

## Honey for wound care: myth or science?

### Part 1: literature overview

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#### SUMMARY

**For centuries honey has been used for wound care in various cultures all over the world. However, modern western medicine often did not recognize its use and even now the use of honey is still considered "alternative healing" by many clinicians. Especially now that antibiotic resistance is more and more prevalent, it is useful to review the use of honey for wound care once again. The action mechanism and the efficacy of several types of honey were studied through laboratory tests. Clinically honey appears to be extremely suitable for the treatment of large infected wounds. In addition to a marked antimicrobial effect the healing of the wound is stimulated by honey and the scar is less noticeable. Contrary to many conventional medicines there are moreover no mentionable side effects or contra-indications.**

#### ABSTRACT

Honey is one of the oldest medicines. Throughout history its use in wound management has been recorded in several cultures throughout the whole world. Up till now, in Western society non-traditional health care practices have been regarded with scepticism, viewing them at best as "useless, but not harmful".

The emergence of multi-drug resistant organisms and homophobia, has created a resurgence of interest in the therapeutic use of honey. Honey of several floral sources has been studied *in vitro* to elucidate the scientific basis for its effectiveness. Clinically, honey is particularly suitable for treating patients with large infected wounds. Honey has antibacterial properties, it enhances wound healing and there is minimal eschar formation when honey is used. In contrast to many conventional drugs, no important adverse effects have been reported.

#### INTRODUCTION

The honey bee (*Apis mellifera*), the largest producer of honey in our parts, has been present on earth for at least 50 million years. From the early ages humans have recognized the value of honey, not just as food but also as a part of religious ceremonies and as medicine. The oldest writings that report the medicinal use of honey is a Samaritan clay tablet from Israel that dates back to 2000 before Christ. The instructions about the use of honey for the treatment of infected wounds, ulcers and eye- and ear problems date from this period. In the Old Egypt bees were already kept and honey harvested for its healing properties. Papyrus rolls were found with various recipes for the treatment of alopecia, burns, abscesses, ulcers

and scabies. These remedies were passed on to the Old Greeks. Hippocrates, sometimes called the father of modern medicine, first reported 'oxymel' (honey and vinegar) as a pain killer and 'hydromel' (honey and water) as an antipyretic. The method of healing was then taken over by the Romans, who were great supporters of the use of honey, either by itself or in combination with other ingredients. During the Middle Ages the use of honey for medicine fell into oblivion, just like so much other valuable scientific knowledge. In the 17th Century again several manuscripts that recommended honey for wound care appeared, however, without actually knowing the action mechanism thereof. That is why the content of the manuscripts was not taken seriously and therefore also not included

in conventional medicine. In remote (and often poor) areas, like in Asia and Africa, the bee hive is viewed as an inexhaustible medicine chest since time immemorial and honey is still used there by the local medicine men. In Russia and Eastern Europe, where often people did not have the means to develop new medicines, the use of honey for the treatment of infected wounds and burns also did not fall completely into oblivion. In 1919 the antibacterial effect of honey was proven in laboratories. However, it took until the 1930's before medical magazines made mention of its germ killing properties. In the mid 1940's more intensive research was done, but with the arrival of antibiotics honey was banned from modern medicine once more.

Currently the Western world again shows an interest in the use of honey as alternative wound covering, but usually only after first all modern techniques have been tried out and appeared ineffective. People are working hard on rediscovering the medicinal value of honey and more and more studies are undertaken to prove its efficacy. The manuka honey types from Australia belong to the most studied. In the history of wound care not just the use of honey is mentioned, but also that of sugar. The physical, chemical and biological characteristics of honey and sugar water (with the same ratio of sugar and water) however, are not equivalent. There where sugar due to dilution loses its antibacterial effect after a specific time, this does not occur with honey (Mathews and Binnington, 2002).

The intention is to give a little more credibility to the use of honey for wound care with this literature overview. The most important and at the same time also the most difficult is to separate the folklore about the medicinal use of honey from that which has been shown scientifically.

## HONEY

Honey is a natural product prepared by bees from nectar. The bees collect the nectar and process it into honey (nectar honey). Aphids and scale insects, however, are also attracted by the sweet phloem sap that is located in the sieve tubes of plants. They suck up the sap, process it and what remains is excreted in the form of honey dew on leaves and branches. The honey dew is then taken up by the bees to be further processed into honey dew honey. Honey is a complex mixture that contains about 180 different substances, both from organic and anorganic origin. The primary ingredients of

honey are sugars (mono- and oligosaccharides) and water. Furthermore honey contains amino acids, minerals, acids, enzymes, vitamins, aromas, hormones, nitrogen and ash. The water content of honey is less than 20%. Honey contains a number of important enzymes. The enzyme glucose oxidase comes from the bee and, in the presence of oxygen, converts glucose into glucono delta lactone which releases hydrogen peroxide. The produced hydrogen peroxide has two important effects: it conserves the honey and it inhibits the growth of micro-organisms. The converted glucono delta lactone turns into gluconic acid under the influence of water. Gluconic acid reduces the pH of the honey mixture, but the amino acids that are present in the honey serve as a buffer. The enzyme katalase comes from pollen and converts hydrogen peroxide into water and oxygen (White *et al.*, 1963; Schepartz, 1966; Dustman, 1971; Weston, 2000). Adding katalase to honey samples *in vitro* has clearly shown that some types of honey contain another important phyto-chemical component with a marked antibacterial effect (Allen *et al.*, 1991). However, to this day this component has not been further identified.

## THE EFFECT OF HONEY ON HEALING WOUNDS

Various properties with a positive effect on healing wounds are ascribed to the use of honey. Such effects are often both direct and indirect. The antibacterial and anti-inflammatory effect ascribed to honey and the stimulation of healing wounds have been documented most.

### The antibacterial effect

Various types of bacteria, among which aerobes and anaerobes, gram positive and gram negative, are sensitive to honey (Efem, 1988; Allen *et al.*, 1991; Molan, 1992; Cooper *et al.*, 1999; Subrahmanyam *et al.*, 2001; Zaghloul *et al.*, 2001; Cooper *et al.*, 2002; Osman *et al.*, 2003; French *et al.*, 2005). The minimum concentration of honey needed to prevent the growth of a certain germ completely (MIC value) varies strongly according to the tested type of honey (Allen *et al.*, 1991; Molan, 1992; Willix *et al.*, 1992). Also an antimycotic activity was shown against *Candida* (Osman *et al.*, 2003), certain types of *Aspergillus* and *Penicillium* (Molan, 1992) and dermatophytes (Brady *et al.*, 1997). By extracting fractions from honey with the help of ethyl acetate an inhibiting effect could be established for all

tested micro-organisms, while the untreated honey had no effect on yeasts and fungi (Zaghloul *et al.*, 2001). All too often it was assumed that the antibacterial properties of honey can be completely explained by the osmotic effect of the sugar fraction. The strong interaction between sugar molecules and water only leaves few water molecules for micro-organisms which inhibits microbial growth (Chirife *et al.*, 1983; Molan, 1995; Cooper *et al.*, 2002). Certain micro-organisms, among which *Pseudomonas aeruginosa*, are only influenced by the osmolarity (Willix *et al.*, 1992). The *in vitro* MIC-value of natural honey for most other bacteria is much lower than this of artificial honey (Cooper *et al.*, 2002). There is also still an inhibition of bacterial growth after the dilution of the honey with fluid from the wound, at which the osmolarity has become much too low already (Cooper *et al.*, 1999). The antimicrobial effect of honey is even potentiated with dilution (White *et al.*, 1963; Bang *et al.*, 2003). After all, by attracting fluid the glucose is enzymatically converted by the enzyme glucose oxidase into gluconic acid and hydrogen peroxide (White *et al.*, 1963). The gluconic acid further reduces the pH: owing to a balance between the neutral lactone and the free acid, the acidification property of honey is constant though mild and is also the growth of bacteria inhibited. The released hydrogen peroxide has direct bactericidal properties.

The constant presence of a low concentration of hydrogen peroxide is more effective than a single high dose, which can cause tissue damage, but does not remain at the site for long (Bang *et al.*, 2003). The hydrogen peroxide production, created by exposing the wound to honey for 1 hour, is 1000 times lower than the generally used 3% antiseptic solution, but is owing to the long-term contact still more effective. In non-diluted honey the low acidity of the honey, in addition to osmolarity, plays a role in suppressing bacterial growth (White *et al.*, 1966; Molan 1995; Cooper *et al.*, 2002). In some types of honey are also not further determined non-peroxidase dependent antibacterial factors present. Their assay value is strongly dependent on the type of honey that is studied (Allen *et al.*, 1991). In order to assess medicinal honey for this property, the Unique Manuka Factor (UMF) scale was created, at which the antibacterial activity of the honey was measured with respect to the equivalent concentration of phenol (%w/v). While in a study of Allen *et al.*, (1991) the non-peroxidase antibacterial activity in several samples of

manuka honey was equivalent to 15-30% phenol, that activity was very low to immeasurable in other types of honey. However, more recent studies into such non-peroxidase activity suggest that it still does concern peroxidase, but to such an extent that there is still residual activity after the administration of katalase (Weston, 2000).

Honey is possibly a good alternative for the treatment of wounds infected with antibiotic resistant germs, provided that such resistance does not have an effect on the action mechanism of honey. In various *in vitro* tests it had already been shown that resistant bacteria are equally sensitive to the bactericidal effect of honey as non-resistant germs (Willix *et al.*, 1992; Subrahmanyam *et al.*, 2001; Cooper *et al.*, 2002; French *et al.*, 2005). Also *in vivo* it has been confirmed that topical use of honey can free wounds from the presence of resistant bacteria (Efem, 1988; Dunford *et al.*, 2000; Visavadia *et al.*, 2006). However, clearing the infection involves more than just a direct antimicrobial effect. Recent *in vitro* studies showed that honey has a stimulating effect on various immune cells (Tonks *et al.*, 2001; Tonks *et al.*, 2003). Furthermore the glucose and the low pH stimulate the bactericidal activity of macrophages (Molan, 1995). The glucose is essential for the "respiratory burst" in the macrophages that produce hydrogen peroxide and is a substrate for the glycolysis, an important source of energy in an environment with little oxygen. The acid pH inside the phagocytic vacuoles of the macrophages also contributes to the killing of the phagocytic bacteria.

By applying a honey dressing the wound is closed off from its environment. This forms a barrier which, on the one hand makes invasion of new germs difficult and on the other hand creates an anaerobic environment that counteracts further multiplication of the micro-organisms that are present. Due to the anti-inflammatory activity of honey the formation of serous exudate is inhibited, which indirectly has a negative effect on the bacterial growth, because exudate is a very suitable medium for the colonisation of bacteria (Molan, 2002).

#### **Anti-inflammatory effect**

Honey reduces the inflammatory reaction even without the presence of an infection (Kumar *et al.*, 1993).

Monocytes are stimulated by honey *in vitro* to produce both pro-inflammatory and anti-inflammatory cytokines (Tonks *et al.*, 2003). There is a histological confirmation of tissue

recovery with a minimal infection one week after the treatment in superficial wounds of the skin (Subrahmanyam, 1998). Clinical observations clearly show that when honey is applied to a wound, less redness, less oedema formation and less exsudate oozing out occur and that there is less awareness of pain (Molan, 2002). The anti-oxidants that are present in the honey probably neutralize the free oxygen radicals, which are responsible for the inflammation and tissue damage (Subrahmanyam, 1996a; Molan, 1999; Tonks *et al.*, 2001). In addition there is also an inhibition of the formation of such free radicals. Due to the osmotic effect there is also a reduction of the inflammatory oedema (Efem, 1988).

### Stimulation of the healing of wounds

The topical use of honey speeds up the healing process of among others wounds of the skin (Bergman *et al.*, 1983; Efem, 1988; Subrahmanyam, 1996b; Oryan and Zaker, 1998). In animal models (mice, rats and rabbits) a thicker granulation tissue and a faster reduction of the size of the wound are shown (Bergman *et al.*, 1983; Oryan en Zaker, 1998; Osman *et al.*, 2003). With prospective clinical studies in large groups of human patients a significantly faster healing was shown after treatment with honey bandages compared to a treatment with other ointments under the bandages (Subrahmanyam, 1993; Subrahmanyam, 1996b; Subrahmanyam, 1998).

Monocytal cells react to honey due to the release of inflammatory and anti-inflammatory cytokines and a reduced formation of reactive oxygen intermediaries (Tonks *et al.*, 2001; Tonks *et al.*, 2003). Such cytokines modulate the activity of various cell types that play a role in the healing of wounds. Due to macrophage activation in non-healing wounds the chronic inflammatory process can be adjusted to cell proliferation and ultimately to healing (Tonks *et al.*, 2003). In addition to the direct bactericidal property the released hydrogen peroxide also stimulates the angiogenesis (Tur *et al.*, 1995) and therefore also the oxygen supply and the impingement of fibroblasts. Hydrogen peroxide also speeds up the healing of wounds by improving the growth of fibroblasts and on the one hand to mobilize epithelial cells from the edges of the wound and on the other hand to activate still vital epithelial cells from hair follicles (Efem, 1988; Burdon, 1995; Molan, 1998). Honey has a low pH, which also stimulates the healing of

wounds due to an indirect effect on the amount of available oxygen at the level of the wound (Bergman *et al.*, 1983). Due to the hygroscopic effect a drawing of lymph to the site of the wound occurs (Bergman *et al.*, 1983; Efem, 1988). Lymph among others contains macrophages that guarantee further cleaning of the wound. On top of that lymph contains dissolved nutrients. The forming of new tissue is stimulated because the cells are fed (Molan, 1999). Honey does not just feed the wound with a cellular source of energy (Bergman *et al.*, 1983), but also with minerals, amino acids and vitamins. The moist environment benefits the epithelialisation rate (Efem, 1988; Visavadia *et al.*, 2006). In the moist environment the myofibroblasts can better contract, so the edges of the wound are pulled together.

Honey also has a debriding effect (Efem, 1988; Subrahmanyam, 1993; Visavadia *et al.*, 2006). The moist environment allows the effect of the proteases, through which scabs, pus and dead tissue are released from the site of the wound. On top of this the lymph, drawn by the osmotic effect of the sugar fraction, helps remove the debris from the wound (Bergman *et al.*, 1983). An added benefit of a moist environment without scabbing is that the epithelialisation can run its course without obstruction, which causes the healing to go faster and the scar to be smaller (Subrahmanyam, 1998). With the treatment of burns the ultimate scars are less noticeable and there is also less depigmentation present (Subrahmanyam, 1996b).

### Other properties

Some clinical studies reported about a softening effect of the topical use of honey on open wounds (Ndayisaba *et al.*, 1993; Subrahmanyam, 1993). Another pleasant effect for the patient and his/her nurse is the deodorizing effect of honey, because the bacteria metabolise sugars, instead of amino acids and proteins, from the serum and necrotic tissue (Nychas *et al.*, 1988). This causes lactic acid to be formed instead of bad smelling ammonia and sulphur components.

### THE USE OF HONEY AS WOUND COVERING

The honey is spread on absorbing bandages after which it is placed on the wound. If honey is applied directly to the wound it has a tendency to run off even before the bandages have been applied. The honey must be spread evenly across the bandage and the quantity depends on the

type of wound. Wounds with a deep infection require more honey in order to achieve an effective antibacterial activity through diffusion in the wound. The guideline is thirty millilitre of honey for a dressing of 10 by 10 cm (Mathews en Binnington 2002). Deep wounds or abscesses can best be "filled" with honey. On top of the honey bandage a closing layer must be applied, so no honey or exsudate can run from the bandage (Molan, 1998; Molan, 1999). Often a polyurethane foil is used for this.

Honey does not adhere to the wound, certainly not after dilution due to fluid from the wound. Honey bandages, due to the minimal adhesion, can easily and painlessly be removed again (Subrahmanyam, 1993). The redressing can take place with minimal tissue trauma and a minimal bleeding. With the removal of the bandage the debris, which is still present in the wound, is also removed. The high solubility of honey in water makes sure that the remaining debris can rapidly be rinsed away with water before a new bandage is put on. How frequently the bandage must be changed, depends on the degree of contamination and on the amount of fluid the wound produces. In most cases changing the bandage once is sufficient, but sometimes, initially, the bandage needs to be changed several times per day if the bandage appears to be too wet when it is changed. The exsudation will reduce due to the anti-inflammatory effect of the applied honey, which gradually reduces the need for changing the bandages.

Once the wound stops producing fluid, changing the bandage twice a week is sufficient for maintaining a "reservoir" of antibacterial activity to diffuse in the wound. Honey can be used long-term because it does not irritate and there are no negative effects to the tissues.

#### POSSIBLE DISADVANTAGES OF THE USE OF HONEY FOR WOUND CARE

In exceptional cases a burning sensation can occur with the application of honey in the wound (Ndayisaba *et al.*, 1993; Molan, 1998; Osman *et al.*, 2003), probably due to the low acidity. On the other hand there are also clinical indications that the topical use of honey to open wounds has a softening effect (Ndayisaba *et al.*, 1993; Subrahmanyam, 1993).

Another possible side effect is an allergic reaction to honey. However, this is rare and primarily due to the pollen that are present and bee proteins (Helbling *et al.*, 1992). By filtering the honey before use all pollen can be removed.

An imaginable problem is an infection of the wound with germs that are present in the honey. Bacteria can be present in honey but the growth thereof is usually ruled out. However, some yeasts are capable of growing in honey, although they are not clinically relevant. In honey with a water content that is too high they can at most cause deterioration. In addition also *Bacillus spp.* can be present in honey, which form spores, but they too cannot cause a disease (Snowdon and Cliver 1996). Extensive studies have shown that the only clinically relevant germs are *Clostridium botulinum* and other *Clostridia* (Snowdon and Cliver 1996). There are only spores of the *Clostridia* present in the honey because the vegetative forms cannot survive in it. However the spores can remain present for several years, even though they strongly reduce in numbers. In a wound they could develop, if the environment becomes anaerobic, multiply and produce toxins. In clinical cases, however, wound botulism due to honey appears to occur very rarely to never. The heat treatment of honey destroys possible contaminations though at the same time also all bacterial activity owing to the formation of hydrogen peroxide (White en Subers, 1964). The pre-treatment of honey with gamma rays effectively kills the spores without any loss of wound healing and anti-bacterial properties (Molan en Allen, 1996).

With use of very large quantities of honey dehydration of the wound can occur in exceptional cases due to the osmotic effect. Adding a physiological solution to the dressing on the wound prevents dehydration. Most commercial honey ointments contain an oil component, which does prevent severe dehydration (Osman *et al.*, 2003).

The risk of hyperglycaemia occurring in human diabetes patients, even with the treatment of large wound surfaces, appears purely hypothetical (Visavadia *et al.*, 2006). The glucose is probably partially absorbed in the wound, but an increase of the blood glucose has not been observed. The use of honey can draw dust and vermin. Although with good bandages this seldom forms a problem.

#### REGISTERED HONEY PREPARATIONS

The registration of products on the basis of honey offers guarantees with respect to origin, processing (heating) and purity (residues of heavy metals or antibiotics) of

the used honey. On top of that most registered honey preparations contain other products, besides pure honey, that have an additional positive effect on the healing of wounds. Dependent on the preparation, vitamins, spore elements, oils and neutralising substances are added. The adding of honey to alginate bandages leads to the occurrence of a honey containing gel, guaranteeing longer contact with the wound.

#### THE USE OF HONEY IN HUMAN MEDICINE

In human medicine a great number of articles about the use of honey for cuts and grazes, amputations, abscesses, fistula, pressure sores and ulcers, infected or non-infected traumatic wounds and wounds over a large surface have already been published. In less affluent countries honey is often used for surgical wounds in hard to reach places such as with wounds after vulvectomy or with infected wounds after Caesarean sections (Moore *et al.*, 2001). Best established is the use of honey for burns (Subrahmanyam, 1996b and 1998). Honey prevents the risk of colonisation by bacteria and neutralizes the excess of free oxygen radicals, which prevents deeper wounds. Also less scar formation and less depigmentation occur.

Chronic wounds, which after more than one year to even 5 years no longer heal even though all types of conventional treatments were applied, appear to react to the use of honey (Efem, 1988). Perhaps the stimulation of the cell growth and the development of a new capillar bed by the honey are the new stimulant needed to get the healing process back on track. Also in such wounds bacterial colonisation is effectively cleaned.

#### THE USE OF HONEY IN VETERINARY MEDICINE

With respect to veterinary medicine the number of publications about the clinical use of honey is more limited. For small pets honey can be used for all types of skin wounds, but primarily there have been case histories about burns, probably because it concerns injuries on a large surface. One extremely important observation is that after a honey treatment hair growth occurs again (Mathews and Binnington, 2002). In rabbits (Harcourt-Brown, 2002) honey is applied successfully in chronic abscesses.

Such abscesses are generally difficult to heal because they are well encapsulated and contain a

thick cheese-like content in which antibiotics penetrate badly or not at all. The abscess can be filled with honey twice a day. This therapy can be continued several weeks, provided that the honey is not toxic. Rabbits do indeed lick the wound, but this is more considered to be favourable, because it improves drainage.

The authors have obtained good results several times with the treatment of various wounds in dogs and cats. The personal experiences with the use of honey and honey preparations as wound covering is documented in detail in the second part of honey for wound care.

#### CONCLUSION

Honey is a valuable alternative for the classic wound dressings, especially considering the increasing antibiotic resistance. In comparative studies between honey dressings and the more conventional wound dressings it appears that honey is usually the better choice. Honey has several wound healing qualities and the possible side effects are negligible, definitely if commercial honey preparations are applied. Honey is cheap in use: the purchase price is low and the patient heals faster than with a conventional treatment. Fewer surgical excisions and grafts are needed and care can be continued at home sooner. In addition, honey is biodegradable.

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