Alternative Wound Management: Translating Science into Practice

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GENERAL PURPOSE: To present a scoping review of preclinical and clinical trial evidence supporting the efficacy and/or safety of major alternative wound care agents to summarize their effects on validated elements of wound bed preparation and wound management paradigms.

TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant will:

1. Differentiate the effectiveness of the topical wound care agents included in this review.
2. Compare the preventive efficacy of intravenous agents administered to trauma and surgical patients.
3. Select the effectiveness of products in this review that are left in place after surgical procedures.
4. Identify an oral agent that can be helpful in mitigating the effects of COVID-19.

ABSTRACT

Effective wound healing is achieved by well-timed host, cell, and environment interactions involving hemostasis, inflammation, formation of repaired dermal structures, and epithelialization, followed by months to years of scar remodeling. Globally, various natural or synthetic agents or dressings are used to optimize wound environments, prolong drug release, aid in fluid absorption, provide favorable healing environments, and act as a mechanical barrier against wound trauma. In this scoping review of evidence from the PubMed and clinicaltrials.gov databases, authors examined clinical study evidence supporting the efficacy and safety of selected phytochemicals, vehicles, polymers, and animal products considered "naturally derived" or "alternative" wound interventions to provide a summary of preclinical evidence. Agents with the most clinical evidence were honey, alginates, polyurethane, gelatin, and dextran. Practice implications are described in the context of the TIMERS clinical paradigm.

KEYWORDS: alginates, alternative, dextran, gelatin, honey, hydrogels, natural, phytochemicals, polymers, polyurethane, wound care

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INTRODUCTION

The World Health Organization has estimated that 312.9 million surgical procedures were performed in 2016[1] and that millions of children and adults suffer the physical and emotional trauma of burns, conferring more than $300 million of economic burden on patients and systems.[2] In 2014, in the US alone, 8.2 million Medicare beneficiaries had at least one chronic or acute wound or related infection (an estimated cost of US$28.6 to US $96.8 billion).[3] Although the true clinical, economic, and patient-centered burden of wounds remains to be clarified, wound care is clearly a global concern affecting hundreds of millions of people annually.

Wounds may be classified based on their locations, depth, nature or cause of injury,[4,5] and whether they are acute or chronic.[6] Acute wound healing requires good circulation, immune function, and a moist environment free of dead tissue or foreign matter supporting function of the many cells and molecules that participate in repair.[7–9] Chronic wounds are often resistant to treatment and need prolonged time to heal. Repair can be hindered by environmental factors such as trauma, desiccation, and infection; or host factors such as immune deficiency, compromised circulation, or respiratory

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function, which delay the normal progression through these healing phases.[6]

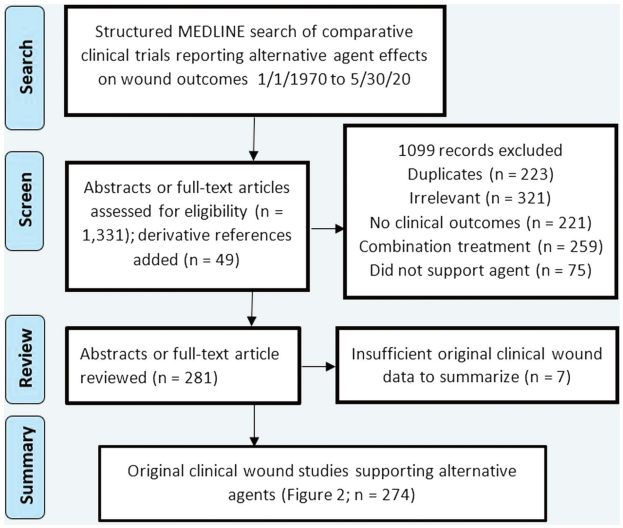
The rich global heritage of naturally derived wound healing products, sometimes loosely described as "alternative" agents, have received increased attention recently, and many researchers have explored their safety and efficacy in wound management.[7–9] Preclinical evidence presented in the Table suggests many ways that various agents obtained from plant or animal sources as well as certain smart excipients may affect wound environments.[10–21]

Supporting evidence for translating theory into practice for alternative wound care agents has been described as

Table. PRECLINICAL EVIDENCE SUPPORTING THE USE OF PHYTOCONSTITUENTS IN WOUND HEALING

Phytoconstituent	Preclinical Evidence
Curcumin (*Curcuma longa*)	Curcumin makes up between 2%-9% of turmeric. It is extracted from the rhizomes of *C longa* and has important antioxidant, anti-inflammatory, and antibacterial properties that make it useful for treating wounds. Curcuminoids upregulate prostaglandin synthesis and inhibit leukotrienes, stimulating collagen synthesis, which leads to tissue repair. Curcumin acts as a potent wound healing agent by altering urokinase plasminogen activator expression, which facilitates fibrinolysis and cellular migration necessary in the wound healing process.[10,11]
Gotu kola (*Centella asiatica*)	*Centella asiatica* contains triterpenes, asiaticoside, madecassoside, Asiatic acid, and madecassic acid, which trigger collagen synthesis and increase local vascular endothelial growth factor to support wound healing. *Centella asiatica* extract increases remodeling of collagen and granulation tissue production, as reflected by increasing DNA and protein synthesis.[12,13]
Aloe vera	There is considerable historic evidence that the multipurpose herbal extract of the leaves of the aloe vera plant possesses antimicrobial and anti-inflammatory properties and promotes proliferation and migration of fibroblasts and keratinocytes crucial in cutaneous repair.[14]
Marigold (*Calendula officinalis*)	Thermal injury generates abundant free radicals that are associated with inflammation and infection. *Calendula officinalis* inhibits inflammation by suppressing activities of proinflammatory cytokines and cyclooxygenase 2. *Calendula officinalis* contains free radical scavengers including triterpenoids, flavonoids, and alkaloids such as lycopene, lutein quercitin, lupeol, and beta carotene. These properties contribute to its effectiveness in burn wound healing as demonstrated by substantial in vivo evidence.
Female ginseng *(Angelica sinensis)*	*Angelica sinensis* extracts contain ferulic acid, which has analgesic and antimicrobial properties and stimulates cell proliferation. It promotes collagen secretion, calcium ion regulation, and cellular mobility. In addition, female ginseng acts as a scavenger of reactive oxygen species that reinforce wound healing activity.
Neem (*Azadirachta indica*)	*Azadirachta indica* promotes wound healing in rats by enhancing granulation tissue formation, re-epithelialization, and collagen synthesis and maintaining skin elasticity.[15] It exhibits recognized antimicrobial, antifungal, antioxidant, and anti-inflammatory activity. As a humectant in wound formulations, it helps promote moist wound healing.[16]
Rosemary (*Rosmarinus officinalis*)	Two principal components of *R officinalis* extracts are carnosol and ursolic acid, which contribute to wound healing via various mechanisms: as a local antioxidant at the wound site, stimulating revascularization, fibroblast proliferation, and decreasing microbial and collagenase activity. A 21-d in vivo study identified significant dose-dependent activity of 15%, 10%, and 5% of rosemary extract on reducing wound area.[17]
Green tea (*Camellia sinensis*)	Flavonoid-rich green tea exhibits antioxidant, antimicrobial, anti-inflammatory, and antiallergic effects contributing to its potency in wound healing. In one study[18] conducted on excision wounds in rats, 400 mg/mL of *C sinensis* extract applied topically for 10 d reduced expression of inflammatory cells and increased collagen deposition with dense neovascularization in granulation tissue of healing wounds. Another study reported significantly greater area reduction in 14 d for second-degree burns on rats treated topically with green tea compared with petroleum jelly or silver sulfadiazine 1% cream.[19]
Henna (*Lawsonia inermis*)	*Lawsonia inermis* contains various alkaloids, tannins, flavonoids, steroids, glycosides, and saponins that play important roles in wound healing, exhibiting antioxidant, antimicrobial, and collagen synthesis activity. Thirty grams per 100 mL of *L inermis* extracts in gelatin oxidized starch electrospun nanofiber mats increased re-epithelialization and collagen formation and reduced the inflammatory macrophage zone surrounding burn sites on mice as measured by immunohistochemical staining.[20] Another study in rats reported significantly faster wound contraction with increased hydroxyproline content and tensile strength of full-thickness excisions treated topically with 5% or 10% ointment of *L inermis* compared with 0.2% nitrofurazone ointment.
Aromatic oils (tea tree oil, chamomile oil)	Extensive clinical and preclinical research has identified the antiseptic, antibacterial, and anti-inflammatory activity of tree tea oil in burn wound healing. Further, chamomile oil has been assessed for its wound healing activity in rats. A chamomile oil-loaded topical formulation (solid lipid nanoparticles and cream) showed better wound closure healing on days 8 and 16 compared with the untreated group.[21]

Figure 1. PRISMA FLOW DIAGRAM



"promising"[22] but remains to be summarized in the context of clinical practice for wound bed preparation[23,24] and management paradigms.[25,26]

Purpose

The authors conducted a scoping review of preclinical and clinical trial evidence supporting the efficacy and/or safety of major alternative wound care agents to summarize their effects on validated elements of wound bed preparation and wound management paradigms.

METHODS

The PubMed reference database was searched from January 1, 1970, through November 20, 2020, for original and derivative clinical trial references addressing the MeSH (Medical Subject Headings) terms for "clinical trial" combined with those for each of the agents listed in the Table. Randomized controlled trials (RCTs) or nonrandomized clinical trials were included if they reported a significant improvement ($P < .05$) in one or more measured and valid wound outcomes.[27] Case studies were included to support wound safety, but in vivo and in vitro studies were excluded, as were those unrelated to cutaneous wound care or the alternative agents in question. Further, studies combining an alternative agent with other agents, preventing evaluation of its specific effects, were excluded from analysis.

All authors evaluated the clinical literature search results and a single investigator extracted from qualifying clinical studies the first author's last name, year of publication, type of clinical study (randomized, nonrandomized, or case series), number of patients studied, and wound etiology. Data were used to populate a spreadsheet, which calculated the number of studies supporting each agent. The usefulness of each agent was then described based on its reported outcomes related to elements of the TIMERS (Tissue management, reducing Inflammation and Infection, Moisture balance, Edge and Epithelial advancement, Regeneration and Repair, or Social issues) wound management mnemonic.

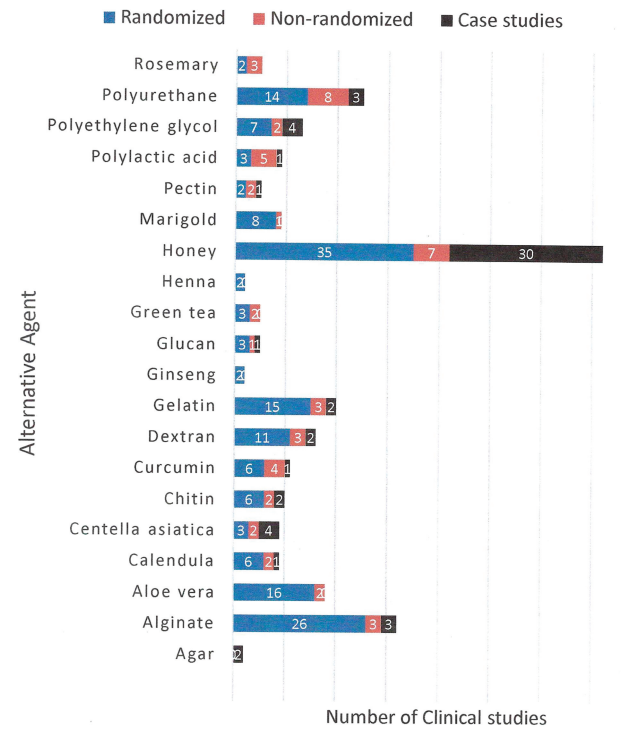
RESULTS

Of 1,380 references screened, 281 abstracts or full-text articles were reviewed, and 274 studies on 28,315 patients were included in the analysis (Figure 1). Agents with more than 10 RCTs supporting clinical wound outcomes (Figure 2) were honey, alginate gels or fiber dressings, polyurethane gel or adhesive dressing, aloe vera gel, or dextran powder. Results are discussed below indicating each agent's potential roles in wound management using the TIMERS paradigm or meeting other aspects of patient or wound clinical needs.

Two case series involving 24 patients supported the safety of agar hydrogel (TIMERS component: E) in epithelializing skin graft donor sites (SGDSs).

Thirty-two clinical trials involving 2,147 patients included alginate dressings (TIMERS components: I, M, E). These dressings contain highly absorbent calcium alginate or calcium sodium alginate fibers or yarns that support hemostasis or form a gel when in contact with a moist wound surface; accordingly, they can be lifted off or washed

Figure 2. NUMBER OF CLINICAL STUDIES SUPPORTING EACH ALTERNATIVE AGENT



off at dressing removal. They improved healing or reduced infection rates of SGDSs compared with gauze dressings, with similar wound healing outcomes to hydrofiber, film, or silicone dressings, which all healed SGSD at least 7 days more slowly than SGDSs dressed with a hydrocolloid dressing.[28] The benefits of alginate dressings were less clear for venous leg ulcers,[29] diabetic foot ulcers,[30] or pressure injuries,[31] because alginate dressings were often used in combination with other dressings or agents. Healing and pain improvement were similar for chronic or acute wounds dressed with an alginate or a silver dressing.[32] In participants with chronic wounds and high bacterial burdens, topical silver alginate powder reduced wound area and signs of infection over 4 weeks compared with a foam dressing.[33] Studies of such combined interventions or studies where "standard care" included alginates with other dressings were not included in Figure 2 because it was not possible to discern the specific effects of the alginate component of the dressing.

This review included 18 clinical trials on aloe vera use for 1,113 patients (TIMERS components: I, E). Systematic reviews reported improved healing of patients with burns and burn wound infection managed with aloe vera, with effects comparable with those of topical antibiotics or antiseptics.[34] Improved healing was reported for pressure injuries cleansed with a spray containing physiologic saline, aloe vera, and decyl glucoside compared with isotonic saline, but it was not clear that aloe vera caused the healing effect.[35]

Calendula officinalis (Marigold) or *C flos* extract was examined by 9 clinical studies involving 1,086 patients (TIMERS components: I, E). Marigold was typically delivered as a 3% ointment or hydroglycolic spray, with varying effects.[36] Reduced pain and improved healing were reported for gynecologic surgical wounds, venous leg ulcers, and diaper dermatitis, but not diabetic leg ulcers or partial-thickness burns compared with standard of care. The extract improved radiation dermatitis symptoms compared with trolamine, with similar healing benefits to topical aqueous gel.[36]

Centella asiatica was included in 9 clinical studies on at least 426 patients (TIMERS components: I, E) with chronic or surgical wounds and second-degree burns; this agent reportedly improved healing, nerve injury, and scar tissue.[37]

The search for chitin or chitosan returned 10 clinical studies on 681 patients (TIMERS component: E) revealing improved hemostasis and healing of military or civilian full- or partial-thickness acute or chronic wounds including SGDSs, diabetic foot ulcers, pressure injuries, venous ulcers, and oral surgery sites.[38,39]

Carrageenan searches returned no clinical studies reporting any clinical benefit related to wound healing. This agent was mainly used in preclinical studies as a pain- or inflammation-inducing agent in rodents or a primer for liver or lung endotoxin shock studies in vivo.[40]

Curcumin, also called diferuloylmethane, was surveyed in 11 clinical studies on 1,227 patients (TIMERS component: I) and reduced radiation mucositis, dermatitis, or periodontal inflammation when delivered orally or as a topical gel often encapsulated in liposomes.[41,42] Considerable preclinical research has been conducted to develop a formulation with adequate solubility and systemic absorption to optimize its safe delivery and efficacy in wound management.[43]

Dextran, involved in 16 studies on 9,519 patients (TIMERS components: T, I), was used as a topical dextranomer powder to heal chronic wounds or burns.[44,45] Adding 6% dextran-70 (70,000 molecular weight) administered infusion to lactated Ringer's solution was more effective than lactated Ringer's solution alone in preventing acute respiratory distress syndrome and improving low BP associated with shock in trauma patients en route to the hospital.[46] However, later studies reported that hypertonic saline (7.5%) prevented posttraumatic hypotension as effectively without adding dextran-70.[47] To prevent postsurgical deep vein thrombosis (DVT), 500 to 1,000 mL of dextran-40 or dextran-70 during the first 2 to 6 hours postoperatively, followed by 500 mL per day for 1 week, was effective in preventing DVT compared with 0% dextran. However, researchers reported the possibility that dextran may worsen progressive hypercoagulation in these trauma patients.[48] Dextran infusions prevented more postsurgical hematomas than low-molecular-weight heparin, whereas heparin interventions limited more DVTs than dextran did. Topical treatment of chronic wounds with dextranomer paste was less effective in healing sloughy pressure injuries than similar treatment with an amorphous hydrogel.[49] In general, dextran polymer formulations showed initial promise in emergency resuscitation and preventing postsurgical DVT, as well as debriding chronic wounds, but their efficacy and safety were exceeded by other agents in at least 18 subsequent RCTs.

Gelatin was used in 20 studies on 1,560 patients (TIMERS component: E). It was typically applied as a foam sponge drug delivery system or to aid in hemostasis or healing of ruptured tympanic membrane[50] or as a packing agent following nasal,[51] sinus,[52] or other surgery. It was often combined with collagen or fibrin glue to deliver growth factors or other agents in studies excluded from this analysis because the effects of the gelatin per se were unclear. The efficacy of other agents exceeded gelatin as a posttraumatic infusion in reducing capillary leakage. As a sealant for vascular prostheses, gelatin transiently increased circulating leukocytes for 2 weeks after grafting without other notable adverse effects.[53] Gelatin can be used as an acceptable absorbable

hemostatic sponge,[54] but if left in place after the removal of thyroid cancer, it may mimic residual or recurrent thyroid carcinoma during follow-up ultrasound surveillance.[55] When injected into individuals with severe brain trauma, gelatin solutions improved intracranial pressure, Glasgow Coma Scale scores at 1 to 2 weeks, and 3-month Glasgow Outcome Scale scores compared with traditional management.[56]

Two studies on 139 patients involved ginseng (TIMERS component: I) saponin glycosides administered with peripheral blood monocytes improved circulation measures and 6-minute walking distance of patients with critical limb ischemia compared with peripheral blood monocytes administered alone. It was often included in complex Chinese traditional medicine formulations, but its effects in these were unclear. It has been reported to protect against myocardial ischemia-reperfusion injury,[57] but anabolic effects during or after exercise have not been confirmed in an RCT.[58] Researchers have raised concerns that patients taking unreported botanic supplements such as ginseng, ginkgo biloba, garlic, ginger, valerian, kava, St John's wort, ephedra, or echinacea may experience unforeseen serious complications during surgery.[59]

Glucan, derived from yeast cell walls or certain mushrooms, was licensed as a drug in Japan in 1983. This review included 5 studies on 1,363 patients using glucan (TIMERS components: I, E). Most of its clinical trials combined a glucan with a monoclonal antibody to limit cancer metastases, improve gastrointestinal disorder outcomes, lower cholesterol, or address immune disorders, all of which are beyond the scope of this review.[60] Further, β-glucans have been reported to modulate inflammation, coagulation abnormalities, and digestive disorders associated with COVID-19.[61] In critically ill patients with trauma wounds, high-protein parenteral supplements with β-1,3-glucans reduced pneumonia, sepsis, organ failure, and ventilator time.[62,63] Further, 1.4 g daily doses of β-1,3/1,6-glucan for 5 days preceding coronary artery bypass graft surgery reduced ischemia-reperfusion injury.[64] Oral 0.5 mg/kg of yeast-cell-wall PGG glucan (one dose preoperatively and three doses postoperatively) reduced the incidence of serious postoperative infections or death following noncolorectal surgery in high-risk patients, but was associated with adverse events in colorectal surgery.[65] Finally, topical use of water-insoluble β-1,3-glucan purified from baker's yeast (*Saccharomyces cerevisiae*) was associated with venous ulcer healing in one case series.[66]

Green tea is derived from the tea tree *Melaleuca alternifolia*. Five studies on 264 patients (TIMERS component: I) reported on green tea. Its catechins had antimicrobial properties and anti-inflammatory effects on the cyclooxygenase and lipoxygenase eicosanoid pathways, but when taken orally (1,080 mg of catechins in 1,350 mg of green tea extract with 50 mg of vitamin C per day) for 3 months did not reduce skin erythema, leukocyte response, or eicosanoid responses to a UV light inflammatory challenge. Pretreating skin with green tea polyphenol extracts protected volunteers' skin from sun damage.[67] If applied within 30 minutes after thermal burns, a green tea extract spray reduced burn pain, but water cooled the burned skin more[68] and was similarly effective in treating postpartum nipple pain.[69]

Two studies on 100 patients (TIMERS components: I, E) discussed henna. Henna derived from *Lawsonia inermis* improved healing and pain when applied topically to episiotomies compared with placebo.[70] In an ointment formulation, it improved healing, pain, pruritus, and discharge of radiation dermatitis sites when applied immediately after 45 to 50 Gy radiotherapy compared with a similar application of 1% hydrocortisone cream.

Honey was the most well-studied alternative agent in this review; investigators noted 32 clinical studies on 2,147 patients (TIMERS components: T, I, M, E). Honey is a humectant made by honeybees. Trials on a wide variety of acute surgical, trauma, or burn wounds; radiation-induced mucositis;[71] and chronic pressure injuries, venous leg ulcers, or diabetic foot ulcers support the promotion of a moist wound healing environment, improved healing, and better debridement or wound infection outcomes with a variety of honey sources.[72] These results have been confirmed by independent systematic reviews on various etiologies of acute or chronic wounds.[73–75]

Marigold (*Tagetes*) and Calendula (*Calendula*) are both in the Asteracea family and not always distinguished from one another in the literature. These researchers noted 9 clinical studies on 960 patients (TIMERS components: I, E). Calendula ointment shortened the inflammation phase of acute healing and improved radiation dermatitis,[76] similar to the effects of aqueous cream, and had mixed effects on chronic venous or diabetic ulcers or acute burn wounds.[36] In gynecologic surgery, *Calendula* ointment improved episiotomy healing and pain or cesarean section healing compared with standard of care.[77,78]

Neem (*Azadirachta indica*) returned no studies where it was applied to wounds alone as a topical or systemic intervention. It was often combined with other topical wound treatments such as turmeric. This reduced the clarity of its effects in wound care.

Pectin, a hydrocolloid substance derived from fruit, was examined in 5 clinical studies on 167 patients (TIMERS components: M, E). It was often combined with other agents or mixed with other biopolymers to add moist-adherent properties to skin or wound adhesives. Pectin was applied as a skin barrier to prevent or heal tape damage on peristomal areas or near tracheostomy sites[79] or to protect the delicate intact facial skin of premature infants.[80]

Polycaprolactone was frequently studied as a "bio-ink" for three-dimensional printing of tissue scaffolds or as a delivery system for other agents or sensors.[81] Repeated searches found no clinical studies of its effects on any human skin wound.

Polylactic acid (PLA; 9 studies on 248 patients; TIMERS component: E) may foster periodontal, cleft palate, or tendon healing. The SGDSs dressed with a PLA copolymer dressing healed similarly to those dressed with a cellulose nanofiber dressing with comparable pain, but the PLA dressed wounds had thicker, less elastic scars 1 month postoperatively.[82] When used to guide flexor tendon repair, PLA membranes reduced adhesions, improving interphalangeal joint function compared with untreated sites, as did freeze-dried amniotic membranes, but PLA elicited more complications.[83] The use of bioabsorbable PLA screws instead of metallic screws proved reliable and effective for ankle fracture fixation, avoiding a second surgery to remove metallic screws, with similar results for PLA rotator cuff anchors, but using PLA knee joint fixation screws was associated with complications including bone resorption.[84] Most studies on PLA-bone screw interactions were excluded from this work unless they also pertained to skin wounds.

Polyethylene glycol (PEG) was included in 13 studies involving 1,171 patients (TIMERS components: T, I, M). Certain PEG hydrogels have been reported to be effective in preventing surgical adhesion as a topical debriding agent or as a dural sealant after spinal surgery.[85] When used before radiation therapy to expand space between prostate cancer and the bowel, it has reduced adverse effects of radiation. Its use in presurgery bowel preparation reduced electrolyte disturbance for elective colorectal procedures with mixed efficacy.[86,87]

Polyurethane film or foam was mentioned in 25 studies on 1,565 patients (TIMERS components: I, M, E). It was reported to prevent pressure injury development in older adults recovering from hip fractures. Resorbable polyurethane used as postoperative nasal packing improved endoscopic sinus surgery outcomes. Postsurgical polyurethane wound drains reduced thrombus formation and pain on removal compared with polyvinyl chloride drains;[88] further, polyurethane adhesive removed and reapplied every 48 hours did not damage periwound skin around venous leg ulcers as much as hydrocolloid adhesive wound dressings did.[89] Adhesive wound dressings with a polyurethane film or foam backing reduced healing time, pain, and infection rates in surgical sites, acute wounds, or chronic wounds compared with gauze dressings.[90–92] Evidence on dressings where a polyurethane foam or adhesive was used at the wound interface is summarized in Figure 2.

Rosemary (*Rosmarinus officinalis*) is an evergreen shrub from South America and the Mediterranean coast with preclinical evidence of antioxidant, anti-inflammatory, anticancer, and antihyperglycemic properties.[93] No studies were found supporting its effects on patients with wounds. Ursolic acid extracted from rosemary (150 mg once daily for 12 weeks) lowered body mass index, weight, waist circumference, and fasting glucose and increased insulin sensitivity in 12 patients with diabetes mellitus compared with a placebo,[94] but effects on wounds were not studied.

DISCUSSION

This scoping review suggests that many naturally derived agents previously categorized as "alternative practice" merit consideration given their potential to improve wound outcomes. Those backed by evidence from at least 10 RCTs include honey, alginate gel or fiber dressings, polyurethane gel or adhesive dressings, aloe vera gel, and dextran powder. Some of these have already entered the ranks of agents or delivery systems used in clinical practice, been cleared by regulatory authorities for mainstream clinical use, and drawn the attention of Cochrane or other reviewers. Opportunities abound for improvements in managing hemostasis, scarring, or adhesions. These agents may support recognized aspects of healing such as fibroplasia, angiogenesis, and epithelialization; improve wound inflammation, infection, and pain; or maintain moisture balance to minimize the need for frequent dressing changes. Further clinical research is needed to determine if these alternative agents improve outcomes compared with current standard of practice, either combined with current products or as adjunct interventions.

This review limited itself to the agents with which the authors were familiar. Other alternative agents in use elsewhere in the world may merit similar reviews and/or clinical studies.

CONCLUSIONS

The preclinical evidence and clinical literature reviewed suggest that honey, alginate gels or fiber dressings, polyurethane gel or adhesive dressings, aloe vera gel, and dextran powder have clinical evidence of potential efficacy in wound management. Many other alternative agents are supported by sufficient clinical research to suggest their potential as smart excipients or novel active agents within future multifaceted wound management delivery systems.

PRACTICE PEARLS

- Ten or more RCTs support continued research and practice using honey, alginate gel or fiber dressings, polyurethane gel or adhesive dressings, aloe vera gel, or dextran powder on various clinical wounds.

• Several agents previously considered "alternative" are now cleared by regulatory authorities and have become mainstream wound care treatments. These agents may improve wound hemostasis, inflammation, infection, pain, angiogenesis, fibroplasia, and epithelialization.
• Substantial research suggests that alternative products have potential as smart excipients or novel active agents within future multifaceted wound management delivery systems.
• Exploring these and other alternative wound management agents may have the potential to improve outcomes for patients with wounds. ●

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