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REVOLUTIONIZING WOUND CARE: THE POWER OF MULTIFUNCTIONAL HEALING BANDAGES

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ABSTRACT

Wound care technology has witnessed significant advancements aimed at addressing the complex challenges associated with wound healing. In this review include the innovative realm of multifunctional healing bandages, designed to simultaneously offer anticoagulant, antiseptic, and pain-relieving properties. Wound management is a multifaceted process that involves preventing excessive bleeding, mitigating the risk of infection, and promoting patient comfort. Traditional wound care products often focus on individual aspects, potentially leading to sub-optimal outcomes. This review highlights the emerging paradigm of integrated wound care through the formulation and development of bandages that synergistic-ally harness the therapeutic potential of anticoagulant, antiseptic, and pain-relieving agents.Through an exploration of the underlying mechanisms, we delve into the science behind each component: anticoagulants to prevent blood clot formation, antiseptics to manage and prevent infections, and pain-relieving agents to enhance patient well-being. We discuss the challenges and opportunities in combining these agents within bandage formulations, ensuring stability, effectiveness, and safety. Clinical efficacy studies are presented, showcasing the potential benefits of multifunctional bandages.

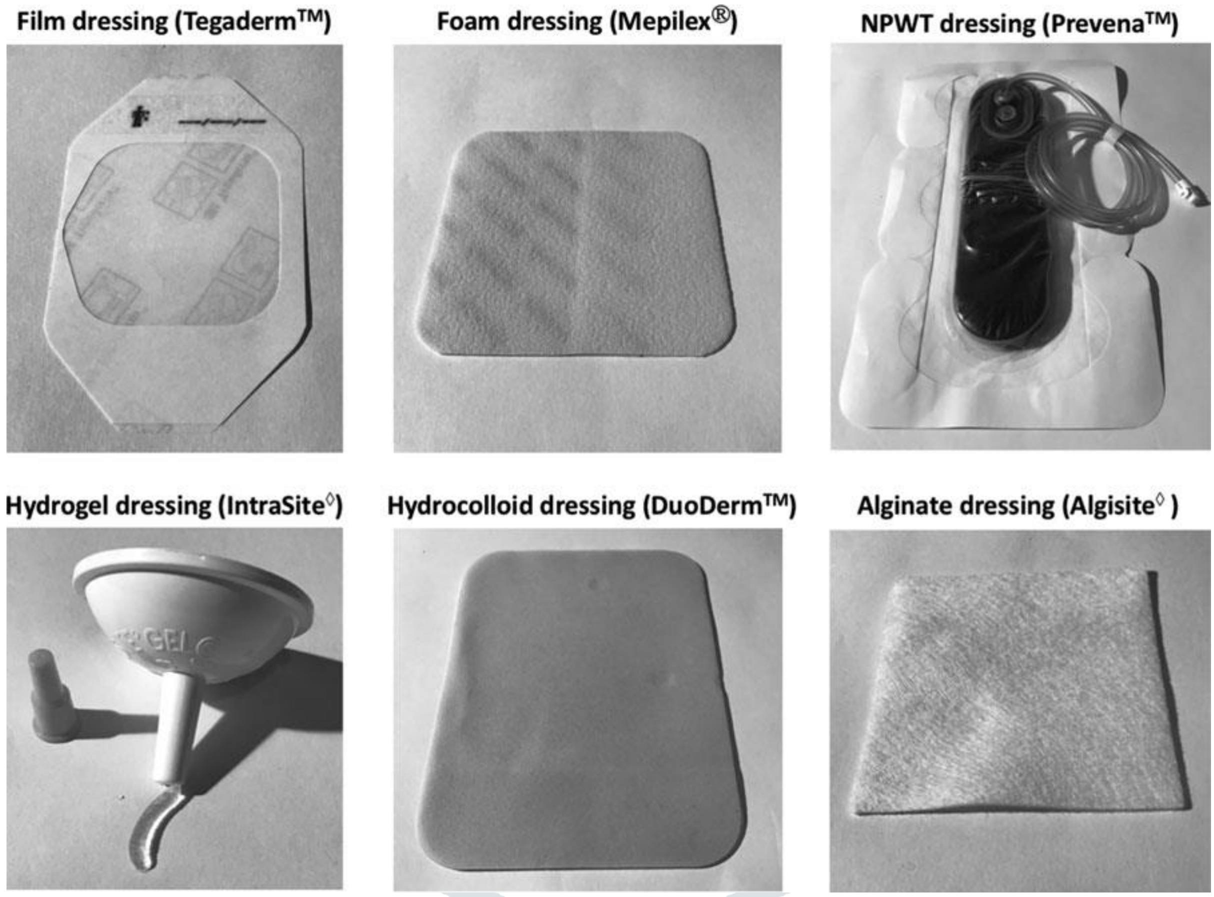
In conclusion, the advent of multifunctional healing bandages marks a paradigm shift in wound care, offering a holistic approach to address the intricate challenges of wound management. The convergence of anticoagulant, antiseptic, and pain-relieving properties within a single bandage opens new avenues for more efficient, patient-centric wound healing strategies. This review underscores the potential impact of these bandages in shaping the future of wound care and invites continued research and adoption of this groundbreaking technology.

KEY WORDS : Bandages, Hemostatic, Wound, Pain, Injury.

INTRODUCTION

A wound is defined as a disruption in the continuity of the epithelial lining of the skin or mucosa resulting from physical or thermal damage. According to the duration and nature of healing process, the wound is categorized as acute and chronic. An acute wound is an injury to the skin that occurs suddenly due to accident or surgical injury. It heals at a predictable and expected time frame usually within 8-12 weeks depending on the size, depth and the extent of damage in the epidermis and dermis layer of the skin. Chronic wounds on the other hand fail to progress through the normal stages of healing and cannot be repaired in an orderly and timely manner. Chronic wounds generally results from decubitis ulcer, leg ulcer and burns. Wound healing is a dynamic and complex process of tissue regeneration and growth progress through four different phases (i) the coagulation and haemostasis phase (immediately after injury); (ii) the inflammatory phase, (shortly after injury to tissue) during which swelling takes place; (iii) the proliferation period, where new tissues and blood vessels are formed and (iv) the maturation phase, in which remodeling of new tissues takes place .

TYPES OF WOUND DRESSING



FACTORS AFFECTING WOUND HEALING PROCESS

Wound healing is the result of interactions among cytokines, growth factors, blood and the extracellular matrix. The cytokines promote healing by various pathways such as stimulating the production of components of the basement membrane, preventing dehydration, increasing inflammation and the formation of granulation tissue. These pathways are affected by various local and systemic factors. Local factors which includes hypothermia, pain, infection, radiation and tissue oxygen tension directly influence the characteristics of the wound where as systemic factors are the overall health or disease state of the individual that affect individual's ability to heal. In addition to these factors, poor nutrition, age and protein, vitamins and mineral deficiency can also prolongs healing times.

ANTICOAGULANT MECHANISM IN BANDAGES

CONVENTIONAL HEMOSTATIC MATERIALS

When hemorrhage is severe and beyond the capacity of the intrinsic hemostasis mechanism of the human body, hemostatic materials are needed to stop bleeding. The mechanism of hemostatic materials usually involves 2 pathways, namely the active pathway and the passive pathway. The active pathway works to trigger hemostasis by specifically initiating the coagulation cascade, while the passive pathway achieves hemostasis via the specifics.

BLOOD DERIVED HEMOSTATIC MATERIALS: FIBRIN, THROMBIN AND FIBRINOGEN

1. Fibrin: Fibrin is one of the main components in the hemostatic clot formation and can be derived from human plasma surface properties of the hemostatic materials, such as hemocompatibility and antiinfection. Fibrin glue is a simple, effective and low-cost hemostatic agent for unsutured surgical bleeding. In 1990, Raccuia *et al.* measured the hemostatic efficiency of oxidized cellulose, collagen and fibrin glue in a rat kidney injury model and found that the fibrin glue has superior hemostatic ability compared to the other 2 materials.

2. Collagen: Collagen is the most abundant protein in a mammal's body, constituting the extracellular matrix of most connective tissues. Collagen-based hemostatic materials can activate the intrinsic pathway of the secondary hemostatic process.

3. Zeolite and kaolin: Zeolite and kaolin, which are microporous aluminosilicate minerals with large surface areas, have shown high hygroscopicity and excellent hemostatic performance. The hemostatic mechanism of zeolite is via the absorption of blood and the release of $Ca2+$ into the blood and to spur the intrinsic path of coagulation cascade.

4. Gelatin: Gelatin is a water-soluble protein is derived from collagen hydrolysis. Gelatin is highly absorbent and can absorb 5–10 times its dry weight in water. Gelatin and microbial transglutaminase were used to prepare an *in situ* gel-forming adhesive that can form gels within 30 minutes under damp conditions and stop bleeding in 2.5 minutes in a rat liver and femoral artery injury model and 4 minutes in a porcine model. A novel chemical crosslinked gelatin sponge was prepared and used in a 12-year-old male patient who was suffering from bleeding of a pharyngeal angiofibroma. The result showed that the gelatin sponge can stop bleeding immediately and degrades after 2 weeks.

5. Alginate: Alginate, a natural polymer with negative ions, can be extracted from seaweed. Because of its biocompatibility and low cytotoxicity it is commonly used for medicinal purposes, including in wound dressings. Alginate can form a gel or be crosslinked with divalent ions, such as $Ca2+$.

6. Chitosan: Chitosan is a natural cationic polysaccharide that is made from deacetylated chitin and widely applied in different fields, such as the food and cosmetic industries. Because of its biocompatibility, biodegradability, noncytotoxicity and antibacterial properties, chitosan can be used in tissue engineering.

7. Cyanoacrylate: Cyanoacrylate is a synthetic hemostatic polymer with good tissue adhesive properties that has been used as a hemostatic material since 1942. Cyanoacrylate has been commonly used as a clinical tissue adhesive due to its rapid hemostasis, reducing keloid formation, decreasing pain scores and low cost.

HIGH-PERFORMANCE HEMOSTATIC MATERIAL

ANTIBACTERIAL HEMOSTATIC AGENTS

Antibiotics are used clinically to treat bacterial infections; however, overuse of antibiotics may lead to drug resistance problems. To minimize the usage of antibiotics, antibacterial agents have been used to endow hemostatic materials with antibacterial properties. Antibacterial agents include organic (i.e. quaternary ammonium salts) and inorganic agents (i.e. silver ions and graphene oxide).

1. Hydrogels: Hydrogels can also be designed as a superelastic hemostatic materials because of their high hemostatic performance and biocompatibility. A conductive self-healing hydrogel wound dressing was fabricated from chitosan-g-polyaniline (QCSP) and poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGS-FA). The hydrogels have a self-healing ability and their gelation time is 86 seconds.

2. High porosity (aerogel): Aerogels have attracted numerous attentions because of its outstanding properties, such as ultralow density, wide surface area, high mechanical properties, high porosity and so forth . Various materials have been used to prepare the aerogels, including silica, polyurethane, cellulose and carbon.

3. Polypeptide: Peptides are compounds composed of 2 to 50 amino acids and peptide bonds. A polypeptide contains 10 to 50 amino acids.Though different hemostatic materials, such as chitosan, collagen, cellulose nanofibers and fibrin, have been developed and the commercial hemostatic products and their limitations also remain for clinical and emergency situations.

ANTISEPTIC COMPONENTS RELATED TO BANDAGES

Antiseptics are used on the surfaces of the body, mainly on the skin, mucous membranes and surface wounds. The preventative and medicinal uses of antiseptics can be distinguished. These agents are often used in hospitals and healthcare facilities to control the risk of infection as well as to prevent nosocomial infections. Antiseptics are applied by medical staff to decontaminate the skin of the hands, pre-operatively clean the skin of the surgical site, and cleanse chronic and acute wounds. They are also used to treat open wounds and sometimes infections of the skin.

COMMONLY USED ANTISEPTIC COMPONENTS

1. Alcohol

Several alcohols have been shown to be effective antimicrobials, ethyl alcohol (ethanol, alcohol), isopropyl alcohol (isopropanol, propan-2-ol) (used in the United States) and *n*-propanol (in particular in Europe) are the most widely used for both hardsurface disinfection and skin antisepsis.Classified as Category I, they are safe and effective for health care personnel handwash, surgical hand scrub and patient preoperative skin preparation. The alcohol killing mechanism appears to stem from membrane damage and rapid denaturation of proteins, with subsequent interference with metabolism and cell lysis protein coagulation and denaturation .

2. Iodine

Iodine has been regarded as one of the most efficacious antiseptic to reduce infectious complications and topical iodine forms have been used for wound treatment. The simplest form of iodine is Lugol’s solution, which has irritating and caustic properties.Tincture of iodine, containing approximately 2% iodine, has been long used as a preoperative skin preparation. Iodophors are the most common form of topical iodine and depend on the release of free iodine as the active agent.

3. Biguanides: chlorhexidine gluconate and polyhexanide/polyhexamethylene biguanide

Chlorhexidine, a biguanide antiseptic, is probably the most widely used biocide in antiseptic products, in particular, in hand washing and oral products but also as a disinfectant and preservative. It is produced in two forms: a 0.05% dilution for wound cleansing and a 4% solution for use as a surgical skin preparation and hand scrub. Recently 2% solutions have been made available for surgical skin preparation Polyhexanide/polyhexamethylene biguanide (PHMB) is considered to be highly histocompatible non cytotoxic and is one of the most frequently used wound antiseptics nowadays.

4. Halophenols (chloroxylenol)

Chloroxylenol (4-chloro-3,5-dimethylphenol; p-chloro-m-xylenol) is the key halophenol used in antiseptic or disinfectant formulations. Chloroxylenol is bactericidal. Because of its phenolic nature, it would be expected to have an effect on microbial membranes. At concentrations of 0.5–4.0% it acts by microbial cell wall disruption and enzyme inactivation. It has good activity against gram-positive bacteria, but it is less active against gram-negative bacteria, *Mycobacterium tuberculosis*, fungi and viruses.

5. Bisphenols (triclosan)

Triclosan and hexachlorophane are the most widely used biocides in this group, especially in antiseptic soaps and hand rinses. Both compounds have been shown to have cumulative and persistent effects on the skin. Hexachlorophene is primarily effective against gram-positive bacteria. It is a chlorinated bisphenol that interrupts bacterial electron transport, inhibits membrane bound enzymes at low concentrations and ruptures bacterial membranes at high concentrations.

6. Silver compounds

Silver and its compounds have long been used as antimicrobial agents.Currently, the antibiotic silver sulfadiazine is the most clinically relevant silver compound. It is thought to mainly act at the DNA level as silver ions bind to the helix thereby blocking transcription. Irrespective of the source of silver, whether released from solutions, creams and ointments or nanocrystalline silver, silver is highly toxic to both keratinocytes and fibroblasts.

7. Hydrogen peroxide

H2O2 is a widely used biocide for disinfection, stationmaster and antisepsis. It is a clear, colourless liquid that is commercially available in a variety of concentrations ranging from 3% to 90%. This readily available oxidant is rapidly converted to the highly reactive hydroxyl radical that damages an array of cellular components. Relatively high concentrations need to be applied because of the significant catalase activity of several key pathogenic bacteria.

PAIN RELIEF STRATEGIES IN BANDAGES

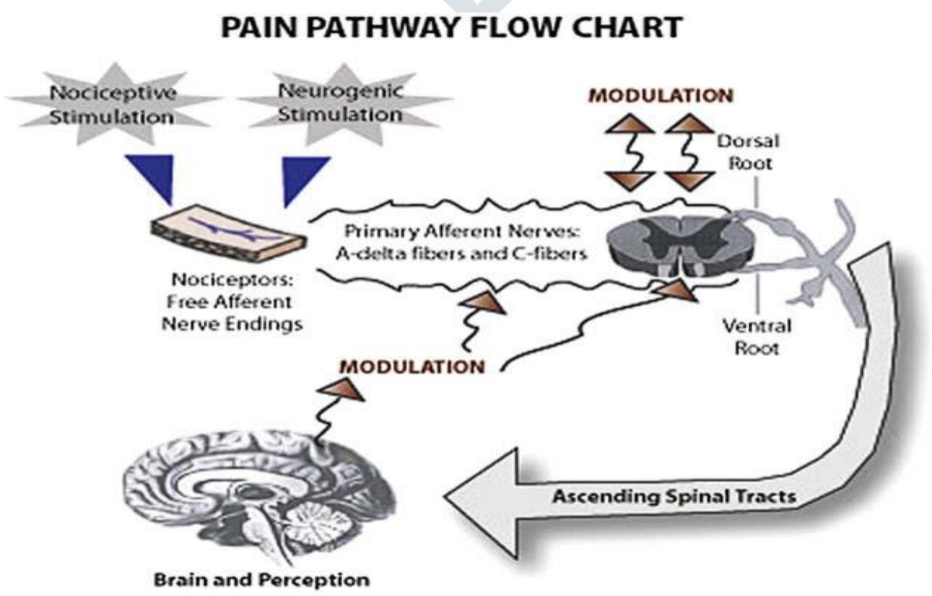
The World Health Organization developed a three-step approach to pain relief in cancer patients, and this can be modified for wound care.The inflammatory nature of chronic wounds and pressure ulcers are the basis for pharmacological pain management.

Step 1: A non-opiod analgesic (NSAID) with or without an analgesic adjuvant. Adjuvants include tricyclic antidepressants, anticonvulsants, antihistamines, benzodiazepines, steroids, and phenothiazines. Adjuvants are given for their indirect benefits in pain management.

Step 2: If pain is not controlled: Continue the initial medication and add an opioid, such as codeine or tramedol, and an adjuvant.

Step 3: When a patient does not respond to second-step medications, these should be discontinued and a more potent oral narcotic initiated.

The benefits of a pharmacological approach to wound pain must be weighed against the risks before this plan is initiated. ‘‘Analgesia can facilitate ambulation, which encourages wound healing and reduces the risk of complications like deep vein thrombosis, pulmonary complications and pressure ulcers. However, the adverse effects of analgesics must be considered, effects such as respiratory depression, nausea, constipation and sedation. Analgesia may also mask further symptoms and complications.



TRADITIONAL USE OF MEDICINAL PLANTS IN WOUND HEALING

1. Aloe vera: Applied to wounds for over 5000 years by Egyptians, Romans, indigenous peoples of Africa Asia, and the Americas. *Aloe vera* continues to be a first-line treatment for burns, ulcers, and surgical wounds. *Aloe vera* contains many natural bioactive compounds, including pyrocatechol, saponins, acemannan, anthraquinones, glycosides, oleic acid, phytol, as well as simple and complex water-soluble polysaccharides. Acetone extracts from the leaves of *Aloe vera* exhibit stronger antimicrobial activity than alcohol and aqueous extracts. Gram-positive bacterial species appear to be more sensitive than Gram-negative species to *Aloe vera*. Compounds with known antimicrobial activity are saponins, acemannan, and anthraquinone derivatives.

2.Arctium lappa: *Arctium lappa,* commonly known as burdock, is a widely cultivated perennial herb. Arctium lappa is used in North America, Europe, and Asia to treat sore throat and skin pathologies such as boils, rashes, and acne. Scientific analyses demonstrate *Arctium lappa* has antioxidant, anti-inflammator, antidiabetic, antimicrobial, antiviral, anticancer, and hepatoprotective properties. *Arctium lappa* is also reported to regulate cell adhesion and gene expression in canine dermal fibroblasts, affecting the β-catenin signalling pathway, known to be a key regulator of wound healing.

3.Astragalus propinquus and Rehmannia glutinosa: Root of *Astragalus propinquus* is a common TCM for the treatment of urinary retention and oedema.The root of Rehmannia glutinosa has been broadly used in hemorheology and diabetes-related diseases. A formulation combining the root of *Astragalus propinquus* and Rehmannia glutinosa was initially reported to be clinically effective for the treatment of diabetic foot ulcers.

4.Ampelopsis japonica: Growing throughout eastern Asia and eastern North America, the roots of *Ampelopsis japonica* are used as a traditional treatment for burns and ulcers, among other indications. Multiple pharmacological activities have been documented for Ampelopsis japonica, including neuroprotective, antimicrobial, and anticancer activities. Lee et al. demonstrated that ethanol extracts from dried roots of Ampelopsis japonica accelerated the healing of cutaneous scald injury in rats .

5.Andrographis paniculata: *Andrographis paniculata*, also known as green chiretta, is used in China, India, and south east Asian countries as a traditional treatment for fever, snake bite, dysentery, infections, wounds, and itchiness. Extracts from *Andrographis paniculata* exhibit antioxidant, anti-inflammatory, antidiabetic, anticancer, antimicrobial, antiviral, antimalarial, hypotensive, immunostimulatory, and hepatoprotective activities. In one study, wound closure in rats was observed to be significantly enhanced after treatment with a 10% aqueous leaf extract of *Andrographis paniculata*. Animals treated with Andrographis paniculata exhibited reduced inflammation, reduced scarring, increased angiogenesis, and an increased number of collagen fibres in healed wounds.

6.Angelica sinensis: The dried root of *Angelica sinensis* is widely used in TCM prescriptions for the management of female maladies, inflammation, headaches, mild anemia, fatigue, and hypertension. *Angelica sinensis* possesses pharmacological activities including anti-inflammatory, anticancer, antioxidant effects, and immune modulator. Extracts from Angelica sinensis have been shown to activate an antiapoptotic pathway and enhance cell proliferation, collagen secretion, and cell mobility in human skin fibroblasts. Extracts have also been shown to stimulate glycolysis and calcium fluxes, increasing cell viability during tissue repair.

7.Blumea balsamifera: Endemic throughout the tropics and subtropics of Asia, *Blumea balsamifera* (also known as ngai camphor) is used widely as a traditional medicine. In the Philippines, Blumea balsamifera is known as sambong and is used as a diuretic. In Ayurveda, *Blumea balsamifera* is known as kakoranda and is used to treat fevers, coughs, aches, and rheumatism. Leaf extracts are directly applied to treat eczema, dermatitis, skin injury, bruises, beriberi, lumbago, menorrhagia, rheumatism, and skin injury.

8.Calendula officinalis: *Calendula officinalis*, commonly known as pot marigold, is a very widely distributed plant used for the treatment of a variety of skin conditions, such as wounds, burns, and dermatitis [104, 105]. A range of pharmacological activities are ascribed to *Calendula officinalis*, including anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, and anticancer activities.

9. Caesalpinia sappan: Heartwood of *Caesalpinia sappan* is well known for its qualities as a dye and has been used in TCM to improve blood circulation and reduce oedema and pain. Homoisoflavonoids isolated from Caesalpinia sappan have been found to possess antiallergic and anti-inflammatory attributes and to inhibit viral neuraminidase activity. Ethanol extracts of *Caesalpinia sappan* exhibit effective antibacterial activity against Staphylococcus aureus, methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, and Klebsiella pneumoniae. Unexpectedly, the ethanol root extract from *Caesalpinia sappan* also stimulates dermal fibroblast proliferation, migration, and collagen synthesis in turn improving cutaneous wound healing.

10. Celosia argentea: *Celosia argentea*, also known as silver cock's comb, is used in traditional medicine to treat skin sores, eruptions, ulcers, mouth ulcers, and other skin diseases. Leaf extracts of this plant possess antioxidant , hepatoprotective , antidiabetic, and antimicrobial activities. Priya et al. demonstrated that an alcohol extract of *Celosia argentea* accelerates burn wound closure in rats by increasing collagen and hexosamine content in granulation tissue wounds.

CONCLUSION

In summary, the research on "Revolutionizing Wound Care : The Power of Multifunctional Healing Bandages"demonstrated the game-changing potential of these advanced technologies. Multifunctional healing bandages offer accelerated healing, reduced infections, and enhanced patient comfort by combining various innovations like antimicrobial agents, growth factore, and real monitoring. While challenges like regulatory hurdles and cost remain, these bandages signify a promising shift towards more efficient and patient-centered wound care, showcasing the synergy of medical and material science advancements.

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