

## Manuka honey as a medicine

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### *Honey - an ancient remedy "rediscovered"*

The usage of honey as a medicine is referred to in the most ancient written records, it being prescribed by the physicians of many ancient races of people for a wide variety of ailments (Ransome 1937). It has continued to be used in folk medicine ever since, but in recent times there has been a renaissance of the use of honey in the medical profession: an editorial in the *Journal of the Royal Society of Medicine* (Zumla and Lulat 1989) discussing this expressed the opinion "The therapeutic potential of uncontaminated, pure honey is grossly underutilized. It is widely available in most communities and although the mechanism of action of several of its properties remains obscure and needs further investigation, the time has now come for conventional medicine to lift the blinds off this 'traditional remedy' and give it its due recognition." Some examples of the reports being published are given here:

Cavanagh *et al.* (1970) described 12 cases of wound breakdown after radical vulvectomy being dressed with honey. The wounds, of a type notoriously difficult to keep free from infection, were found to become sterile in 3–6 days, have a clean healthy granulating (healing) appearance, required the minimum of surgical removal of dead tissue, and to not need skin grafting as would normally be required. Honey was found to be non-irritant and much more effective than topical antibiotics, the time in hospital being reduced from the usual 7–8 to 3–4 weeks.

Efem (1988) reported clinical observations on the healing with honey of 59 cases of wounds and skin ulcers that had not been healing for 1–24 months with conventional treatment. The wounds were found to become sterile and odourless in 1 week, pus and gangrenous tissue separating by themselves painlessly. Swelling and exudation of lymph subsided rapidly and there was rapid development of new tissue to repair the wounds. The honey caused no adverse reactions.

Efem (1993) reported a trial where 20 cases of Fournier's gangrene (a form of necrotising fasciitis) were treated by daily application of honey with no surgery, compared with 21 similar cases treated by surgical removal of infected tissue and systemic antibiotics. Similar outcomes were achieved with both treatments but with a faster response to treatment with honey, the wounds becoming sterile within 1 week with honey, and with the group treated with honey not requiring plastic surgery.

Subrahmanyam (1991) reported a randomised controlled trial in which honey was compared with silver sulfadiazine for efficacy as a dressing for burns. With silver sulfadiazine, the most widely used agent to prevent or clear infection in burns, 7% of the patients had infection in the burns controlled within 7 days, whereas with honey 91% of the wounds were sterile within 7 days. Honey was observed to remove dead tissue and offensive smell from the burns. Healthy granulation tissue was observed to appear nearly twice as fast with honey, and new skin cover developed faster also. There was better relief of pain, less exudation of lymph, and less irritation with honey. Honey also gave a lower incidence of raised scars and contractures.

A detailed review of the published literature on the use of honey in wound healing has been published by Molan (1998). This literature provides a convincing body of evidence from clinical observation, clinical trials and experiments on animals for the effectiveness of honey as a wound dressing. The published literature reporting other therapeutic uses of honey has also been reviewed by Molan (1999b). This review also cites historical and traditional therapeutic uses of honey. Some examples of the modern professional reports are given here:

Haffejee and Moosa (1985) reported a clinical trial in which honey was used in place of glucose in a rehydration fluid (solution of electrolytes) given to infants and children admitted into hospital with gastroenteritis. The treatment with honey gave a statistically significant reduction in the duration of diarrhoea caused by bacterial infection (58 hours *cf* 93 hours).

Salem (1981) reported a clinical trial in which 45 patients with dyspepsia were given no medication other than 30 ml of honey before meals 3 times daily. After treatment with honey the number of patients passing blood (from peptic ulcers) in their faeces had decreased from 37 to 4; the number of patients with dyspepsia had decreased from 41 to 8; the number of patients with gastritis or duodenitis seen on endoscopy had decreased from 24 to 15; the number of patients with a duodenal ulcer seen on endoscopy had decreased from 7 to 2.

Emarah (1982) reported treating with honey 102 patients with a variety of ophthalmological disorders not responding to conventional treatment, such as keratitis, conjunctivitis and blepharitis. The honey was applied under the lower eyelid as eye ointment would be applied. Improvement was seen in 85% of the cases, with no deterioration seen in any of the other 15%. There was reported a transient stinging sensation and redness of the eye soon after putting honey in the eye, but never enough to stop the treatment in any of the cases.

### ***Getting honey accepted as a respectable medicine***

Despite the many published clinical reports of the therapeutic effectiveness of honey there is a tendency for some practitioners to dismiss out of hand any suggestion that treatment with honey is worthy of consideration as a remedy in modern medicine. An editorial in *Archives of Internal Medicine* assigned honey to the category of "worthless but harmless substances" (Soffer 1976). Other medical professionals have clearly shown that they are unaware of the research that has demonstrated the rational explanations for the therapeutic effects of honey (Editorial 1974, Condon 1993). Many have attributed the therapeutic action of honey to just the osmotic effect of its sugar content (Seymour and West 1951, Keast-Butler 1980, Mossel 1980, Bose 1982, Green 1988, Somerfield 1991, Tovey 1991, Condon 1993). There has also the long-standing suspicion in the medical profession of any remedy that has a reputation for being a "cure-all", and a suspicion of the claims made for the plethora of "alternative remedies" that are being promoted in modern times. Therefore many practitioners demand a much higher standard of evidence of effectiveness for honey than is the case for products of the pharmaceutical industry.

Quen (1975), in a discussion of the ethics of running trials on remedies for which there is no rational explanation for how they work, has expressed the opinion: "The premature acceptors, and the premature rejectors, are equally anti-scientific". With a world-wide move under way towards evidence-based medicine it is important that more clinical trials are run on the use of honey, that give results that cannot be refuted by sceptics. But to get the interest of the medical profession to run such trials it has been necessary to find rational explanations for why honey has the therapeutic effects that are observed. The published literature on the experimental observations that explain how honey exerts its therapeutic effects has been reviewed by Molan (2001b). But it has taken more than this to get the medical profession interested in using honey as a therapeutic agent. The problem is best summarised by a quotation: "Prejudice is a great time saver — it enables one to form opinions without bothering to get the facts." (Australian Bee Journal, January 1944). It has needed a major educational campaign to make people aware of the facts: besides informational articles written for medical journals (Molan 1998, Molan 1999a, Molan 2000a, Molan and Betts 2000, Molan and Cooper 2000, Molan 2001a) and professional magazines for nurses (Molan 2000b, Betts and Molan 2001a, Molan and Betts 2001), 10 papers have been presented at medical conferences, 14 lectures have been given to medical professionals, 41 lectures to community groups, 5 items for science or medical TV programmes have been filmed, 16 articles have been written for magazines and newspapers for the general public, 42 interviews have been given for radio stations, 20 interviews for TV news have been given, and 112 interviews have been given for print media and web news sites. These have all been spread across many different countries. As well as that an informational website on the medicinal properties of honey has been set up (<http://honey.bio.waikato.ac.nz>).

With all of these educational opportunities the emphasis has been put on explaining how honey exerts its therapeutic effects, rather than just trying to persuade people that it gives good therapeutic outcomes. Mostly it has been in the context of honey being used in wound healing as that is where most of the evidence is to be found.

### ***The bioactivity of honey in wound healing***

There are many reasons why honey has such a good therapeutic effect on wounds, particularly on infected non-healing wounds. These have been discussed in detail by Molan (2001b), and are just briefly outlined here:

The physical properties of honey play a part in its effectiveness as a wound dressing. Because of its viscosity honey provides a protective barrier which prevents cross-infection. Also, because of its osmolarity drawing fluid out from tissues it creates a moist healing environment. That gives optimum healing as tissue growth not slowed by drying, fibroblasts are able to pull wound closed, and epithelial cells grow level with the skin surface so there is no pitted scar resulting. It also means that dressings do not stick to the surface of wounds as they sit on a layer of diluted honey. Also that there is no growth of new tissue into dressing, so there is no pain when changing dressings and the new tissue is not torn away. The osmotically induced outflow also creates 'drainage', flushing away from the tissues in the wound any harmful substances from bacterial contaminants. The sugar content of honey also aids in the rapid removal of malodour from wounds that is observed, as bacteria use glucose in preference to amino acids and thus produce lactic acid instead of bad-smelling amines and mercaptans.

The remarkably rapid effect of honey in cleaning up wounds, an autolytic debridement in which adherent dead cells and fibrin clots, a rich breeding ground for bacteria, are digested free by protease activity in the wound tissue and lift off easily, is due to a combination of the osmotic outflow and a bioactive effect of honey. Honey contains the enzyme glucose oxidase which becomes active when honey is diluted and produces hydrogen peroxide (Molan 1992a). Change in the conformation of protein molecules brought about by oxidation by low levels of hydrogen peroxide is a physiological switching mechanism between active and inactive forms of some proteins. There are two types of protein-digesting enzyme involved in wound tissues: the matrix metalloproteases of the connective tissue (Murphy *et al.* 1982), and the serine proteases produced by the neutrophils (Tonnesen *et al.* 1988). The serine proteases are normally inactive because of the presence of an inhibitor, but hydrogen peroxide inactivates the inhibitor, so the protease becomes active (Ossanna *et al.* 1986). The metalloproteases are normally present in an inactive conformation, but hydrogen peroxide changes the conformation of these and makes them active (Weiss *et al.* 1985, Peppin and Weiss 1986).

A similar mechanism switching nuclear transcription factors within cells to their active forms. There is a large amount of evidence for hydrogen peroxide being involved in many cell types in the body as a stimulus for cell multiplication (Burdon 1995). It is a normal part of wound healing, where the inflammatory response that is a natural consequence of injury or infection produces hydrogen peroxide, and this serves to stimulate the growth of fibroblasts and epithelial cells to repair the damage (Burdon 1995). Burdon (1995) has proposed that low concentrations of hydrogen peroxide might be used to stimulate wound healing, rather than the expensive cell growth factors produced by biotechnology for this purpose. But it has been pointed out by Chung *et al.* (1993) that this is feasible only if the concentration could be carefully controlled. Honey provides such a controlled delivery of hydrogen peroxide, the enzymic production giving a slow release achieving equilibrium concentrations of 20 - 95  $\mu\text{mol/l}$  (Bunting 2001). This would account for the "kick-starting" the healing process seen to occur when honey is applied to wounds that have remained unhealed for a long time.

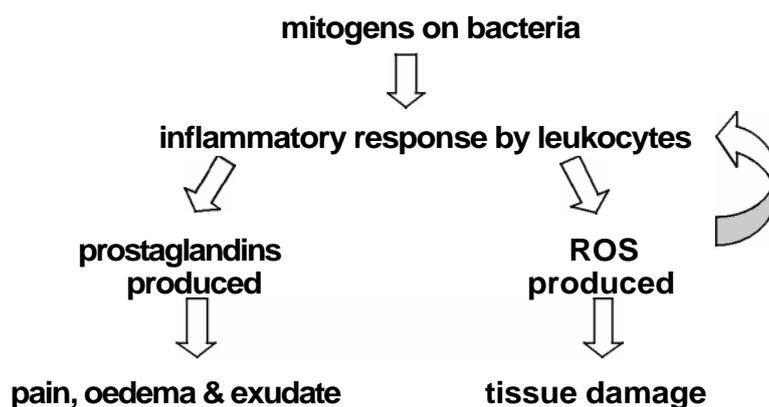
The hydrogen peroxide produced in honey would also be a factor responsible for the rapid rate of healing observed when wounds are dressed with honey. Additional to the actions mentioned above, low concentrations of hydrogen peroxide activate insulin receptor complexes (Czech *et al.* 1974, Helm and Gunn 1986, Koshio *et al.* 1988). This activation triggers a chain of molecular events in the cell that stimulates the uptake of glucose and amino acids, and promotes anabolic metabolism, giving cell growth. But there appears to be an additional factor involved, as Tonks *et al.* (2001) have reported that honey stimulates cytokine release from monocytes (the start of the normal sequence that gives rise to activation of tissue repair), and that greater stimulation resulted from a honey with a low production of hydrogen peroxide than from one with a higher production. Additional to these effects promoting tissue growth, honey provides vitamins, minerals, amino acids and sugars for the growing cells.

The provision of glucose to the wound tissues is important also for allowing maximal activity of phagocytes to clear infecting bacteria. Glucose is essential for the 'respiratory burst' in macrophages, the reaction that generates hydrogen peroxide, the dominant component of the bacteria-destroying activity of these cells (Ryan and Majno

1977). Also, honey provides substrates for glycolysis, the major mechanism for energy production in the macrophages. This would allow them to function in damaged tissues and exudates where the oxygen supply is often poor (Ryan and Majno 1977). Additional to this nutritional optimisation of the body's immune system, honey enhances immunity through a bioactive effect. Abuharfeil *et al.* (1999) have found that concentrations of honey as low as 0.1% stimulate the proliferation of lymphocytes in cell culture and activate phagocytes from blood, and Tonks *et al.* (2001) have found that that honey at a concentration of 1% stimulates monocytes in cell culture to release cytokines which activate the many facets of the immune response to infection.

Tonks *et al.* (2001) also found that monocytes already activated by exposure to mitogens had their production of reactive oxygen species reduced by honey. This is an important bioactivity of honey, as a feedback loop (see Figure 1) allows the reactive oxygen species produced as a consequence of the inflammatory response to destroy bacteria to initiate a greater inflammatory response which can be very deleterious to the healing process. Apart from inflammation creating pain, it causes opening of the circulation which leads to exudation of lymph from open wounds which can be difficult to manage, and oedema in surrounding tissue which can restrict circulation through capillaries and increase diffusional distances from capillaries to tissue cells. This reduces the availability of oxygen and nutrients to cells and thus restricts the cell growth necessary to replace tissues to repair wounds. Furthermore, the reactive oxygen species, being or giving rise to free radicals, are very damaging to the surrounding tissues, such that a wound will not heal if excessively inflamed. A further problem that comes from prolonged inflammation, where it is not sufficient to stop healing, is that it can give rise to over-growth of fibroblasts such that keloid scars, contractures and fibrosis can result.

**Figure 1.** The inflammatory response to bacterial infection. (ROS = reactive oxygen species.)



It is probably the very effective anti-inflammatory activity of honey that is responsible for the minimisation of scarring by honey dressings on wounds, although it may also be the antioxidants in honey removing free radicals that is involved. Honey has a direct anti-inflammatory effect, not a secondary effect resulting from the antibacterial action removing inflammation-causing bacteria. The anti-inflammatory effects of honey have been demonstrated in histological studies of experimental wounds in animals where there was no infection involved (Burlando 1978, Kandil *et al.* 1987, El-Banby *et al.* 1989, Gupta *et al.* 1992, Postmes *et al.* 1997, Oryan and Zaker 1998). A direct demonstration of the anti-inflammatory properties of honey, where honey decreased the stiffness of inflamed wrist joints of guinea pigs, has also been reported (Church 1954). Honey has been found to have a significant antioxidant content (Frankel *et al.* 1998), measured as the capacity of honey to scavenge free radicals. The antioxidant activity of honey has also been demonstrated as inhibition of chemiluminescence in a xanthine-xanthine oxidase-luminol system that works via generation of superoxide radicals (Ali and Al-Swayeh 1997). It also sequesters iron and thus inhibits the formation of free radicals from hydrogen peroxide through the Fenton reaction (Bunting 2001). But its antibacterial activity rapidly clearing infecting bacteria which provoke an inflammatory response would also play a large part.

### ***The antibacterial activity of honey***

Two millennia before bacteria were identified as the cause of disease physicians were aware that particular types of honey were best for treating particular ailments. Dioscorides, c.50 AD, stated that a pale yellow honey from Attica was the best, being “good for all rotten and hollow ulcers” (Gunther 1934), and Aristotle, 384-322 BC, discussing differences in honeys, referred to pale honey being “good as a salve for sore eyes and wounds” (Aristotle 350 BC). Although this wisdom has long been forgotten by medical professionals it has continued in folk medicine around the world (Molan 2001b). It was because of the reputation of manuka honey in New Zealand folk medicine for its antiseptic properties (K. Simpson, personal communication) that the research on it was started at the University of Waikato. This one bioactivity, the unusual antibacterial activity found in it, has made manuka honey world famous.

The antibacterial activity of honey was first recognised in 1892, by van Ketel (Dustmann 1979). The studies carried out on this since have been reviewed by Molan (1992b, 1992a). It has been found that mostly the activity is due to the hydrogen peroxide produced enzymically in honey, but there have been some reports of minor additional antibacterial components. A survey of 345 samples of New Zealand honeys from 26 different floral sources carried out by Allen *et al.* (1991) found that when catalase was added to destroy hydrogen peroxide the honey from only one of the floral sources, manuka (*Leptospermum scoparium*), had any significant amount of antibacterial activity remaining. This was unique amongst the many reports on other honeys around the world in that this non-peroxide component was a major contributor to the antibacterial activity, although a subsequent survey of 340 samples of Australian honeys from 78 different floral sources (C. Davis, Queensland Department of Primary Industries: personal communication) made a similar finding for honey from jellybush (*Leptospermum polygalifolium*).

This novel antibacterial activity has been subsequently studied to determine the potential usefulness of manuka honey as a therapeutic agent. In this research it has been compared with honey that has the usual type of antibacterial activity due to hydrogen peroxide. In the survey carried out by Allen *et al.* (1991) a large number of the samples of honey from the different floral sources were found to be of low activity (36% of the samples had activity near or below the level of detection in an agar diffusion assay), the rest having almost a Gaussian distribution over a thirty-fold range of activity. The non-peroxide activity in the samples of manuka honey was found to be similarly distributed. Consequently in the studies on the effectiveness of the antibacterial activity a representative manuka honey and a honey with activity due to hydrogen peroxide were selected to be each near the median level of their respective type of activity. The manuka honey was also selected to have a low level of activity due to hydrogen peroxide, and in some of the studies catalase was added to break down any hydrogen peroxide that may have been formed. The results are summarised as follows, expressed as the minimum concentration of honey (% v/v) that will completely stop the growth of each species of microorganism:

Seven common wound-infecting species of bacteria (Willix *et al.* 1992):

manuka honey: 1.8-10.8%                      other honey: 2.6-7.1%

20 isolates of *Pseudomonas* from infected wounds (Cooper and Molan 1999):

manuka honey: 5.5–8.7%                      other honey: 5.8–9.0%

58 clinical isolates of *Staphylococcus aureus* (Cooper *et al.* 1999):

manuka honey: 2–3%                              other honey: 3–4%

82 epidemic strains of MRSA (Allen *et al.* 2000):

manuka honey: 4–7%                              other honey: 3–7%

56 strains of VRE (Allen *et al.* 2000):

manuka honey: 5–10%                              other honey: 8–20%

16 clinical isolates of ? -haemolytic streptococci (Cooper RA, Halas E and Molan PC: paper in preparation):

manuka honey: 4.5–9.7%                              other honey: 5.3–9.8%

20 strains of *Burkholderia cepacia* isolated from the sputum of cystic fibrosis patients (Cooper *et al.* 2000):  
manuka honey: 2.1–5.0%                      other honey: 2.8–5.3%

Seven species of dermatophytes commonly causing tinea (Brady *et al.* 1997):  
manuka honey: 10–50%                      other honey: 520%

7 isolates of *Helicobacter pylori* from biopsies of gastric ulcers (Al Somai *et al.* 1994):  
manuka honey: 5%                              other honey: >40%

Twelve species of bacteria commonly causing gastroenteritis (Brady NF and Molan PC: paper in preparation):  
manuka honey: 2–11%                      other honey: 3–8%

Seven species of bacteria commonly causing mastitis in dairy cattle (Allen and Molan 1997):  
manuka honey: 5–10%                      other honey: 5–10%

These results all show that the activity is sufficient to expect a good therapeutic antibacterial action if the honey were used clinically. But they showed that in most cases the manuka honey was not much different in its effectiveness as a honey with the usual sort of antibacterial activity. However, there are several reasons why manuka honey could be expected to be more effective than other honey when used therapeutically. The enzyme catalase which breaks down hydrogen peroxide is present in the tissues and serum of the body, so activity of honey due to hydrogen peroxide will be less than is seen in laboratory testing in media without catalase. Also, the enzyme which produces hydrogen peroxide is inactive until honey is diluted, and its activity is low at the acidic pH of honey. Although the two types of honey antibacterial activity may be seen to be fairly equal in laboratory testing where the honey is diluted and neutralised by the culture medium, in therapeutic use there would be a much higher activity diffusing into body tissues from manuka honey than from other honey if the honey is not substantially diluted and neutralised by body fluids.

However it should be borne in mind that the results tabulated above were obtained with honeys with median levels of activity. As people became aware of the special antibacterial activity in manuka honey it became apparent that there was a lot of manuka honey with undetectably low levels of this antibacterial activity being purchased for therapeutic use in ignorance of the fact that not all manuka honey was active. An easily understood activity rating system was devised so that purchasers could know the antibacterial potency of the honey being purchased. This is based on an agar diffusion assay of antibacterial activity using *Staphylococcus aureus* ATCC 9144 as the test species and phenol as the reference standard (Allen *et al.* 1991). A 'Unique Manuka Factor' rating is used on the labels of manuka honey. (The 'Unique Manuka Factor' is the non-peroxide antibacterial activity in manuka honey.) The numbers used in the 'Unique Manuka Factor' rating are the concentration of phenol with the same antibacterial activity as the honey. (*E.g.* a honey with a rating of 15 for its content of Unique Manuka Factor has the same activity against the *S. aureus* test species as a solution of 15% phenol has.)

### **Results from clinical usage of manuka honey**

With high-activity manuka honey being available commercially, especially that which has been sterilised by gamma-irradiation (a process that does not reduce the activity: Molan and Allen 1996), there have been several clinical cases published where the results have been remarkable. Three, using manuka honey with a 'Unique Manuka Factor' rating of 12, have reported healing wounds infected with MRSA (Dunford *et al.* 2000b, Betts and Molan 2001b, Natarajan *et al.* 2001). Another, also using manuka honey with a 'Unique Manuka Factor', rating of 12, reported rapidly healing widespread serious skin ulcers resulting from meningococcal septicaemia that were heavily infected with *Pseudomonas*, *Staphylococcus aureus* and *Enterococcus* and had not responded to all modern conventional treatments over a period of 9 months in intensive care (Dunford *et al.* 2000a). Also, Cooper *et al.* (2001) have reported a case of hidradenitis suppurativa that had been giving recurrent abscesses for 22 years and had given a non-healing wound for the past 3 years that had had three attempts at surgical removal of infected tissue and a wide range of antibiotics,

antiseptics and wound dressings. This was healed (with no recurrence of infection in the two years since) within 1 month by dressing with manuka honey with a 'Unique Manuka Factor' rating of 13. Another case reported was of a large wound from surgical removal of an area of necrotising fasciitis which was heavily infected with *Pseudomonas* after surgery so could not have a skin graft applied: this was rapidly cleared of infection by application of a dressing of manuka honey with a 'Unique Manuka Factor' rating of 12 then successfully skin-grafted (Robson *et al.* 2000). Betts and Molan (2001b) have reported a trial using manuka honey with a 'Unique Manuka Factor' rating of 12 on a wider range of types of infected wounds (venous leg ulcers, leg ulcers of mixed aetiology, diabetic foot ulcers, pressure ulcers, unhealed graft donor sites, abscesses, boils, pilonidal sinuses, and infected wounds from lower limb surgery). Infection was rapidly cleared and all wounds were healed successfully other than ones where there was an underlying failure in arterial blood supply creating non-viable tissue.

### ***Research still to be done on the bioactivity of honey***

Because of the tendency of many medical professionals to cling to the belief that only pharmaceutical products are of value, it is necessary to provide a higher standard of evidence of effectiveness than is usually provided to gain acceptance of new forms of treatment. Consequently, a clinical trial comparing honey with best modern practice for the healing of leg ulcers is under way at Aintree Hospital, Liverpool. Also there is a trial under way in the Ophthalmology Department at Christchurch Hospital using honey to treat blepharitis; in the Department of Oral Surgery at the University of Illinois, Chicago, using honey to prevent the development of dry socket after removal of impacted third molars; and at the Dental School at the University of Otago using honey to decrease dental plaque and gingivitis. A clinical trial is being discussed to investigate the use of honey in palliative care of cancerous wounds. Also, veterinary trials are being planned for treating mastitis in dairy cows, and for preventing gastroenteritis in pigs, chickens and calves.

Research is under way assaying the antioxidant and anti-inflammatory activities in honey with a view to being able to select for marketing honeys with high levels of these activities, and to identify the components responsible for these bioactivities. Further research is still to be done to identify the components of honey that stimulate the immune response and stimulate wound tissue growth, and the component responsible for releasing bacteria from skin cells and mucosa. The development of assays for these bioactivities will allow selection for marketing honeys with high levels of these also.

### ***Conclusion***

The establishment by research that there are bioactive components in honey, and the wide dissemination of this knowledge, has led to a general acceptance that honey is a respectable therapeutic agent, and to a rapidly increasing uptake of its usage by clinicians as well as by the general public. The finding that there are multiple bioactive components involved in the therapeutic action makes it a much more attractive option to use the natural product rather than to attempt to identify individual active components and use synthesised copies of those.

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