Clinics in Dermatology (2009) **27**, 502–506

ELSEVIER

Clinics in Dermatology

Cosmeceuticals and natural products: wound healing

Stephen C. Davis, BS*, Robert Perez, PhD

Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Avenue, Room 2089, Miami, FL 33136, USA

Abstract Despite several technologic and strategic advances in the field, wound care has returned to the roots of medicine and embraced some of the remedies used millennia ago. Some of the many potentially beneficial natural products include the β-glucans, honey, aloe, cocoa, and oak bark extracts. There has recently been a surge of interest for their possible roles in wound healing.

Introduction

In recent years, modern societies have become more cognizant of holistic or "natural" treatments to disease and are embracing the development of such products. Although some people view these ideas as somewhat primitive or ignorant, many of the remedies are the result of thousands of years of empiric observation. These remedies have their roots in the ancient civilizations of the East as well as those of the Native American and Native South American cultures. Several of the more "modern" treatments, such as penicillin, morphine, aspirin, and Taxol, are considered natural products; however, most natural products are considered dietary supplements in the United States, are not regulated, and the active ingredients are not standardized.[1]

This lack of standardization has made it more difficult to determine the true efficacy of these products. Although many natural products have claimed to have healing effects, most do not have well-controlled scientific data to back their claims. Various preparations may actually have a therapeutic effect on compromised skin; however, the beneficial effect may be due to the vehicle and not the active agent. Many vehicles thought of as inert may have a significant effect on wound healing and can be used alone or as vehicles for active agents. One study, for example, found that various lots of United States Pharmacopeia petrolatum could either enhance or retard healing.[2]

Honey

Control of the microbial flora of wounds is desirable in nearly every type of wound. There are also suggestions that a small amount of bacteria may be beneficial to the wound-healing process.[3] This presents a dilemma for the clinician, who must balance between infection and minimal colonization of a wound. The situation may become dire in cases of chronic wounds where patients may be immunodeficient. Although honey has a long tradition of use within medical systems[4] and has enjoyed a resurgence in its popularity within the last 15 years,[5] some clinicians believe there is insufficient evidence to support its benefits, despite it being the oldest known wound dressing.[6,7]

For years, researchers have believed that honey gains its broad antimicrobial activity[8] from hydrogen peroxide generated by a glucose oxidase deposited into the honey by bees and by the high osmolarity due to the sugar

* Corresponding author. Tel.: +1 305 243 4897.
E-mail address: sdavis@med.miami.edu (S.C. Davis).

0738-081X/$ – see front matter
doi:10.1016/j.clindermatol.2009.05.015

content.[7,9] These may, however, be just a couple of many sources of antimicrobial activity, because honey is a complex mixture of potentially beneficial natural products such as flavanoids and other phytochemicals.[10,11]

Almost all medicinal honey research has been conducted on manuka (*Leptospermum scoparium*) honey,[5] which has little peroxide generation potential. The nonperoxide antimicrobial activity of this honey has been attributed, at least in part, to a yet uncharacterized "unique manuka factor."[12,13] Regardless of the source of the antimicrobial activity, manuka honey has been demonstrated to be effective against several human pathogens, including *Escherichia coli*, *Enterobacter aerogenes*, *Salmonella typhimurium*, *Staphylococcus aureus*, and methicillin-resistant *S aureus (*MRSA).[5,14]

In addition to various antimicrobial effects, honey may be beneficial to a healing wound. Until the 1960s, wound care protocols called for covering and concealing the wound while removing excess exudates. Since then, clinicians and researchers have adopted the concept of "tissue, infection/inflammation, moisture, and edge" (TIME). This approach, first published in 2003,[15] has now become the standard in wound care strategy. Based on the ideas of the TIME principle, maintaining a moist wound bed has become a cornerstone for proper maintenance and healing of a wound.[16] Although moist wounds have been shown to heal 40% faster,[17] too much fluid is detrimental to a wound and can result in maceration of the surrounding healthy tissue and bacterial infection.[16]

In vitro and *in vivo* studies have demonstrated the ability of honey to retain a proper amount of moisture in the wound.[18,19] Honey has several properties that make it almost an ideal addition to wound dressing. Primarily, honey is safe and aesthetically pleasing, because it is considered as a more "natural" agent. Honey is perceived to "clean" wounds and often results in significant deodorization of wounds.[20] Besides being pleasing, honey possesses angiogenic activity and aids in the formation of granulation tissue and reepithelialization.[18]

Animal studies and human clinical trials have demonstrated the anti-inflammatory activity of honey. These effects initially were thought to be a direct result of the removal of bacteria from the wounds by honey; however, the activity was also present in laboratory-induced wounds that remained infection free. These results indicate that honey has an innate anti-inflammatory properties.[21,22] Clinical trials involving patients with superficial burns demonstrated the anti-inflammatory effects of honey in humans. The results were observed using standard histologic and biochemical analysis of the wounds.[23]

Aloe

Preparations of aloe vera (*Aloe barbadensis*) have been used since ancient times for various ailments, especially those of the skin.[24] Today, a multitude of products contain aloe preparations of varying compositions and potencies. These are incorporated into various gels and creams for a range of skin disorders, hair products, and even into various tissues and paper products.[25] Most commercial preparations of aloe are derived from the internal gel of the aloe leaf and not from the aloe sap. Whole leaf aloe extracts have been shown to possess anti-inflammatory and antibacterial properties *in vitro* and in animals.[26] Although whole leaf extracts are antibacterial to some human pathogenic bacteria, the activity depends on the amount of anthraquinones, which are found in the sap and not in the gel.[27] These compounds have been used for millennia as purgatives due to their potent laxative nature.[24]

There is some evidence that aloe may be beneficial to a healing wound. Molecular analysis of human liver and lung cell lines treated with a more than 99% pure carbohydrate extract of aloe demonstrated an up-regulation of granulocyte-colony stimulating factor and stem cell factor.[28] Similar extracts have shown significant activity for the repair of radiation damage, pressure ulcers, and other wounds.[29-32] Silver sulfadiazine is often used to control the microbiologic flora within burn wounds; however, silver sulfadiazine has been known to retard healing in some instances due to its cytotoxicity towards human keratinocytes and fibroblasts.[33] These effects were reversed when silver sulfadiazine was used with aloe preparations.[34]

Aloe preparations have been shown to increase intercellular communication and proliferation of human fibroblasts. This is achieved by increases in the stimulatory effects of basic fibroblast growth factor-2 when combined with aloe extracts. These effects were minimal in fibroblasts cultured in the absence of fibroblast growth factor-2.[35]

Like honey, aloe is an extremely complicated mixture of natural products. Fractionation of extracts and purification of compounds from aloe resulted in the identification of β-sitosterol, an angiogenic factor that may be beneficial to the healing process, because angiogenesis is a key step in the repair mechanism. The compound was shown to be angiogenic in the chorioallantoic membrane assay and to stimulate neovascularization in the mouse Matrigel plug assay. The compound also gave positive results in the human umbilical vein endothelial cell motility assay. These findings indicate that β-sitosterol may prove beneficial in the management and treatment of chronic wounds.[36]

Aloe has been used to treat wounds and burns for centuries.[1] It is also thought to reduce tissue loss from ischemia owing to its ability to decrease thromboxane A2, thromboxane B2, and prostaglandin 2α, which produce platelet aggregation and vasoconstriction.[32] Aloe also contains other ingredients that have anti-inflammatory and antipruritic activity, salicylic acid and magnesium lactate, respectively,[37] which could easily influence the repair process.

β-Glucans

The β-glucans are a structural component of the cell walls of bacteria, fungi, and plants. The long-chain polysaccharide polymers consist of glucose monomers in a β(1,3)(1,6) linkage. The polymers have been incorporated in bioartificial skins by combination with gelatin or collagen. Although these products have enjoyed some success, they have been used traditionally as vehicles for fibroblast formulations or as bandage-like coverings for burns or autograft sites.[38,39]

β-Glucans are not found in mammalian systems and are considered to be pathogen-associated compounds. As such, they are capable of inciting immune responses in animals and humans.[40] One study found that β-glucans extracted from beer yeast (*Saccharomyces cerevisae*) were capable of potentiating leukocyte functions in human whole blood and monocytic cell cultures without inducing cytokine production.[41] Furthermore, β-glucans have been shown to lack pyrogenic properties in humans at therapeutic levels.[42]

In a rat wound model, β-glucan increased the cellular response to the injury, resulting in double the number of leukocytes in the wound at 6 hours after treatment, and 3.5 times the amount 18 hours after treatment when compared with an untreated control and a negative control (dextran). The effects were similar for bacterial infection in a rodent pneumonia model. In addition, the animals treated with β-glucan had a 60% reduction in pulmonary bacteria.[43] These results are interesting, because little progress has been made in well-defined pharmacologic interventions to improve neutrophil or macrophage function. Such an intervention may prove to be an indispensable tool to the wound care clinician, because early migration of these cells into a wound area is essential for prompt and healthy healing.[44]

Cocoa

External application of cocoa has been reported to have a variety of benefits, including soothing burns, disinfecting skin wounds, and acting as a moisturizer for the skin.[45] Ingestion of cocoa has also been associated with photoprotection against ultraviolet (UV)-induced erythema and improved dermal blood circulation and skin hydration.[46] Research has shown that flavanoids, which are secondary plant metabolites found in cocoa and a variety of fruits and vegetables, have antioxidant attributes.[47] Topical application of green tea polyphenols has also been shown to decrease UVB-induced erythema.[48]

Although several studies have investigated the beneficial effects of nutritional cocoa, including a recent study showing consumption of flavanol-rich cocoa acutely increased microcirculation of the skin,[49] there are limited studies on its use topically. The beneficial antioxidant effects of cocoa and its ability to enhance vascularity may be important in the wound-healing process (Figure 1). In a preliminary study (unpublished), the authors investigated the effect of hydrolyzed and pure cocoa butter on 180 second-degree burn wounds, using a well-established porcine model.[50,51] From past experience, the authors assessed burns for complete epithelization starting on day 7, because they seldom see any of the wounds completely epithelized at this early assessment time. In the cocoa butter study, however, the authors observed that all wounds treated with pure and hydrolyzed forms were 40% and 100% completely epithelized, respectively. Using this model for the past 20 years, the cocoa treatments have appeared to be one of the best treatments the authors have examined to date; however, additional studies are needed to determine the significance of this pilot study.

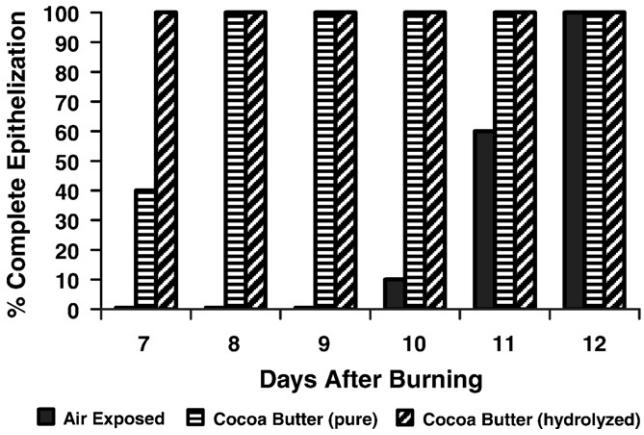

Fig. 1 Effect of cocoa on epithelization of second-degree burns.

Oak bark extracts

Tree bark extracts, including that of *Quercus rubras*, have been used traditionally by the native elders of Vancouver Island to treat illnesses ranging from digestive tract ailments to dermatologic complaints.[52] Oak bark contains tannin and has a significant astringent property that is thought to coagulate surface proteins of cells, which causes a reduction in permeability and secretions.[53] One study demonstrated that *Quercus rubra* had the most antistaphylococcal activity of eight chosen plant extracts.[54]

Wound infection is known to impair the repair process in both acute and chronic wounds.[55] Most of the infections are polymicrobial,[56] and most of these bacteria are aerobic gram-positive cocci (predominately *S aureus* and the hemolytic streptococci).[5] Wound infections, especially those associated with *S aureus*, are a major concern for health care providers (Figure 2). The incidence of MRSA has continued to grow throughout the years.[57] High rates of MRSA isolated from outpatient skin and soft-tissue specimens have been found, especially in the United States and France.[58] Using a wound infection model,[59,60] the authors studied the effect of an oak bark extract product (Bensal HP, 7Oaks Pharmaceuticals) on its ability to kill MRSA and also examined its wound healing

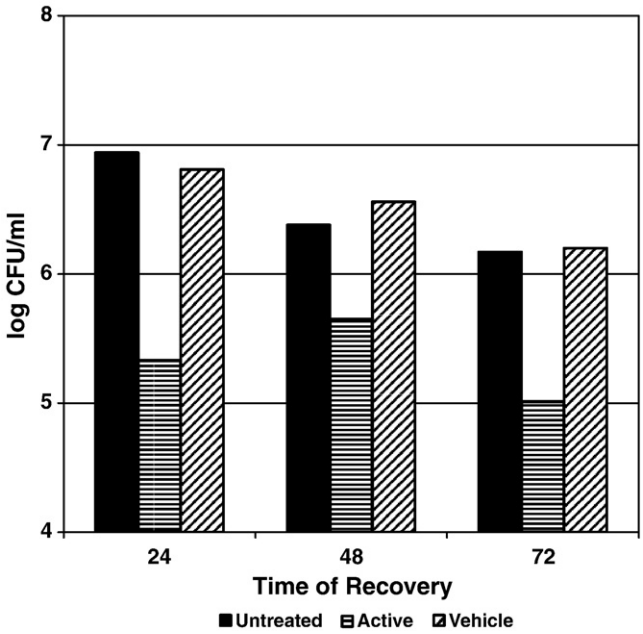

Fig. 2 Effect of an oak bark extract formulation on methicillin-resistant *Staphylococcus aureus* (log CFU/mL).

properties. The Bensal HP product consists of benzoic acid (6%), salicylic acid (3%), and extract of oak bark, *Quercus rubra* (3%).

The authors found that wounds treated with the oak bark formulation had approximately a log and half reduction of MRSA colonies at 24 hours compared with all other treatment groups. At 48 and 72 hours, at all assessment times, a log CFU/mL reduction in MRSA counts was seen with the oak bark formulation compared with the other treatments. It is possible that the benzoic and salicylic acids that are found in the oak bark extract may have contributed to its antimicrobial effects, because both have been shown to have antimicrobial activity.[61-63]

Conclusions

Natural compounds contain a wealth of interesting and possibly beneficial pharmaceutically active compounds. The use of these natural compounds has been increasing dramatically in the United States, with other countries now requiring standardizations of herbal therapies of dermatologic disorders.[1] This is due to the complexity of the sources, complexity of isolating the active components, and being able to study them in a well-controlled setting. Studies have shown that honey, aloe vera, β-glucan, cocoa, and oak bark extracts can be used fairly effectively in various *in vitro* and *in vivo* settings. Although *in vitro* studies are extremely important to help determine the initial appropriate dose of potential agents, additional *in vivo* studies are necessary to take into account the effect of the antimicrobial agent in the presence of wound fluid, growth factors, and antimicrobial peptides, among others.[64] With only a few clinical trials warranting their use for pharmaceutical intervention in wound care, additional studies are needed with controlled extract formulations that are reproducible. Unfortunately, this may prove difficult, further delaying the application of these potentially beneficial agents in a clinical setting.

Acknowledgment

Patricia M. Mertz and William H. Eaglstein provided support and participated in some of the studies.

References

1. Bedi MK, Shenefelt PD. Herbal therapy in dermatology. Arch Dermatol 2002;1138:232-42.
2. Mertz PM, Eaglstein WH. Inert vehicles do effect wound healing do effect wound healing. J Invest Dermatol 1980;74:9011.
3. Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis 2004;17:91-6.
4. Zumla A, Lulat A. Honey: a remedy rediscovered. J Res Soc Med 1989; 82:384-5.
5. Lusby PE, Coombes AL, Wilkinson JM. Bactericidal activity of different honeys against pathogenic bacteria. Arch Med Res 2005;36: 464-7.
6. Molan PC. The evidence supporting the use of honey as a wound dressing. Low Extrem Wound 2006;5:40-54.
7. Ingle R, Levin J, Polinder K. Wound healing with honey–a randomized controlled trial. S Afr Med J 2006;96:831-5.
8. Tonks AJ, Cooper RA, Jones KP, Blair S, Parton J, Tonks A. Honey stimulates inflammatory cytokine production from monocytes. Cytokine 2003;21:242-7.
9. Henriques A, Jackson S, Cooper R, Burton N. Free radical production and quenching in honeys and wound healing potential. J Antimicrob Chemother 2006;58:773-7.
10. Molan PC, Betts JA. Clinical usage of honey as a wound dressing: an update. J Wound Heal 2004;13:353-6.
11. Hsu S. Green tea and the skin. J Am Acad Dermatol 2005;52:1049-59.
12. Molan PC, Russell KM. Non-peroxide antibacterial activity in some New Zealand honeys. J Apicult Res 1988;27:62-7.
13. Weston RJ. The contribution of catalase and other natural products to the antibacterial activity of honey: a review. Food Chem 2000;71: 235-9.
14. Visavadia BG, Honeysett J, Danford MH. Manuka honey dressing: An effective treatment for chronic wound infections. Br J Maxillofac Surg 2006;44:38-41.
15. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen 2003;11:1-28.
16. Shultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound bed preparation and a brief history of TIME. Int Wound J 2004;1:19-32.
17. Eaglstein WH, Mertx PM, Falanga V. Occlusive dressings. Am Fam Physician 1987;35:211-6.
18. Bergman A, Yanai J, Weiss J, Bell D, David MP. Acceleration of wound healing by topical application of honey: an animal model. Am J Surg 1983;145:374-6.
19. Allen KL, Molan PC, Reid GM. A survey of the antibacterial activity of some New Zealand honeys. J Pharm Pharmacol 1991;43:817-22.
20. Ahmed AK, Hoekstra MJ, Hage JJ, Karim RB. Honey-medicated dressings: transformation of an ancient remedy into modern therapy. Ann Plast Surg 2003;50:143-7.

21. Church J. Honey as a source of the anti-stiffness factor. Fed Proc Am Physiol Soc 1954;13:26.
22. Bilsel Y, Bugra D, Yamaner S, Bulut T, Cevikbas U, Turkoglu U. Could honey have a place in colitis therapy? Effects of honey, prednisolone, and disulfiram on inflammation, nitric oxide, and free radical formation. Dig Surg 2002;19:306-12.
23. Subrahmanyam M. A prospective ramdonised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns 1998;24:157-61.
24. Marshall JM. Aloe vera gel: what is the evidence? Pharm J 1990;24: 360-2.
25. Gallagher J, Gray M. Is aloe vera effective for healing chronic wounds? J Wound Ostomy Continence Nurs 2003;30:68-71.
26. Robinson MC, Stenberg BD, Heggers JP. Wound healing alterations cause by infection. Clin Plast Surg 1990;17:485-92.
27. Tian B, Hua YJ, Ma XQ, Wang GL. Relationship between antibacterial activity of aloe and its anthaquinone compounds. Zhongguo Zhong Yao Za Zhi 2003;28:1034-7.
28. Talmadge J, Chavez J, Jacobs L, et al. Fractionation of Aloe vera L. inner gel, purification and molecular profiling of activity. Int Immunopharmacol 2003;4:1757-73.
29. Roberts DB, Travis EL. Acemannan-containing wound dressing gel reduces reduces radiation-induced skin reactions in C3H mice. Int J Radiat Oncol Biol Phys 1995;32:1047-52.
30. Thomas DR, Goode PS, LaMaster K, Tennyson T. Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial. Adv Wound Care 1998;11:273-6.
31. Tizard IR, Busbee D, Maxwell B, Kemp MC. Effects of acemannan, a complex carbohydrate, on wound healing in young and aged tars. Wounds 1994;6:201.
32. Klein AD, Penneys NS. Aloe vera. J Am Acad Dermatol 1988;18: 714-20.
33. McCauley PL, Li YY, Poole B, et al. Differential inhibition of human basal keratinocyte growth to silver sulfadiazine and mafenide acetate. J Surg Res 1992;52:276-85.
34. Muller MJ, Hollyoak MA, Moaveni Z, Brown H, Herndon DN, Heggers JP. Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin. Burns 2003;29:834-6.
35. Abdullah KM, Abdullah A, Johnson ML, et al. Effects of Aloe vera on gap junctional intercellular communication and proliferation of human diabetic and non-diabetic fibroblasts. J Alt Comp Med 2003;9: 711-8.
36. Moon EJ, Lee YM, Lee OH, et al. A novel angiogenic factor derived from Aloe vera gel: b-sitosterol, a plant sterol. Angiogenesis 1999;3: 117-23.
37. Robinson MC, Heggers JP, Hagstrom WJ. Myth, magic, witchcraft, or fact? Aloe vera revisited. J Burn Care Rehabil 1982;3:157-62.
38. Lee SB, Jeon HW, Lee YW, et al. Bio-artificial skin composed of gelatin and (1à3), (1à6)-b-glucan. Biomaterials 2003;24:2503-11.
39. Delatte SJ, Evans J, Hebra A, Adamson W, Othersen HB, Tagge EP. Effectiveness of beta-glucan collagen for treatment for partial-thickness burns in children. J Pediatr Surg 2001;36:113-8.
40. Brown GD, Gordon S. Fungal b-glucans and mammalian immunity. Immunity 2003;19:311-5.
41. Adams DS, Nathans R, Pero SC, Wakshull E. Activation of a rel-A/ CEBP-b-related transcription factor heteromer by PGG-glucan in murine monocytic cell line. J Cell Biochem 2000;77:221-33.
42. Babineau TJ, Hackford A, Kenler A, et al. A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients. Arch Surg 1994;129:1204-10.
43. LeBlanc BW, Albina JE, Reichner JS. The effect of PGG-b-glucan on neutrophil chemotaxis in vivo. J Leukoc Biol 2006;79:667-75.
44. Ley K. Integration of inflammatory signals by rolling neutrophils. Immunol Rev 2002;186:8-18.
45. Dillinger TL, Barriga P, Escarcega S, Jimenez M, Lowe DS, Grivetti LE. Foods of the gods: cure for humanity? A cultural history of the medicinal and ritual use of chocolate. J Nutr 2000;130:2057S-72S.
46. Heinrich U, Neukam K, Tronnier H, Sies H, Stahl W. Long-term ingestion of high flavanol cocoa provides photoprotection against UV-induced erythema and improves skin condition in women. J Nutr 2006; 136:1565-9.
47. Middleton Jr E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. Pharmacol Rev 2000;52:673-751.
48. Katiyar SK, Perez A, Mukhtar H. Green tea polyphenol treatment to human skin prevents formation of ultraviolet light B-inducted pyrimidine dimmers in DNA. Clin Cancer Res 2000;6:6864-9.
49. Neukam K, Stahl W, Tronnier H, Sies H, Heinrich U. Consumption of flavanol-rich cocoa acutely increased microcirculation in human skin. Eur J Nutr 2007;46:53-6.
50. Davis SC, Mertz PM, Eaglstein WH. Second degree burn healing: the effect of occlusive dressings and a cream. J Surg Res 1990;48:245-8.
51. Mertz PM, Davis SC, Franzén L, et al. Effect of an RGD peptide-containing artificial matrix on epithelial sheet migration and experimental second-degree burn wound healing. J Burn Care Rehabil 1996; 17:199-206.
52. Turner NJ, Hebda RJ. Contemporary use of bark for medicine by two Salishan native elders of southeast Vancouver Island, Canada. J Ethnopharmacol 1990;29:59-72.
53. Brown DJ, Dattner AM. Phytotherapeutic approaches to common dermatologic conditions. Arch Dermatol 1998;134:1401-4.
54. Molochko VA, Lastochkina TM, Krylov IA, Brangulis KA. The antistaphylococcal properties of plant extracts in relation to their prospective use as therapeutic and prophylactic formulations for the skin. Vestn Dermatol Venerol 1990;8:54-6.
55. Robson MC. Wound infection: a failure of healing caused by an imbalance of bacteria. Surg Clin North Am 1997;77:637-50.
56. Hunt JA. Fott infections in diabetes are rarely due to a single microorganism. Diabet Med 1992;9:949-52.
57. Sahm DF, Marsilio MK, Piazza G. Antimicrobial resistance in key bloodstream bacterial isolates: electronic surveillance with the Surveillance network database–USA. Clin Infect Dis 1999;29:259-63.
58. Jone ME, Karlowsky A, Draghi C, et al. Rates of antimicrobial resistance among common bacterial pathogens causing respiratory, blood, urine and skin and soft tissue infections in pediatric patients. Eur J Clin Microbiol Infect Dis 2004;23:445-55.
59. Mertz PM, Davis SC, Brewer LD, Franzén L. Can antimicrobials be effective without impairing wound healing?: The evaluation of a cadexomer iodine ointment. Wounds 1994;6:184-93.
60. Davis SC, Cazzaniga AL, Eaglstein WH, Mertz PM. Over-the-counter antimicrobial bandages and proliferation of a common wound pathogen. Arch Dermatol Res 2005;297:190-5.
61. Ivanova A, Delcheva I, Tsvetkova I, Kujumgiev A, Kostova I. GC-mS analysis and anti-microbial activity of acidic fractions obtained from Paeonia peregrina and Paeonia tenuifolia roots. Z Naturforsch [C] 2002; 57:624-8.
62. Polonio RE Mermel LA, Paquette GE, Sperry JF. Eradication of biofilm-forming Staphylococcus epidermidis (RP62A) by a combination of sodium salicylate and vancomycin. Antimicrob Agents Chemother 2001;45:3262-6.
63. Kupferwasser LI, Yeaman MR, Nast CC, et al. Salicylic acid attenuates virulence in endovascular infections by targeting global regulatory pathways in Staphylococcus aureus. J Clin Invest 2003;112:222-33.
64. Davis SC, Bouzari N. Development of antimicrobials for wound care: in vitro and in vivo assessments. Wounds 2004;16:344-7.