, chitosan, carrageenan, alginate, xanthan gum, gellan gum, guar gum, pullulan, collagen, and elastin, among others (20–22). In contrast, synthetic options include hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, ethylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, and acrylic derivatives. One of the critical challenges in the formulation of films is to guarantee the compatibility of the excipients between the natural matrix-forming polymer, stabilizer, active principle, and the rest of the ingredients (when necessary) in the same solvent. Any incompatibility on solubility will cause precipitation, affecting the appearance of the film, its mechanical properties, and the release capacity of active ingredients. The active ingredient to counteract infections in the wound can remain dissolved or dispersed, and several natural polymers can even possess some activity against microorganisms. Therefore, the total effect against possible infections would be derived from the sum of the activities produced by the active ingredient, the matrix-forming polymer (e.g., chitosan), and even those that the plasticizer could have. In sum, a film with these characteristics would counteract infections with three different mechanisms that would help reduce antibiotic resistance. Even if desired, an additional antibiotic might be combined with this prototype, but in a lower concentration. More sophisticated prototypes include visual indicators for monitoring pH or possible infections and films that incorporate electronic circuits to precisely monitor some physiologic indicators remotely.

## Conclusion and perspectives

Various proposals for wound dressings that are commercially available offer a degree of aid in wound care; however, there is still a lack of genuinely useful materials. Hence, there is an interest in using films as skin covers due to their easiness of application, flexibility, and mechanical protection, approaching an artificial substitute for skin. Mostly, biodegradable and bioabsorbable skin coverings represent a useful tool in the medical field. For this reason, since the wide range of polymers of natural origin, it is possible to have a diverse variety of options in new materials, taking advantage of their abundance and economical price. Even more impressive, some of these polymers can participate in some mechanisms for wound healing and infection prevention, as chitosan. In this way, the films can be multifunctional. With the increase in the discovery of new natural products and more applications such as biodegradable plastics, an expansion in the diversity of films is expected, combined with the development of multifunctional prototypes such as microneedle adaptation and remote monitoring electronic devices. The effect of some natural polymers in counteracting the presence of microorganisms is exciting and desirable because it will continue to be a requested strategy against antibiotic resistance. Therefore, the development of films from natural sources for infections during wound healing is a promising area in both the availability of a wide range of polymers and the imperative need to improve wound care.

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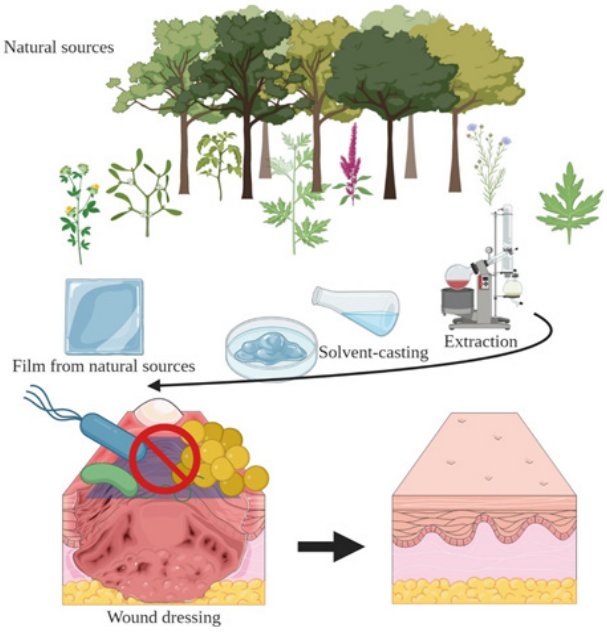


**Figure 4.** Developing films from natural sources for infections during wound healing.

to Gerardo Leyva-Gómez. Image templates made available by BioRender (BioRender.com) and Servier Medical Art (smart.servier.com) were used to design figures.

## Conflicts of interest

The authors declare no conflict of interest.

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