Are all wound products created equally? The re-emergence of natural honey

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Abstract:

A major impediment to treating diabetic foot ulcers is the vast array of costly wound dressings that many health practitioners currently use. These vary tremendously from cotton and potato peel, to biosynthetics, tissue engineering, growth factor biological dressings, nanocrystalline silver, and skin substitutes. Many options for wound care can be confusing for health care professionals while increasing cost and bacterial resistance. Clinically, an ideal wound dressing must be efficacious, provide an optimum environment for epithelialization, stimulate angiogenesis, prevent scar tissue, and provide antimicrobial coverage while being aesthetically acceptable and cost-effective. Honey is a natural alternative wound care product providing all the aforementioned properties at a much more cost-effective price.

Key words: Advanced Wound Products, Chronic Wounds, Diabetic Foot Ulcer, Natural Honey, Wounds, Wound Healing

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INTRODUCTION

Wound care discipline contains as many different management modalities and options as the number of health care workers caring for wounds. Although many wound care specialists depend on “tried and true” management options, there seems to be an endless flow of new wound care products and technologies in the field. Many of these wound care products are enhanced and updated versions of previous modalities, whereas others are the end products of entirely new scientific fields of clinical research. The race to introduce new and novel wound products often precedes rigorous clinical trials, and the efficacy is then determined by clinical judgment. This may lead to unanswered questions regarding indications, side effects, and appropriate use and cost.

The objective of this review is to discuss alternative wound care products; modern day dressings; and several new technologies in relation to chronic diabetic foot ulcerations, burns, and various other wounds. Silver dressings are potent antimicrobials and have been used for centuries in wound care. Although new forms of delivery are continuously being developed to increase their efficacy, some concerns regarding their in-vitro cytotoxic safety still remain. Lasers and ultrasound devices are relatively new in wound care management, and their applications are continually growing to include new options for wound management that previously had very few alternatives. Wound healing conditions are optimized in the wound environment with the help of advanced wound care products. With the discovery of tissue engineering and biosynthetics, skin substitutes are proving to be novel, effective therapies that provide temporary wound coverage leading to a change in the paradigm of wound care. Wound healing is modulated, or augmented, with biologic substances and growth factors although infection, cost, and failure are concerns. Finally, natural

honey can provide an alternative treatment modality to the above wound healing options, particularly in chronic wounds not responding to other management strategies.

Around 370 million people worldwide have diabetes, and this number is increasing.[1] Diabetes UK estimates that by 2030 approximately 552 million people worldwide will have diabetes.[2] Among diabetes complications, diabetic foot ulcers (DFUs) are relatively common. In the UK alone, 5-7% of diabetics currently have, or have had, a DFU.[3]

Economies worldwide are burdened heavily by the cost of treating DFUs. The average estimated cost of an outpatient-treated DFU was estimated at $28,000 (US dollars) over a two-year period according to a study conducted in 1999 in the US.[4] Another study, conducted in 1997, revealed that the average inpatient cost of lower limb complications was $16,800 (US dollars) for DFU, $25,241 (US dollars) for toe or toe plus other distal amputations, and $31,436 (US dollars) for major amputations.[5,6]

DFUs are usually chronic and complex in nature resulting in a huge impact on the mortality, morbidity, and quality of patients' lives.[7,8] Patients who are affected by a DFU are at an increased risk of myocardial infarction, premature death, peripheral vascular disease, and fatal stroke compared to those without a history of DFU.[9] Unlike other chronic wounds, the onset and progression of a DFU is often aggravated by a multitude of diabetic changes including vascular disease, neuropathy, and altered foot dynamics.

Individuals suffering from a DFU often neglect foot care and adopt an unhealthy life style due to a negative attitude stemming from concomitant depression. Furthermore, DFUs are characterized by altered protein synthesis and defective neutrophil function, along with the diminished tissue perfusion that frequently accompany diabetes.[7] Consequently, health workers are challenged with unique and specific management dilemmas.

As a discipline, wound management possesses an extensive variety of management modalities and options. For example, the number of new dressings available on the UK Drug Tariff increased from 4 in 1988, to 57 in 1998, and to 262 by February 2007.[7]

Historically, wound dressings have varied tremendously from potato peel and cotton, to biosynthetics, skin substitutes, and tissue engineering. Health care professionals may be confused by this unprecedented number of wound care options. In addition, complications include bacterial resistance to treatment and increased cost. An ideal wound dressing should provide an optimum environment to allow epithelialization, angiogenesis, and a moist environment promoting healing without scar formation, while being aesthetically acceptable and cost-effective.[10,11,12]

Wound management depends on a variety of factors such as the nature and duration of wounds being treated, co-morbidities, age of the patient, type of wound dressing, nutritional status, perfusion, oxygenation, existence of biofilm, the physical and chemical properties of the available dressings, offloading and socio-economic status,[10] psychological well-being of the patient, and logistics of the health care setting.

It is important to remember that wound products should be assessed and tested in relation to their physical, biological, and chemical properties; clinical efficacy for a certain type of wound; and the stage of wound healing, prior to inclusion in routine clinical practice.

This review discusses the current, state-of-the-art wound-healing products as well as more traditional products like natural honey and other alternative wound management products.

Wound care products are discussed in terms of their advantages and shortcomings. Furthermore, the need for dressings with improved properties is debated. With the wide range of wound care products, the aim should be to find the most appropriate modality to optimize wound healing.

Classification of Dressings

There are various ways of classifying wound care products (dressings) depending on their mechanism of action in the wound

environment (ie, occlusive, adherence, absorbent, debridement),[11] nature of material used to produce the dressing (ie, alginate, hydrocolloid, collagen),[12] and the physical nature of the dressing (ie, film, foam, ointment, gel).[13,14] Alternative classification criteria include traditional, modern, and advanced dressings; skin replacement products; and wound healing devices.

These classifications, like the preceding ones, do not take into account alternative or complementary dressings used worldwide. Some of these alternatives, complementary elements, and dressings are considered below.

Silver

The medical use of silver to prevent and treat wound infection has been used through the ages. The use of silver is recorded as early as 69 BC, and it still remains among the most widely used current therapeutic options.

Regardless of the form of a silver-containing product, elemental silver needs ionization for it to be an effective antimicrobial agent.[15]

Maintaining silver in adequate concentration with long enough residual activity is the key factor to formulating the most effective product where silver ions readily bind to protein and chloride in the wound bed fluid.[16]

Wound products containing silver have maintained their place in wound management due to silver's broad-spectrum coverage, particularly against antibiotic resistant bacteria. Silver also has a very broad spectrum of microbial coverage that includes mold, yeast, and fungi when used in adequate concentrations for an adequate length of time.[17]

To prevent resistance, silver requires maintenance in the wound in a high concentration and with lasting residual activity. Hence, silver products such as silver nitrate requires around 12 applications per day to maintain activity. Silver sulfadiazine has similar activity. Both are able to provide high enough initial concentrations (3176 mg/L and 3025 mg/L, respectively).[18]

Despite silver being noted for its broad-spectrum antimicrobial coverage, bacterial resistance has been documented as early as 1975,[19,20] specifically among burn patients where silver salts had been used as an antiseptic agent. Silver resistant strains include E. Coli, Enterobacter Cloacae, Pseudomonas ptutzeri, Klebsiella pneumoniae, Acinetobacter baumannii, and Salmonella typhi.[19,20,21] A Salmonella strain that was resistant to silver caused septicemia and the death of three patients, which led to the closure of the burn unit at Massachusetts General Hospital.[22]

Nanocrystalline silver, on the other hand, is more efficacious than silver sulfadiazine and silver nitrate. Wright (1998) and colleagues demonstrated that a nanocrystalline silver dressing killed MRSA in 30 minutes, whereas other silver preparations had no effect. Similarly, Yin et al. showed that nanocrystalline silver killed Staphylococcus aureus after 1 hour, while silver sulfadiazine took 4 to 6 hours.[23,24]

Several studies show that nanocrystalline silver leads to faster wound healing, decreased need for antimicrobials, decreased cellulitis, and less burn sepsis.[25,26,27]

However, nanocrystalline silver has also been shown to cause cytotoxicity, especially towards fibroblasts and keratinocytes which leads to inhibition of keratinocyte growth and delay in re-epithelialization. In-vitro studies have further shown nanocrystalline silver to be specifically toxic to cultured skin substitute.[28,29,30] Studies carried out by Du Toit and Page (2009)[31] have shown significant cytotoxicity when nanocrystalline silver was applied to keratinocytes and fibroblasts, the essential cells needed for tissue repair. These findings align with those of Poon (2004), Burd (2007), and Frazer et al. (2004).[32,33,34]

A study by Paddle-Ledinek et al. (2006)[35] demonstrated cell toxicity arising from wound dressings such as Contveet-H (Coloplast), Avance® (Molnlycke Health care), and Aquacel® Ag (Convatec). Rapidly proliferating cells, such as donor sites and superficial burns are therefore at risk of cytotoxity, if exposed to nanocrystalline silver.

A recent literature review conducted by Khundkar et al. (2010)[36] expressed a word of caution comparing nanocrystalline silver to other silver preparations; only 1 in 31 articles was rated as level of evidence 1 (randomized controlled trial -RCT- of sufficient size for a narrow confidence interval), with the majority of articles rated as level of evidence 5 (expert opinion or based on bench research).

Utilizing MEDLINE (OVID), Greer et al. (2012)[37] conducted a systematic review of RCTs published from 1995 through August 2012. Four fair quality RCTs (n=280 randomized) of silver products were identified; three were silver versus different advanced wound care products. In one study (n=66), ulcers managed with silver ointment were more likely to heal than those managed with standard care (39% versus 16%; Absolute Risk Difference (ARD)=23%, 95% Confidence Interval (CI) 2% to 43%). Healed ulcers with mixed results were reported in three studies. Additionally in two studies, there was no difference in healing between silver products (dressing or cream) versus oak bark extract or calcium based dressing.

Skin Substitutes

Bioengineered skin substitutes, both cultured autologous-engineered skin and biosynthetic skins substitutes, are available to provide skin coverage for participants with significant body surface area burns leading to decreased mortality and increased survival. Although skin substitutes are available in large quantities with negligible immunologic reaction or risk infection, they are expensive.

Biobrane is a new, temporary wound dressing made of knitted nylon mesh attached to a thin silicone membrane and covered with Porcine Polypeptides. It is used to cover donor sites in split thickness skin grafting and on clean, superficial, and mid-dermal deep burns. Its efficacy is equivalent to silver sulfadiazine in wound healing without the frequency of dressing change.[38,39]

Transcyte has a similar composition to Biobrane with human fibroblasts cells added to it. It can be used as a temporary cover for excised burns prior to grafting or as a dressing for superficial burns that do not require skin grafting.

Where burns are concerned, especially facial burns, Transcyte has shown to be superior to sulfadiazine or antibiotic creams in terms of infection, healing time, and scar formation.[40,41]

Apligraf is made of an epidermal layer of allogenic neonatal fibroblasts and keratinocytes from neonatal foreskin on layered Type 1 bovine collagen. Apligraf leads to acceleration in healing times if used as an adjunct covering to auto graft. It can also be used alone in chronic wound ulcers demonstrating accelerated healing times when compared to controls.[42,43]

Dermagraft is composed of a bio-absorbable polyglactin mesh, which contains neonatal fibroblasts. It can be used as a temporary or permanent cover for excised burns wounds, pressure ulcers, and venous ulcers. Fibroblasts produce growth factors dermal collagen and fibronectin to aid wound healing. Studies demonstrate it to be similar in efficacy to allograft for healing time, wound infection, and graft take.[38,39,44,45] Although this advanced wound product seems to be efficacious, the cost and controversy associated with its use regarding legal and ethical issues limit its use in everyday clinical practice.

Integra is a temporary semi biologic, bilayered dressing consisting of a matrix of glycosaminoglycan and Type 1 bovine collagen under a silicon superficial sheet.[38,46] The patient's endothelial cells and fibroblasts migrate through the pores (70-200 micrometer). The silicon sheet is removed upon granulation of the wound, and a superficial auto graft layer is implanted above the neodermis to cover the wound area. Full and partial thickness wounds are the primary indications for its use along with pressure ulcers, and vascular and complex traumatic soft tissue reconstruction over exposed soft tissue and joints.[47]

The medical field has witnessed various success with the use of skin substitutes; however, serious issues remain including a high failure rate, irritation, cross contamination, and

religious and ethical issues. They are relatively expensive compared to cadaveric skin from skin banks. Biological skin equivalents were assessed via a literature review carried out by Greer et al.[37] which included seven randomized controlled trials. In these clinical studies (n= 576 randomized), Dermagraft demonstrated statistically significant healing time in two of the studies (30% versus 18% in one study and 305 versus 185 days in the other). Subjects receiving metabolically active Dermagraft demonstrated significant healing in the third trial. However, a pooled analysis showed an overall non-significant benefit of Dermagraft compared to standard care for wound healing (RR= 1.49, 95% CI 1.20 to 2.08, I2= to 0.0%).[37]

Apligraf was compared to standard care in two moderate quality trials (n=339 randomized), and it demonstrated significant advantage in wound healing (55% versus 34%: ARD=21%, 95% CI 9% to 32%, RR=1.58, 95% CI 1.20 to 2.08).[36] Despite the fact that advanced wound products have an essential role in a variety of wounds, their inclusion in routine medical practice is hampered not only by cost, but also by the risk of cross infection including hepatitis and HIV, antigenicity, and legal and ethical issues surrounding stem cell research.[48]

Growth Factors and Biological Wound Dressings

The wound healing process is regulated by a variety of mediators including cytokines, eicosanoids, growth factors, and nitric oxide. Eicosanoids are arachidonic acid metabolites such as thromboxane, prostaglandins, and leukotrienes. Prostaglandin E1 is the most well known, which inhibits platelet neutrophil activation, decreases blood viscosity, and causes vasodilation.[47] Inflammation is regulated by cytokines, which modulate haematopoietic cells. Cytokines include interleukins, lymphokines, interferons, and colony-stimulating factors. Granulocyte and macrophage colony-stimulating factor (GM-CSF) are the most widely examined.

Fibroblasts and keratinocytes are stimulated by growth factors via trans membrane glycoproteins.[49] They are classified into five main categories, the most famous being the FDA approved platelet derived growth factor (rh PDGF) which has been studied by Steed et al. They studied 118 subjects suffering from DFUs.[50] In this study, they demonstrated statistically significant wound healing (48% versus 25%) and greater reduction in wound size.

These findings were supported by additional studies that demonstrated increased odds of wound healing and decreased risk of amputation in patients suffering from diabetic foot ulceration.[51,52] Greer et al. examined nine RCTs (n=990) comparing PDGF to placebo gel or standard ulcer care (n=6), an advanced wound care therapy (n=2), or both (n=1).[36] Two of these trials were of high quality, five were moderate, and two were poor. At study completion the PDGF group showed a greater percent of wound healing in comparison to standard care (7 trials). However, there was evidence of marked heterogeneity (58% versus 37%; ARD=21%, 95%CI 14% to 29%; RR=1.45, 95% CI 1.03 to 2.05). The PDGF treated group had significantly less time to healing in four trials (29 versus 41 days) with one trial reporting no difference. However, when compared to biologic dressing, carboxyl methylcellulose gel, or silver sulfadiazine, there was no significant differences in relation to time of healing or percentage ulcers healed. Although encouraging clinical results were reported by Khan and Davies[53] examining the potential role of growth factors in managing chronic leg ulcers, inconsistent clinical end points, and small sample size prevented definite conclusions to be drawn.[54]

The PDGF treatment is not without its critics. The National Institute for Health and Clinical Excellence (NICE) recommends that autologous platelet-rich plasma gel and PDGF should not be offered as treatment for diabetic foot problems unless part of a clinical trial (NICE, 2012).

Herbal Wound Therapy

Herbal wound therapy varies across cultures and nations. These include, but are not limited to, boiled potato peel,[55] fenugreek and garlic,

as well as various herbal combinations used by the Egyptians in 100BC including turmeric and castor oil. Traditional Chinese and Indian medicines contain a variety of herbs still widely used in clinical practice for a variety of both acute and chronic wounds. Miscellaneous herbal medicines used in wound care management include Parkiabiglobosa, Jacqand, Bridelia, and Ferruginea which are thought to increase proliferation of dermal fibroblasts. Carapa Guianensis leaves are found to enhance skin breaking strength due to their hydroxyproline content, thereby enhancing wound healing potential and contraction.[56]

Improved wound healing was demonstrated when using methanol extracts of Heliotropium Indicium Linnare.[57] Melaleuca Alternifolia and tea tree oil are used in wounds for their antiseptic, antiviral, and antifungal properties.[58] Historically, burns have been treated by Aloe Vera, but clinical evidence remains unclear. The clinical use of Aloe Vera in burn wounds was studied by Maenthaisong et al. who conducted a systemic review[57] after searching MEDLINE, CINAHL, Cochrane library, DARE, Health Star, a Chinese database, and several Thai local data bases (1918-2004) including burn studies only. The review included four clinical trials which were fit for inclusion criteria (n= 371), and the duration of wound healing was used as an outcome measure. The summary weighted mean differences in healing time of the Aloe Vera group was 8.79 days shorter than those in the control group (p=0.006).

There is insufficient data to draw firm conclusions from these studies, mainly due to a lack of standardization of products used and outcome measures. However, cumulative evidence tends to favor using Aloe Vera for first and second degree burns. According to Krishan,[60] Aloe Vera is the sole herbal wound material that showed clear efficacy in-vitro, animal, and human trials. Kehua Zhou et al. searched English and Chinese databases for oriental medicine and chronic wound care[61] in their systemic review. They identified and selected 17 RCTs on venous ulcers, 26 RCTs on pressure ulcers, and 93 RCTs on diabetic ulcers. They concluded that individual herbs and herbal formulas seem to be efficacious in treating chronic wounds.

Ultrasound

To stimulate normal physiological response to injury, therapeutic low intensity (0.125-3 w/cm^2) ultrasound is used to stimulate tissue repair by stimulating fibroblasts to synthesize collagen. In the medical literature only a few published clinical trials have demonstrated that ultrasound can accelerate wound healing, including those due to varicose vein insufficiency.[62,63]

Galitsky and Levina[64] demonstrated that trophic ulcer sites had enhanced ‘take’ of skin graft when therapeutic ultrasound was used. Similarly, McDiarmid et al.[65] had used therapeutic ultrasound in managing infected pressure ulcers, which led to improvement in the healing rate of treated wounds. Clinical studies had utilized non-contact low frequency ultrasound (NLFU) in the management of a variety of wounds since 2006 with various success rates including for ischemic wounds.[66,67] Eight published trials reporting the effect of NLFU treated patients were included in a meta-analysis conducted by Driver and colleagues.[68] They concluded that using NLFU was associated with a substantial and consistent wound reduction and a faster healing rate. Healing rate over time indicated that 32.7% of wounds healed on average by six weeks (95% CI 23.5% -42%) and 41.7% by twelve weeks.

However, most of these studies were of a non-comparative design, had a small sample size, and lacked blinding. Positive findings need to be confirmed through rigorous placebo-controlled randomized controlled trials.

Lasers and Wound Healing

Applying low doses of laser energy resulted in stimulation of regeneration of mechanically induced wounds and burns.[72] In-vitro studies demonstrated that wounds exposed to low frequency laser therapy (LLLT) had increased epithelial growth, fibroblast migration, proliferation, and enhanced collagen

synthesis. Furthermore, enhanced keratinocyte cell motility,[69,70] growth factor release, and transformation of fibroblasts to myofibroblasts[71] were attributed to using low level laser therapy during in-vitro studies. Although the efficacy of LLLT in wound healing has been demonstrated in many clinical studies,[72] others have failed to replicate these findings.[73,74,75]

To confuse the situation further, fibroblast proliferation was not demonstrated in in-vitro studies by many researchers after using LLLT on a variety of wounds.[76,77,78] These conflicting results may be attributed to variation in treatment protocols, lack of control groups, and non-blinding investigators.[78,79] One plausible explanation may be that certain tissues (cells) may absorb light while others do not, and the intensity of light absorption also varies from one tissue to another, as well as the cell size and composition. Although laser therapy is used extensively in the cosmetic field, its use may be associated with formation of non-viable atypical cells and chromosomal damage.[80] Additionally, low dose laser has been found to stimulate growth areas and tumor cell proliferation.[81]

A systematic review was conducted by Cullum et al.[82] examining 19 electronic data basis including Cochrane controlled trials, CINAHL, EMBASE, and MEDLINE. Randomized controlled trials were selected if they included objective outcome measures such as wound healing rate or wound incidence. They concluded that there is insufficient reliable evidence to support using laser therapy in chronic wound healing.

Natural Honey and Wound Healing

Since antiquity honey, a natural product of bees of the genera Apis and Meliponinae has been considered for its medicinal properties. Surgical dressings impregnated with honey have been used by the Ancient Egyptians to promote wound healing.[83] Judeo-Christian and Islamic traditions have considered honey as a gift from God. The Islamic Holy Quran has also described honey as a medicinal agent: “And your Lord revealed to the bees: Make hives in the mountains and in the trees and in what they build. Then eat of all the fruits and walk in the ways of your Lord submissively. There comes forth from their bellies a beverage of many colors, in which there is healing for mankind. Verily in this is a sign for those who give thought.” [The Quran, Surah Al-Nahl, verse 68 & 69]

Since first introduced in 1999, licensed medical wound care products containing medical-grade honey are now widely used in the medical field. Silver containing wound care product sales have risen 200% between 1999 and 2009 as a result of large companies backing strong marketing campaigns.[84]

In-vitro studies have demonstrated that natural honey has a comparable antibacterial efficacy to silver, yet it has none of the cytotoxicity related to silver use,[31] especially affecting keratinocytes and fibroblasts essential for tissue repair. Furthermore, Frazer et al. (2004) and Poon (2004) have shown similar evidence of keratinocyte cytotoxicity upon exposure to silver. Natural honey by comparison was not shown to be toxic and favored cell proliferation[31] and angiogenesis. Natural honey has long been recognized for its antimicrobial activities,[85] both in in-vitro and in-vivo studies. Its texture, water content, and constituents makes it an ideal cost-effective dressing. Natural honey has been shown to exert a broad range of antimicrobial activity against bacteria, fungi and viruses.[86,87] Wound infection is often caused by Gram positive bacteria, and a very low concentration of natural honey has been shown to be effective in inhibiting the growth of Staphylococcus aureus, the most common cause of wound infection.[88,89,90] Furthermore, natural honey inhibits the growth of vancomycin resistant staphylococcus aureus (VRSA), methicillin resistant staphylococcus aureus (MRSA),[91,92,93,94] and coagulase negative staphylococci.[95]

A recent study demonstrated growth inhibition of 15 cultures of streptococcus species isolated from a variety of wounds.[96] In-vitro studies have demonstrated the inhibitory activity of natural honey against most commonly implicated bacteria in wound infection, such as Pseudomonas aeroginosa,[88,91,93] enteric

bacteria,[97] Stenotrophomonas species,[98] and Acinetobacter baumannii.[89,92]

Chronic DFUs are characterized by biofilms.[99] In-vitro studies have shown that natural honey disrupts established biofilms and inhibits their formation, especially those of VRSA and MRSA.[88] Interestingly, natural honey has demonstrated antiviral activity in in-vitro studies[100] and reduced duration and pain threshold and crusting of genital herpetic infections.[101]

The exact mechanism in which natural honey exerts its antimicrobial activity remains unclear, although honey may destroy bacteria mainly through the release of hydrogen peroxide. This is produced by glucose oxidation catalyzed by the action of the bee enzyme glucose oxidase. Additional antimicrobial activity is linked to the release methylglyoxal, defensin-1, low pH, and flavonoids which cause inhibition of ATP metabolism and nucleic acid synthesis.

Honey is comprised of approximately 40% fructose, 30% glucose, 5% sucrose, and 20% water. It also contains several amino acids, antioxidants, vitamins, minerals, and glucose oxidase. Glucose oxidase produces hydrogen peroxide and gluconic acid, which gives honey its acidic pH of 3.2-4.5. Hydrogen peroxide is released at 1/1000th the concentration of wound rinse solution, just enough to kill bacteria without compromising keratinocytes or fibroblasts - the very cells required for development of granulation tissue. Honey has a unique property of providing a moist wound healing environment because 17-20% of its content is water. Natural honey also has a hyperosmolar medium. This leads to absorption of water out of bacterial cell walls resulting in the death of bacteria through the destruction of its cell wall.[102-111]

Medical literature reports hundreds of case studies explaining the efficacy of natural honey in chronic wound management, including diabetic foot ulcers.[112-114,121-129]
However, there are few RCTs to support this. In one RCT, honey was demonstrated to promote improved wound debridement compared to hydrogel.[102] Furthermore, natural honey has other bioactivities including deodorizing action,[103] osmotic effect, anti-inflammatory activity,[104] enhanced rate of healing,[105,106] provision of water to the wound bed,[103] provision of an external barrier to pathogens,[107] and antioxidant activity[108,109] by reducing the release of reactive oxygen intermediates.[110]

Although recently the number of publications reporting using honey has increased, systematic reviews have been critical of their study design.[115,116,117] Moore et al. (2001)[115] concluded that clinical evidence to support using honey in the treatment of superficial wounds and burns was of low quality.

By contrast, a review of 19 RCTs with a total of 2,554 participants suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings.[117] This was supported by a meta-analysis of systematic reviews of topical and systematic antimicrobial interventions for wounds. A total of 44 Cochrane reviews out of 149, which had been graded into five categories based on their size, homogeneity, and the effect size of outcome, were selected. Of 109 evidence-based conclusions, robust evidence was found to support using topical honey to reduce healing times in burns.[118]

A recent systemic review[130] examining published RCTs and clinical controlled trials (CCTs) using two electronic databases, PubMed, and ISI Web of Science, looked at the efficacy of honey compared to other dressing materials. Four RCTs and two CCTs met the inclusion criteria for the effect of honey on chronic ulcers. The authors stated that more evidence could be noticed for the wound healing stimulating capacity of honey, for which two out of four RCTs report a statistically significant reduction in wound size, and two CCTs support the positive effect of honey on wound healing. Most evidence had been found for the wound size reducing effect of honey, which was statistically significantly in favor of honey.

A 2014 systemic review[135] searching six electronic databases, including PubMed, the Cochrane Library, ISI Web of Science, and CNKI (China National Knowledge Infrastructure),

evaluating natural honey in chronic DFUs looked at RCTs comparing natural honey to other treatments.[131] They found a total of four RCTs involving 258 participants. Three trials involving 228 participants met the quantitative analysis, and one study involving 30 participants met qualitative analysis. Results of meta and descriptive analyses showed pooled differences in overall treatment time between the honey dressing group and control groups [SMD = -1.28, 95% CI (-2.46, -0.07), P = 0.04]. Pooled differences in mean purge time of wounds after intervention revealed a significant difference between the honey dressing and control groups [SMD = -0.92, 95% CI (1.27, -0.57), P = 0.00]. Pooled differences in the germ purge ratio in different treatment periods after intervention revealed significant differences between the honey dressing and control groups [RR = 2.32, 95% CI (1.51, 3.57), P = 0.00; RR = 1.70, 95% CI (1.02, 2.83), P = 0.04; RR = 1.56, 95% CI (1.19, 2.04), P = 0.00]. Healed area of ulcers pooled differences after intervention revealed a significant difference in favor of honey compared to the control groups [SMD = 1.45, 95% CI (0.59, 2.31), P = 0.00].

Another recent review[117] of 33 RCTs noted that participants using honey had increased from 1965 in 2006 to 3556 in 2011, with abroadening range of wound types included, the choice of dressings available to clinicians and the types of honey employed. With such variations, it is difficult to make generalized deductions about clinical efficacy.

In 2012, Commaratos and his colleagues conducted a RTC investigating the effect of manuka honey-impregnated dressings on the healing of chronic diabetic foot ulcers. Sixty-three subjects with Type 2 diabetes were randomized in two groups: group I patients were managed with honey and group II patients were managed with conventional dressings (CD). Subjects were seen on a weekly basis for four months. Mean healing time was 31 ± 4 days in group I, versus 43 ± 3 days in group II (P< 0·05). In group I patients, 78.13% of ulcers became sterile during the first week versus 35.5% in group II patients; the corresponding percentages for weeks 2, 4, and 6 were 15.6% versus 38.7%, 6.25% versus 12.9%, and 0% versus 12.9% respectively. The percent of ulcers healed did not differ significantly between groups (97% for honey and 90% for conventional dressings).[132]

Our view is that natural honey can be considered a credible alternative dressing for many reasons, including its broad spectrum antibacterial activity, its antifungal and antiviral action, ease of use, acceptability by both patients and health professionals alike, its cost effectiveness, provision of moisture, anti-inflammatory activity, stimulation of angiogenesis, and cell proliferation. To date no honey-resistant bacteria has been isolated from wounds.[120]

Honey-based treatments have been found to be preferential to silver or iodine due to comparative lack of toxicity.[31] Du Toit and Page (2009)[31] observed that silver-impregnated dressings are potentially cytopathic and cytotoxic to proliferating cells in-vitro, and this may be relevant in the clinical decision making process. A newer role for honey in wound healing involves immune modulation,[121] leading to a limitation of inflammation and pain modulation.[122] Natural honey is cost-effective compared to advanced wound products[123,124] and provides moisture and vitamins, and deodorizes wounds.

CONCLUSION

Honey has been used for thousands of years as an adjuvant to wound healing. Every year new studies further elucidate the precise action of honey in wound healing and demonstrate its efficacy in treating various wounds. While many modern day physicians are likely to remain skeptical about the benefits of honey until larger, RCTs support its use, one cannot overlook the great body of literature that associates honey with significant wound healing benefits.

It is difficult to understand that by the 21st century no evidence is yet available. Current evidence suggests that caution still needs to be exercised. Nonetheless, this review should be helpful to designing new, large, RCTs, with blinded assessment and useful clinical outcomes compared with standard wound treatments for all

types of wounds.

These studies will not be easy. With honey, we also need to be aware that it is a natural product, and that those characteristics associated with wound healing may be affected by species of bee, geographical location, and botanical origin, as well as processing and storage conditions. While these trials would be relevant to industrialized countries to compare honey with conventional and advanced treatments, it would be helpful to conduct them in developing countries, where costs are a vital factor.

The discipline of wound management is growing with rapid advances in technology. New wound healing modalities and products increase the choices for health professional as they tackle all features of wound management. While there is still no remarkable alternative for reconstruction using patients' own tissues and carefully carried out meticulous reconstructive procedures, natural honey can help accelerate wound healing. By offering antibacterial properties, enhancing tissue repair factors, maintaining a moist environment, and promoting epithelialization ultimately resulting in optimal wound repair, natural honey may represent an optimal alternative treatment approach in wounds of different etiologies.

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