

Using honey in wound care

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Honey is primarily a herbal product with some modifications that are made by the bees that process the nectar or sap collected from the plants to store as honey. The types of phytochemicals present in a honey depend on the plant source of the honey. The hydrogen peroxide that is formed in honey by an enzyme the bees add, and sometimes also particular phytochemicals from the nectar or sap, give honey antibacterial activity that is sufficient to be effective in clearing infection from wounds. The phytochemicals also give honey its antioxidant activity which is also important in wound care, acting to decrease inflammation. Honey has been used in wound care since ancient times, but was displaced from use by the advent of antibiotics. With the widespread resistance to antibiotics developing in bacteria, it is now being 'rediscovered', and in many cases is proving to give better results than modern wound-care products. It has the advantage of providing moist healing conditions without the risk of bacterial growth, preventing adhesion of dressings to wound tissues, giving rapid removal of pus, dead tissue and debris from wounds, decreasing inflammation and thus decreasing swelling, pain and exudation of serum and preventing scarring, and speeding up the growth of tissues to repair wounds.

Introduction

Although classified as an animal product, honey is primarily a herbal product with some modifications that are made by the animals (bees) that process it. Bees produce honey by gathering nectar from plants (and, occasionally, by gathering sap, such as when honeydew is gathered), adding some enzymes to it, then evaporating off a lot of the water to create a super-saturated sugar solution that can be stored without spoilage. One of the enzymes added, transglucosylase, catalyses the hydrolysis of the sucrose in the nectar (or sap) to form a mixture of glucose and fructose, this mixture being more soluble than the original sucrose so that the concentrated solution has too high an osmolarity for microorganisms to survive in it.

Another enzyme added, glucose oxidase, catalyses the oxidation of some of the glucose to form gluconic acid (the resulting low pH inhibiting microbial growth) and the by-product hydrogen peroxide which kills vegetative cells and spores of microorganisms so that the honey stored in the capped cells of honey-comb is usually sterile. The enzyme which forms hydrogen peroxide becomes inactive as the water content becomes low when the nectar/sap is converted to honey by evaporation of water, but becomes active again if the honey gets diluted.

The antimicrobial properties of honey which preserve the stored nectar/sap for the bees also make honey a good antibacterial agent for medical use. But as well as having the antimicrobial properties that derive from its high osmolarity, its acidity and its production of hydrogen peroxide, honey has therapeutic properties that derive from the many phytochemicals that are in the nectar or sap gathered by the bees and also get concentrated up when water is evaporated to make honey. The types of phytochemicals present in a honey depend on the types of plants from which the honey is derived: the unique composition of

honey from each source is what gives different types of honey their characteristic colours, flavours and aromas. The phytochemicals also influence the stability of glucose oxidase in honey, thus honeys from different sources have different levels of production of hydrogen peroxide.

The Ancient Greeks were aware of the differences between honeys in respect of their therapeutic values, and wrote of some particular types of honey being the best for treating wounds and ulcers (Gunther, 1934; Aristotle, 1910), and another type being best for treating sunburn (Gunther, 1934). Such knowledge is also seen in present-day folk medicine around the world (Molan, 1999). This is in line with research findings that honey can vary as much as 100-fold in the potency of its antibacterial activity. The literature on the nature of the antibacterial components of honey and the reasons for the variability in the level of activity has been reviewed in detail (Molan, 1992a; 1992b).

Ancient and modern usage of honey in wound care

In ancient history the Egyptians, Assyrians, Chinese, Greeks and Romans all used honey, in combination with herbs and on its own, to treat wounds (Zumla and Lulat, 1989). Aristotle (350 BC) wrote of honey being a salve for wounds (Aristotle, 1910), and Dioscorides (c.50 AD) wrote of honey being "*good for all rotten and hollow ulcers*" (Gunther, 1934). The usage of honey for wound care has continued throughout all ages, it being displaced from common use in the medical profession when antibiotics came into use in the 1940s. In recent times it has been 'rediscovered' by the medical profession (Zumla and Lulat, 1989), possibly because the 'antibiotic era' is coming to

an end as increasing numbers of bacterial strains develop resistance to antibiotics.

In 1999 an editorial in *Advances in Wound Care* commented that there is a "tremendous opportunity to re-examine old treatments and apply them in the current environment" (Salcido, 1999). The extent to which this opportunity is being taken up in clinical practice in recent years has been reviewed (Molan and Betts, 2004). This review describes the many honey wound dressings and other forms of honey for wound care on sale as professional products approved by regulatory authorities, and outlines the many successful cases that have been reported with honey after other modern treatments had failed.

There is probably more clinical evidence to support the use of honey in wound care than there is for the various modern wound-care products in common use. The clinical evidence in support of the effectiveness of honey in wound care has been comprehensively reviewed (Molan, 2006). This showed that honey was more effective than the conventional wound care practices used as controls in 17 randomised controlled trials involving a total of 1965 participants, and in five clinical trials of other forms involving 97 participants treated with honey. The exception was that in one of the randomised controlled trials, on bums, early surgical tangential incision was found to be more effective than dressing the wounds with honey for control of infection, but other aspects were better with the honey. Since the honey was not tested for its level of antibacterial activity, the poor control of infection may have been because the honey used was of low activity. The review also showed that honey was more effective than the controls in assisting wound healing in 16 trials on a total of 533 wounds on experimental animals, and that it gave excellent results in the ten publications that reported on multiple cases (with a total of 276 cases).

The properties of honey that make it ideal for wound care

As well as the various bioactivities that honey has which help in wound care, the physical properties of honey are ideal for a wound dressing. The viscosity provides a barrier to keep out infection, and the high sugar content has an osmotic action which draws out fluid from the wound to provide an interface of diluted honey which gives moist healing conditions and prevents the dressing from adhering to the wound tissues. It has been known that wounds heal 50% faster if kept moist (Winter, 1962), but many clinicians still keep wounds dry because of a fear that moist conditions will encourage bacterial growth. But with the antibacterial activity that honey has there is no risk of the moist conditions allowing bacteria to grow. The non-

adherent nature of the watery layer of honey under honey dressings not only gives painless dressing changes but more importantly prevents the tearing away on the dressing of adhered new tissue that has been growing to repair the wound.

The very rapid rates of healing seen when wounds are dressed with honey are due to more than just it creating

a moist non-adherent environment. In an experiment carried out on infection-free wounds on mice, comparing honey with a control moist dressing (saline), honey gave a 114% greater extent of epithelialisation and a 69% greater thickness of granulation tissue (Bergman et al., 1983). Wound healing occurs by granulation tissue filling in any cavity, and epithelial cells migrating across this from the surviving epithelium at the margin of the wound to create new skin cover. Granulation tissue consists of granules of fibroblasts growing around buds of new capillaries where they form. The supply of oxygen is the rate-limiting factor for growth of repair tissue in wounds. Stimulation of angiogenesis (growth of new capillaries) by honey has also been observed in histological studies of experimental wounds in animals (Gupta et al., 1992; Kumar et al., 1993). The acidity of honey (typically pH 3.5-4) would also help with oxygenation, as acidification of wounds speeds the rate of healing by increasing the release of oxygen from haemoglobin (Kaufman et al., 1985).

The glucose content of honey (honey is typically 30%-35% glucose) is also beneficial, as epithelial cells need to load up with glycogen before casting adrift to glide from the wound margin to provide new skin cover on the healing wound, also as phagocytes are dependent on glucose as their energy source for destruction of bacteria and dead cells yet have a limited supply from what is often a very poor circulation in injured tissues. The glucose content of honey would also explain the very rapid removal of malodour from infected wounds that results when wounds are dressed with honey. Honey is more effective than the specialised deodorising wound dressings, and its deodorising action is faster than the clearance of the bacteria that cause the malodour. The malodorous substances produced by bacteria are ammonia, amines and sulfur compounds formed from the metabolism of amino acids from decomposed serum and tissue proteins. If provided with glucose, bacteria metabolise this in preference to amino acids (Nychas et al., 1988).

The antibacterial activity of honey is very important in wound care. The many studies that have been published showing the potency of this activity against the various species of bacteria that cause wound infections has been reviewed (Molan, 2001). A wound will not heal if infected or heavily colonised with bacteria. Toxins produced by bacteria can inhibit growth of repair tissues; proteases produced by bacteria can digest connective tissue and cell growth factors; and bacterial endotoxins can stimulate an inflammatory response which causes oedema which then squeezes capillaries to restrict the blood supply needed by wound tissues for growth to repair the wound. Inflammation, by producing excessive amounts of hydrogen peroxide in the 'respiratory burst' can give rise to oxidative conditions which activate dormant proteases in wound tissues (Flohé et al., 1985; Van Wart and Birkedal-Hansen, 1990), and thus can cause even greater damage, as when ulceration is seen to occur. These proteases, collagenase and elastase digest the matrix of the connective tissue which is laid down to fill in the wound in the healing process, and digest the cell growth factors, which are vital for stimulating the activity of the cells carrying out this repair work. Various wound care

products are being brought on the market which in various ways inhibits the activity of these damaging proteases. The indications from clinical observation are that honey also works in this way, but the mechanism of this is not yet known. It could be through killing the bacteria causing the inflammation, through its anti-inflammatory activity (see below), or through its antioxidant components preventing the oxidative activation of the dormant proteases. But at the same time, whilst preventing digestion of connective tissue, honey somehow gives proteolytic activity that digests the fibrin that holds pus on a wound, and thus very rapidly gives clean wounds though this autolytic debridement. It may be that honey somehow activates the plasminogen that is in wound tissues to give plasmin, a protease that acts on fibrin, but this remains to be investigated. But whatever the mechanism, the debriding action on wounds is a very valuable feature, as debriding removes material that is harbouring a large pool of bacteria producing substances that inhibit healing of the wound.

The very large amount of clinical and experimental evidence for the various bioactivities of honey that are involved in wound care is cited in a paper on the theory and practice of using honey in wound care (Molan, 2002). The direct anti-inflammatory activity of honey, due to as yet unidentified components, is a bioactivity that makes a very large contribution to the effectiveness of honey in wound care. The antioxidant phytochemical components of honey are likely to play a role in this activity, as the inflammatory response is subject to feedback amplification by oxygen radicals derived from the hydrogen peroxide produced by phagocytes. It has been concluded that it is the control of free radicals that is the main action of honey in treating burns (Subrahmanyam et al., 2003); burns being a type of wound that gets very inflamed. It has been shown that application of antioxidants to burn wounds to mop up free radicals reduces inflammation (Tanaka et al., 1995). Trials conducted on the use of honey as a dressing for burns found that honey prevented partial-thickness burns from converting to full-thickness burns which would have needed plastic surgery (Subrahmanyam, 1998), and reduced the amount of scarring (Subrahmanyam, 1991). Scarring results from over-production of collagen by overactive fibroblasts. Proliferation of fibroblast is stimulated by oxygen radicals (Murrell et al., 1989), so the scar-preventing action of honey could be through its antioxidant components or through its anti-inflammatory action decreasing the amount of oxygen radical formation.

Another feature of honey as a wound dressing that comes from its anti-inflammatory activity is that it is soothing on a wound. The painfulness of wounds results from factors released in the inflammatory response sensitising nerve endings. The release of these factors is decreased if inflammation is suppressed. The soothing action is most noticeable when honey is used as first aid on burns and scalds, the pain being taken away in about 20 minutes. Also noticeable is that blistering and ongoing painfulness do not occur when honey is applied immediately after the burn/scald has occurred. Honey is increasingly being used to decrease the damage to skin and to the oral mucosa that

results from the radiation burns that occur when patients are undergoing radiotherapy for cancer. Two clinical trials on this have been published which have shown that honey is very effective in decreasing the severity of oral mucositis (Chiba et al., 1985; Biswal et al., 2003).

The anti-inflammatory activity of honey gives another advantage that is of practical importance in managing wounds that have a high degree of inflammation. Factors produced in the inflammatory process open up blood vessels so serum flows out into the surrounding tissues. Where the skin is broken the serum exudes from the wound and the quantity of exudate can be large enough to create practical difficulties in absorbing it. If honey is kept on the wound (i.e. not allowed to be washed away by the exudate — see below) its anti-inflammatory activity soon suppresses the inflammation so that the quantity of exudate decreases.

Practical considerations

The 'rediscovery' of the use of honey for wound care has missed some of the ancient wisdom. Four millennia ago the Ancient Egyptians mixed cotton fibres and fat into honey to create a dressing that would hold the honey on a wound (Majno, 1975). Honey can only exert its many beneficial actions on a wound if it remains present, but at body temperature it is a very runny liquid. Applying an absorbent dressing over the honey does not help much with retaining the honey on a wound because the water content of honey (typically about 17% of honey is water) is bound up on the sugar molecules in honey, so it does not easily wet absorbent dressing materials. This means that when a dressing is placed over honey on a wound the honey tends to be squeezed out laterally. To get the honey to be retained well it needs to be soaked into the absorbent dressing before it is applied. Various sorts of such honey-impregnated dressings are now available as sterile medical products (Molan and Betts, 2004). The exudate from a wound can flush the honey out of cotton or cellulose fibre dressings, so on highly exudative wounds quite frequent dressing changes may be needed until the anti-inflammatory activity of the honey decreases the amount of exudate by suppressing the inflammation that is causing it. Less frequent changes are needed if honey-impregnated alginate fibre dressings are used instead, because the wound fluid converts the alginate fibres into a soft gel from which the honey is not flushed out (this type of honey dressing is available commercially). A new form of honey dressing has been developed in which the honey has been combined with sodium alginate to gel it into a rubbery material which swells as it absorbs exudate (Molan, 2005). This product, which is still in the process of commercialisation, has a massive capacity to absorb exudate without the honey being flushed from the wound bed.

Another bit of ancient wisdom that has been missed in the 'rediscovery' of the use of honey for wound care has been the fact that honeys differ in their therapeutic qualities. In a very large number of the publications in medical journals reporting on the clinical usage of honey in wound care the honey used has been treated as a generic material without recognition of the very large variation that

is seen in the potency of the antibacterial activity of honey. This has also been the case in some of the honey wound-care products on sale. But other companies have based their products on *Leptospermum scoparium*, manuka honey from New Zealand, or a similar honey from Australian *Leptosperinwn* species, with a high level of a unique (as yet unidentified) phytochemical antibacterial component. The major advantage of using this type of honey is that the phytochemical antibacterial factor is not affected by the enzyme catalase that is present in the cells and serum in wounds and which breaks down hydrogen peroxide, which would destroy a large part of the antibacterial activity in other types of honey. Tubes of this type of honey, and wound dressings made from it, are available from several companies as sterile products registered for use as medical wound dressings.

If the various other therapeutic bioactivities that honey has are due to phytochemicals then these too are likely to vary in potency between different honeys. At present honey on sale for wound care is not selected for levels of activities other than antibacterial activity, but research is under way that should lead to the selection of honeys that have the highest levels of the other activities that are beneficial in wound care.

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