

Insight into Topical Preparations for Wound Healing: Traditional and Modern Dressings

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ABSTRACT

The authors conducted an extensive literature search of the Science Direct, Scopus, PubMed, and Web of Science databases. Published studies and original articles published in reputed peer-reviewed journals reporting original research were considered. Different wound dressings show different properties and may have different applications depending on the types of wounds. Traditional wound dressings (like gauze), mainly used for clean and dry wounds with mild exudate, are cheap and affordable, however, they suffer from many limitations; including adherence to the skin, pain in removal, contamination with bacteria, and other obstacles. On the other hand, modern dressings have many advantages, such as the fact that they do not adhere to the wound, they are easily removed, and many other advantages. The introduction of nanotechnology in the field has accelerated the discovery and the applications, and many new pharmaceutical products for wound treatment will enter the market soon. Therefore, evaluating the advantages and limitations of different types of dressings and determining a suitable type of wound dressing to be applied is crucial. This article aims to explain the different types of wound healing agents or dressings available to treat acute or chronic wounds.

Keywords: Wound healing; Wound dressing; Modern wound dressing; Traditional wound dressing; Nanotechnology based wound dressing.

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INTRODUCTION

Wounds can be defined as damage to the integrity of biological tissue, including skin, mucous membranes, and organ tissue. They can vary from superficial scratches to deep wounds damaging blood vessels, nerves, and muscles [1]. Wounds can be categorized into two main categories: acute and chronic wounds. Acute wounds heal normally through the stages of wound healing and show definite signs of healing within four weeks, whereas chronic wounds do not heal normally (often becoming 'stalled' in one phase) and do not show evidence of

healing within four weeks.

The healing process involves four spatially overlapping processes: (i) coagulation and hemostasis, which begin soon after cellular damage; (ii) inflammation, which also begins soon after; (iii) proliferation, which begins within days of the injury and represents the most important healing phase; and (iv) wound remodeling, which can last a year or more [2, 3].

The main purpose of wound dressing is: a) to provide a temporary protective physical barrier; b) to absorb wound drainage; and c) to offer the moisture required to improve re-epithelialization [3]. The choice of dressing depends on the anatomical and pathophysiological characteristics of the wound and it has two main categories: traditional and modern dressing (Table 1). Traditional dressing (for example gauze) is mainly used for clean and dry wounds or wounds with mild exudate. Despite being highly absorbent and efficient for dry

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to mild exuding wounds, traditional wound dressings such as gauzes require frequent application, which can make dressing changes uncomfortable. Furthermore, they lack adhesion and cannot adequately drain the wound due to their poor drainage properties [4]. Modern dressing (for example hydrocolloids, hydrogel, and alginate) is developed with its ability to enhance wound healing, re-epithelization, and granulation [5]. Recently, nanotechnology-based wound dressing have shown different properties and the ability to overcome the limitations found in modern wound treatment [6]. The recent advancement in polymer science allowed the production of modern dressing with varied actions and multiple benefits (Table 2) [7].

Therefore, the objective of this review is to shed light on traditional and modern dressings and give a clear idea about them by clarifying the advantages and disadvantages of each of them.

TRADITIONAL WOUND HEALING AGENTS

The main functions of traditional dressings are to stop bleeding, specifically in emergency first aid, cushion the wound, absorb wound exudate, and protect the lesion from harmful substances or contamination. Commonly used traditional wound dressings include gauze, plaster, and wool dressing [31]. However, the gauze should be dry and sterile when used for skin wounds in the majority of situations. However, in some conditions, gauze can be soaked with a wide range of compounds, including antimicrobials, iodides, and petrolatum. Such gauze soaked with the antibacterial 0.2% polyhexamethylene biguanide can be used as the primary dressing for tracheostomy sites, drain sites, and intravenous sites. When this type of gauze is applied to infected wounds, it minimizes bacterial penetration and may lower infection rates. Although soaked gauze is not primarily intended to treat wound infection, it could be used as a supportive therapy to systemic antibiotics to treat wound infection [8]. One of the main disadvantages of gauze dressings is that bacterial protection is diminished when the dressing's external surface becomes wet from wound exudate. Additionally, as fluid production declines, gauze dressings are more likely to stick to wounds and are tough to be remove, which is uncomfortable for the patient [15].

MODERN DRESSINGS (OR MOISTURE-RETENTIVE DRESSINGS)

This kind of dressing can improve the healing of wounds by providing a good moist environment, maintaining better absorption of exudate, and promoting granulation and re-epithelialization by managing exudate and providing a moist, warm healing environment, in addition to removing any necrotic tissues that may cause matrix metalloproteinase to linger in an excessive amount. In addition, these dressings may contain bioactive substances [11, 12, 30]. The purchase cost of modern dressings is higher than conventional dressings, but the fact that they require fewer dressing changes and sometimes achieve faster healing rates, lower infection rates, and greater patient satisfaction means the overall cost of treatment is lower [32].

TYPES OF MODERN DRESSING

Several different items can be included in modern dressings, such as Hydrocolloid, Hydrogel, Alginate, Hydrofiber, Foam,

Film, Sponge, and Nanotechnology based wound dressings (Table 2).

Hydrocolloids dressings

This dressing has a self-adhesive inner layer made of hydrophilic colloid particles such as carboxymethylcellulose (CMC), pectin, gelatin, or an elastomer that forms a gel. This layer takes in exudates and enlarges over the lesion to resemble a gel. Besides providing the wound bed with thermal protection, this creates a moist healing environment. The outer layer, which is often made of polyurethane, protects the wound and guards it against bacteria, foreign objects, and shearing [15]. As it is permeable to water vapor, it also can debride wounds and absorb wound exudates [20]. They are used on mild to moderate exudate wounds such as small burns, traumatic wounds, and pressure sores. Since this type of dressing does not hurt when removed, it suggested for managing wounds in the pediatric population [5]. The dressing's opaqueness, which prevents frequent wound examinations, is one of its disadvantages. The gel that forms can also be thick, offensive-smelling, and yellow, which can be mistaken for infection [33].

Hydrogel

They are three-dimensional polymer networks that are created naturally or artificially using chemical or physical crosslinking techniques and have a moisture content of at least 90% [34]. They absorb a small amount of exudate via swelling due to their high-water content, but they can also provide a moist environment for dry wounds, aiding in autolytic debridement and preserving a wet, thermally insulating wound environment [18, 35]. Hydrogels are therefore best suited for dry or uninfected, low-exuding wounds although they can also be used on moderately exuding wounds depending on the gel's capacity to swell [36]. They resemble real tissues in that they are pliable, have an adhesive nature, and have cooling properties that reduce pain perception. They are regarded as the finest option for wound dressing due to their qualities [31]. Hydrogel dressings, which are administered to the wound as a gel, typically need a second covering, such as gauze. The sheets, however, do not require a second dressing since the dressing's semi-permeable polymer film backing, which can have or lack adhesive borders, regulates the passage of water vapor [21]. The challenge with hydrogel dressings is that they tend to accumulate exudate, which causes maceration and bacterial growth that make wounds smell bad. Additionally, hydrogels' limited mechanical strength makes them hard to handle [22]. In a recent Cochrane review on the use of hydrogels in treating diabetic foot ulcers, collected data revealed a higher rate of ulcer healing in the hydrogel-treated group when compared to the group that received conventional contact gauze dressing [37].

Alginate dressings

Alginates are made of polysaccharides derived from seaweed. Alginate gel is created when calcium ions in the dressing interact with sodium ions in wound exudate. Since the gel is very absorbent, it reduces bacterial contamination, and it is the ideal dressing for wounds that exude a lot of fluid. These dressings may absorb 15–20 times their weight, which can significantly improve the overall quality of life for people suffering from draining ulcers [38]. Even though alginate has been shown in certain studies to prevent keratinocyte migration,

Table 1. Characteristics of different dressings.

Traditional wound dressing	Modern wound dressing	Nanofiber wound dressing
Dry material is used as primary or secondary dressings to protect the wound from contamination [8].	Maintain the most suitable environment at the wound/dressing interface [9].	Structure similar to the innate extracellular matrix, which creates the perfect environment for the wound-healing process [10].
May become moistened due to wound drainage, thus favoring bacteria contamination [11].	Absorb excess exudates and prevent leakage [12].	Matrix can incorporate the biocompatibility of natural polymers along with the enhanced mechanical properties that synthetic polymers provide [13].
Low cost and affordable [8].	Provide thermal insulation, mechanical and bacterial protections, and allow gaseous and fluid exchanges [9].	A higher specific surface area is favorable for liquid adsorption and active ingredient loadings [14].
Don't stick to the skin or adhere well to wounds. As a result, they cannot hold fluids or bacteria in the damaged area and can also fall off at any time [15].	Absorb wound odor [12].	High porosity, which facilitates cellular respiration and gas permeation, and prevents wound drying and dehydration [16].
Adhere to the wound, making it painful when removing it and may causing damage [15].	Nonadherent to the wound and easily removable without trauma [17].	The rate of drug release can be controlled by modifying the structure and size of the pores [14, 16].
	Provide some debridement action [18].	Antimicrobial property [16].
	Nontoxic, nonallergic, nonsensitizing [17].	High chemical and thermal stability [19].

Table 2. Comparison of different types of dressings.

	Traditional wound dressing	Modern wound dressing	Nanofiber wound dressing
Environment it provides	Dry material, Can't provide a moist environment but can only provide mechanical protection [17].	Provide a moist environment that would enhance the wound healing process [20].	Provide an environment similar to an extracellular matrix to accelerate wound healing [10].
Main use	For dry clean wound or wound with mild exudate. Not favorable to be used for acute or chronic wounds as far as rapid healing is required [5].	For acute or chronic wounds, the modified chemical environment faces the physical condition for more rapid healing [9].	For acute or chronic wounds to accelerate healing besides delivering drugs at a controlled rate [13].
Risk of contamination	Maceration can cause bacterial contamination [21].	Moist microenvironment may increase the risk of bacterial proliferation [22].	Nano pore size prevents bacteria contamination [19].
Removal	Painful as it can stick to wound [23].	Painless and can be easily removed [24].	Painless and can be easily removed.
Adherence	Low mechanical stability and can easily fall off [25].	Easily attach to wounds	Improve cellular adherence [26].
Absorption Capacity	Have a large capacity to absorb exudate but is limited by maceration [26].	High capacity to absorb fluid, e.g. foam may cause dryness on long residence [27].	High absorption capacity due to the large surface area without causing dryness [28].
Ability to deliver drug	Unable to deliver active ingredient however can be soaked with solution, e.g. gauze soaked in povidone iodine [11].	Can be used to deliver different active ingredients, e.g. drugs, vitamins, antibiotics, or growth factors [29].	Besides delivering different types of active ingredients, they have a high drug-loading capacity and they can deliver-drug at a constant rate of release [30].

Thomas et al. have found alginates can improve the healing process by causing macrophages to create Tumor necrosis factor (TNF), which starts the inflammatory process [39]. Yet, these dressings need secondary dressings since they risk drying up the area and delaying healing [5]. Furthermore, it should

not be applied to dry wounds or gauze dressings [40].

Hydrofiber

Comparable to alginate, a hydrofiber is made of sodium carboxymethylcellulose and can absorb up to 25 times its

weight in liquids when combined with wound exudate to create a gel [15, 41]. The hydrofiber dressings important features are that it is very absorbent and doesn't have lateral wicking; both of these protect the peri-wound [36, 42]. Furthermore, hydrofiber aids in autolytic debridement, so it is applied to wounds with moderate to severe exudate [43]. However, these dressings are not recommended to be applied to dry wounds since they can leave a fibrinous deposit on the wound bed surface [35]. Clinical research showed that hydrofiber dressings manage postsurgical wounds more successfully than passive dressings. According to the results of a systematic review and meta-analysis to determine the best wound dressing material after total hip and knee arthroplasty, wounds treated with hydrofiber dressings had a markedly lower risk of complications than wounds treated with passive dressings [44].

Foam dressings

Foam dressings are made up of hydrophobic (outer) layers to protect the wound from germs and surround the polyurethane or silicone core (hydrophilic foam) [5]. A dressing can manage high amounts of wound fluid since it is constructed of polyurethane or silicone. They come in a variety of thicknesses and in both sticky and non-adhesive forms. The adhesive formulation needs to be used with caution on vulnerable skin [43]. The texture, thickness, and pore size of the foam are factors that govern its high absorbency. Additionally, the open pore structure provides a high rate of moisture vapor transport (MVTR) [45]. One of these products' main characteristics is its ability to maintain a moist wound bed while keeping the wound free of exudates. This technique provides protective shields against infections and dehydration. In addition to speeding up the healing process, it also improves the enzymes' capacity to promote epithelialization and regulate the system's biomechanics [46]. They can be used as a primary dressing or on top of hydrogels and creams [43]. One of their benefits is that they are composed in a way that makes their removal painless [47]. In a comprehensive analysis of clinical trials done to examine the effectiveness of several dressings on postoperative wounds without closure, foam was found to be superior to gauze in pain relief, patient satisfaction, and nursing time [48].

Film dressings

Transparent film dressings are polymer membranes with an adhesive coating on one side and range in thickness. By limiting moisture buildup in the wound, the polyurethane layer lowers the danger of tissue maceration [49]. Films are used to treat wounds of partial thickness with or without exudate, necrosis, or infection and can be used as a primary or secondary dressing. They come in a variety of sizes, both sterile and bulk, are light and elastic, and easily attach to wounds with complex curves and shapes [50]. The main benefit of films is their transparency, which enables doctors to monitor injuries without taking off the wound dressing, reducing the danger of infection, trauma, and pain. However, that patient might find this less appealing because they would rather not see the wound. The use of film dressings for excessively moist wounds or hemostatic application is unsuitable, and in some situations, later removal of the films may result in discomfort and epidermal damage [49, 51]. They are only suitable for fairly shallow wounds since they are too thin to pack into deep wounds [21]. Numerous studies have demonstrated that films can also be used as carriers for

different biomolecules, medications, and growth factors. For example, adipose-derived stem cell (ADSC)-encapsulated silk fibroin-chitosan films were tested for the treatment of diabetic wounds and showed significantly increased rates of wound closure in treated animals; hence, wound healing was drastically enhanced [29].

Sponge

Sponges are soft, flexible wound dressings with interconnecting porous components [52]. Their great swelling capacity is influenced by their porous structure, which makes them suitable for the treatment of oozing wounds. Additionally, they promote cell infiltration and have high water uptake capacities suitable for maintaining a moist environment in the wound bed while preventing bacterial infections from spreading to the injury [53]. Polyvinyl alcohol alginate, chitosan, and graphene oxide sponge wound dressings showed good antimicrobial activity [54]. High adhesive properties are an absolute requirement for controlling bleeding. Additionally, the implant sponge surface adheres to the surface of the injured organ without the use of additional suture material or other techniques [55]. In contrast, the main disadvantages of sponge dressings include the following: they are mechanically unstable, may cause maceration due to their higher content of moisture, and may result in the development of microbial infections in the absence of antibiotics. Furthermore, sponges are ineffective for dry wounds like secondary burns [56].

NANOTECHNOLOGY-BASED WOUND DRESSING

Nanotechnology is the scientific study of nanoparticles (NPs) that have extraordinary functions and size-dependent physicochemical properties. Nanomaterials are made up of nanoparticles, which are classified as inorganic or organic, and nanocomposites, which are classified as colloids, porous materials, copolymers, and gels. Hydrogels, nanofibers, and films are used to incorporate nanoparticles and nanocomposites into scaffolds and coatings (Figure 1) [57].

Because of their tiny size and physicochemical properties, they can deliver biomolecules or drugs intracellularly, protect them from deterioration, and enhance drug penetration into wounds. Furthermore, the encapsulation of drugs and biomolecules inside nanocarriers allows for different drug release profiles that can be tailored to the needs of wound healing [6]. The most common type of inorganic NP is silver nanoparticles (AgNPs). AgNPs are the most commonly used NPs in wound healing due to their antimicrobial, anti-inflammatory, and wound-healing properties (inducing myofibroblast differentiation from fibroblasts and stimulating keratinocyte proliferation and relocation) [58]. Furthermore, no microbial resistance or toxic effects were detected. Another example of nanotechnology is the use of mesoporous silica and carboxymethyl cellulose (CMC) hydrogel as a nanocomposite zinc oxide-impregnated wound dressing, which improved wound dressing properties and zinc oxide-healing activity [59].

NANOFIBER

The average diameter of nanofiber-based wound dressings is less than 1 micrometer [60]. They have extracellular matrix (ECM)-like diameters, making them ideal for the healing process as well as cell growth and adhesion [61]. Among the nanofiber preparation methods, electrospinning is the most widely used due to its numerous advantages, including the

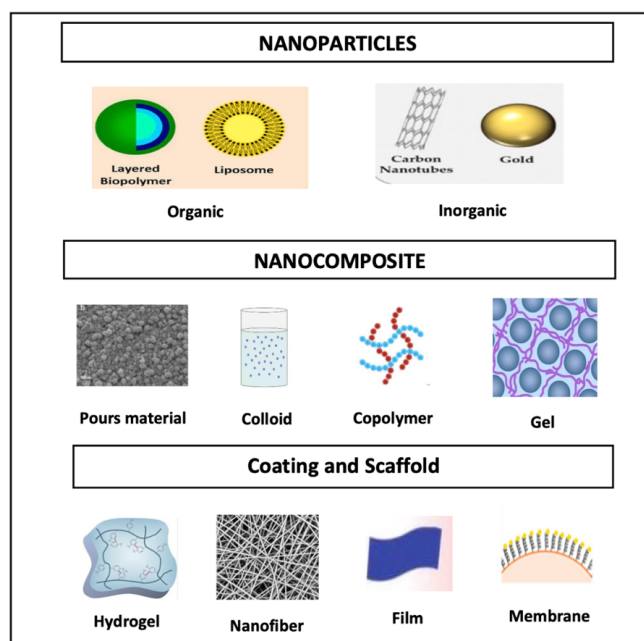


Figure 1. Nanomaterials include nanoparticles, nanocomposites, and various coatings and scaffolding materials.

ability to control the mechanical properties and pore size of nanofibers as well as its cost-efficiency, simplicity, and versatility [62, 63]. In addition, they have good exudate absorption from wound surfaces due to their high permeability and absorption rate, which also help keep the healing environment moist. Furthermore, the large surface area is advantageous for incorporating and transporting bioactive ingredients like drugs and growth factors [14]. As a result, electrospun nanofiber materials are regarded as one of the best options for wound dressing. The majority of nanofibers were made from poly(-esters) (Poly-lactic acid, Poly-glycolic acid, and Poly-lactic-co-glycolic acid), chitosan, gelatin, Hyaluronic acid (HA), and alginate. An adhesive bandage, a sterilized solid hyaluronic acid, gauze with Vaseline, an antibiotic dressing, and a sterilized HA nanofiber wound dressing were all used in a preclinical study to evaluate wound healing activity [64]. The results of this study revealed that the best of the five types of dressings was the sterilized HA nanofiber wound dressing. The reasons might be related to the ability of HA nanofibers to absorb wound exudates more effectively than sterilized solid HA and having much greater air permeability, as well as the fact that the dressing could act as a scaffold, assisting in cell migration and proliferation in the wound and promoting tissue growth and faster wound healing [64].

ROLE OF DIFFERENT POLYMERS IN WOUND HEALING

Various polymers can be utilized for the formulation of ideal wound dressing materials. Ideal polymeric dressings should have high porosity and swelling ability, an adequate water vapor transmission rate, the ability to maintain moisture and a warm environment to accelerate the wound healing process, gaseous permeation, excellent mechanical performance, and the capability to deliver bioactive agents. Many of these characteristics can be provided by different types of polymers.

Pluronic

Poloxamers, also known as pluronics, are nonionic copolymers of polyethylene oxide and polypropylene oxide typically utilized in pharmaceutical formulations as emulsifying or solubilizing agents. Jeong et al. discovered that pluronic-based dressings improved the activity of gelatinases, which are known as matrix metalloproteinase-2 and -9 (MMP 2 and MMP9) while inhibiting MMP-8 collagenase. Consequently, this should conserve naive (good) collagen while speeding autolytic debridement of the wound by degrading damaged collagen [7]. All poloxamers are chemically identical in composition. The only difference is the relative amounts or ratio of propylene oxide, and ethylene oxides [65]. Therefore, there are several different types of poloxamers including:

Pluronic F127 (Poloxamer 407)

It is a thermo-reversible gel that has been utilized as a drug delivery system for both oral and topical administration [66, 67]. It may sufficiently resemble the skin epidermis' normal functions, functioning not only as an "artificial skin" but also as a carrier for mitogenic proteins like epidermal growth factor (EGF), which speeds up wound healing in thermal burns [68]. Kant et al. evaluated the use of hydrogels made with pluronic F127 to enhance wound healing. They stated that applying this kind of gel, for about two weeks to full-thickness excisional wounds made in the dorsal skin of rats encouraged an increase in wound healing and closure. Transforming growth factor (TGF)- β 1 and Vascular Endothelial Growth Factor (VEGF) expression levels increased on days 3 and 7 post-wounding, respectively. Additionally, there was concurrent fibroblast proliferation, leukocyte infiltration, and noticeable angiogenesis, which enhanced the deposition of granulation tissue [69].

Pluronic F68 (Poloxamer 188)

Pluronic F68 is beneficial for wound healing by reducing inflammation and promoting the expression of growth factors [70]. It has also demonstrated the capacity to repair tissue or cell membranes to stop the buildup of additional cellular damage. A recent study showed Pluronic F68's effectiveness in restoring cellular integrity by sealing membrane holes in skeletal muscle cells and fibroblasts following heat shock. Recently, Maskarinec et al. discovered that Pluronic F68 is selectively inserted into damaged membrane regions of lipid monolayers [71].

Carboxymethyl cellulose (CMC)

Carboxymethyl cellulose (CMC) is a cellulose derivative that is frequently utilized in the pharmaceutical industry as an emulsifier, viscosity modifier, lubricant, and stabilizer to create various medicinal dosage formulations [72, 73]. It is compatible with skin, bones, and mucous membranes and has no physiological side effects [74]. The benefit of CMC is manifested through film creation, which aids wound healing by creating a moist environment around the wound, promoting the production of granulation tissue and collagen synthesis where the lesion sits [75].

Carbopol

Several studies showed that carbopol gel formulations were beneficial for accelerating wound healing. One study revealed that carbopol could hasten the delayed healing process in

wounds in diabetic rats when compared to the negative control, and improve the formula's humidity, and keep the environment wet, all of which could speed up the healing process [76]. Additionally, a study that looked at the impact of Carbopol 940 on burn wounds indicated enhanced tissue perfusion and a reduction in the extent of necrotic tissue [77].

Hyaluronic acid

Hyaluronic acid (HA) is a naturally occurring biopolymer [78]. It is a long, unbranched polysaccharide with a molecular weight (MW) of up to 2×10^7 Da that is made up of repeated disaccharides of D-glucuronic and N-acetyl-D-glucosamine [79]. It binds to water, giving it a "Jello-like" stiff, viscous texture [78]. Since HA is a component of the skin's extracellular matrix, it is essential for various stages of the healing process, such as reduced inflammation, improved tissue remodeling, and angiogenesis, as well as stimulated collagen production in endothelial cells, in addition to several known properties (excellent biocompatibility, biodegradability, durability, and absence of toxicity) [79, 80]. In the Edmonds clinical trial, patients with diabetic foot were treated with HA versus standard treatment, and it was discovered that healing at the end of the research was much better with HA versus the usual care [81].

CONCLUSION

The ideal dressing is expected to have the ability to maintain moisture stability, support oxygen exchange, isolate proteases, stimulate growth factors, prevent infection, facilitate autolytic debridement, and stimulate the production of granulation tissue and re-epithelialization. However, currently, there are no dressings that can achieve all these functions. Hence, the specific selection of wound dressings should be based on the patient's primary disease, the characteristics of the dressing, and especially the physiological mechanisms of wounds. The introduction of hydrogels and new polymers rev-

olutionized dressing. In addition, the use of nanotechnology in dressing and wound management has further developed the field and can overcome the limitations that have been found in modern dressing; consequently many new pharmaceutical products for wound treatment could enter the market soon. Furthermore, the wound dressings will act as scaffolds for drug delivery or tissue regeneration products.

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Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

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Competing Interests

The authors declare that there is no conflict of interest.

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