

1 **Using honey to heal diabetic foot ulcers**

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26 **Abstract**

27 Diabetic ulcers seem to be arrested in the inflammatory/proliferative stage of the healing  
28 process, allowing infection and inflammation to preclude healing. Antibiotic-resistant bacteria  
29 have become a major cause of infections, including diabetic foot infections. It is proposed here  
30 that the modern developments of an ancient and traditional treatment for wounds, dressing  
31 them with honey, provide the solution to the problem of getting diabetic ulcers to move on from  
32 the arrested state of healing. Honeys selected to have a high level of antibacterial activity have  
33 been shown to be very effective against antibiotic-resistant strains of bacteria in laboratory and  
34 clinical studies. The potent anti-inflammatory action of honey is also likely to play an important  
35 part in overcoming the impediment to healing that inflammation causes in diabetic ulcers, as is  
36 the antioxidant activity of honey. The action of honey in promotion of tissue regeneration  
37 through stimulation of angiogenesis and the growth of fibroblasts and epithelial cells, and its  
38 insulin-mimetic effect, would also be of benefit in stimulating the healing of diabetic ulcers. The  
39 availability of honey-impregnated dressings which conveniently hold honey in place on ulcers  
40 has provided a means of rapidly debriding ulcers and removing the bacterial burden so that  
41 good healing rates can be achieved with neuropathic ulcers. With ischemic ulcers, where  
42 healing cannot occur because of lack of tissue viability, these honey dressings keep the ulcers  
43 clean and prevent infection occurring.

44

45 **Introduction**

46 In the recently published paper “What is the future of diabetic wound care?”<sup>1</sup> the authors give an  
47 excellent review of the reasons why diabetic wounds do not heal, and provide data on the  
48 magnitude of the problem this causes. They point out that many of the nearly 2 million cases of  
49 chronic diabetic foot ulcers in the USA ultimately result in amputation, with a 2-year survival rate  
50 after these amputations of only 50%–60%. They then go on to discuss at length the need for  
51 new smart matrix therapies, and how the development of these will require a multidisciplinary

52 translational research approach. Considering that the research on tissue-engineered skin  
53 substitutes was started approximately 20 years ago yet this form of therapy has barely started to  
54 get into regular clinical practice, there is obviously an immediate need for an effective therapy  
55 for chronic diabetic ulcers. It is proposed here that the modern developments of an ancient and  
56 traditional treatment for wounds, dressing them with honey, have allowed this immediate need  
57 to be met.

58

### 59 **Historical usage of honey**

60 The ancient Egyptians, Assyrians, Chinese, Greeks and Romans all used honey, in combination  
61 with herbs and on its own, to treat wounds.<sup>2</sup> Aristotle (c.350 BC) wrote of honey being a salve  
62 for wounds and sore eyes,<sup>3</sup> and Dioscorides (c.50 AD) wrote of honey being “good for sunburn  
63 and spots on the face” and “for all rotten and hollow ulcers”.<sup>4</sup> The usage of honey has continued  
64 into present-day folk-medicine; for example, it is a traditional therapy for infected leg ulcers in  
65 Ghana.<sup>5</sup> In recent times It has been "rediscovered" by the medical profession,<sup>2</sup> possibly  
66 because the "antibiotic era" is coming to an end as increasing numbers of bacterial strains  
67 develop resistance to antibiotics.<sup>6</sup>

68

### 69 **Modern clinical evidence for the effectiveness of honey**

70 The clinical evidence in support of the effectiveness of honey in wound care has been  
71 comprehensively reviewed.<sup>7</sup> This review summarises the findings of 17 randomised controlled  
72 trials involving a total of 1965 participants, and 5 clinical trials of other forms involving 97  
73 participants treated with honey. All of these found that honey was more effective than the  
74 conventional wound care practices used as controls, other than one trial on burns where, only in  
75 respect of control of infection, was early surgical tangential incision found to be more effective  
76 than dressing the wounds with honey. The review also summarises the findings 16 trials on a  
77 total of 533 wounds on experimental animals, where again honey was found to be more

78 effective than the controls in assisting wound healing. There is also summarised a large amount  
79 of evidence in the form of case studies that have been reported. Ten publications have reported  
80 on multiple cases, totalling 276 cases. There are also 35 reports of single cases.<sup>7</sup> This evidence  
81 is far greater than that for modern wound dressings. It is possibly the myriad of advertisements  
82 for modern wound dressings, and little for honey, that gives clinicians the impression that there  
83 is much evidence is behind the modern dressings and none behind honey, when in fact only  
84 poor-quality trials exist to support the modern wound dressings that are in use.<sup>8</sup> Perhaps the  
85 most heavily advertised wound dressings are the nanocrystalline silver dressings, but if the  
86 PubMed database is searched for evidence to support their use it can be seen that there is in  
87 fact very little good clinical evidence that has been published other than two recent trials. A  
88 conclusion reached in a recent systematic review of publications on the use of advanced  
89 dressings in the treatment of pressure ulcers has found that their generalised use in the  
90 treatment of pressure ulcers is not supported by good research evidence.<sup>9</sup> There is now a  
91 general movement towards evidence-based medicine. In this, decisions should be made on the  
92 basis of the available evidence. If randomised controlled trials of the highest quality have not  
93 been conducted, then it is necessary to consider evidence of a lower quality. Advertising, other  
94 than that which presents good clinical evidence, should not be allowed to influence decisions.

95

#### 96 **Usage of honey on diabetic ulcers**

97 Although there is a vast amount of literature reporting the effectiveness of honey in healing  
98 wounds, there has been little published specifically on the treatment of diabetic foot ulcers with  
99 honey. Diabetic ulcers are chronic wounds, and there is a large amount of evidence for the  
100 effectiveness of honey on chronic wounds. Seven clinical trials, with a total of 255 participants,  
101 have been conducted using honey on chronic wounds, with positive results for honey being  
102 reported from all of these.<sup>7</sup> There have also been more than one hundred case reports of honey  
103 being more effective than conventional treatment for chronic wounds.<sup>7</sup> Diabetic ulcers were

104 included in one report in the list of recalcitrant wounds and ulcers of varied aetiology that  
105 “showed remarkable improvement” when treated with honey. These were all wounds showing  
106 no signs of healing, or were increasing in size, after 1–24 months of conventional treatment.<sup>10</sup> In  
107 another report, on using honey to treat septic wounds, chronic ulcers, burns, and pyogenic  
108 abscesses, 6 patients were diabetic, 5 having a septic foot and 1 with an abscess in the thigh.<sup>11</sup>  
109 Healing time was 7, 10, 14 and 30 days for four the foot wounds, 15 days for the abscess, and  
110 no improvement after 56 days for a foot wound on one patient who was ill. Another report, on a  
111 single case, was on treatment of diabetic foot ulcers, 8 x 5 cm and 3 x 3 cm, on a 79 year old  
112 patient.<sup>12</sup> The ulcers remained unhealed after 14 months treatment with an orthotic device,  
113 antibiotics, topical therapies by a wound care expert and four lots of surgery. MRSA, VRE and  
114 Pseudomonas were present in wound tissue. After commencing treatment with honey, the  
115 ulcers were granulating within 2 weeks, and healed within 6 and 12 months. Two years later the  
116 ulcers had not recurred. Although honey gave healing of these ulcers where nothing else had  
117 worked, the healing was still fairly slow. This possibly because “supermarket honey” was used,  
118 which is honey that is usually processed in a way that destroys all of the antibacterial activity  
119 and possibly removes other beneficial components. In the other two reports unprocessed honey  
120 was used, which would have had its therapeutic properties undamaged.

121

### 122 **Antibacterial activity of honey**

123 There have been many publications on laboratory studies showing that honey has very broad  
124 spectrum antibacterial activity.<sup>13</sup> But most of these do not take into account that honeys can  
125 vary as much as 100-fold in the potency of their antibacterial activity.<sup>14</sup> Only in the more recent  
126 publications was the testing of the sensitivity of various species of bacteria to honey done using  
127 honeys selected to have antibacterial potency near the median level found in surveys of large  
128 numbers of samples. Laboratory studies with Manuka (*Leptospermum scoparium*) honey with  
129 antibacterial potency near the median level for active Manuka honey have shown the MIC

130 (minimum inhibitory concentration, *i.e.* the concentration down to which honey could be diluted  
131 by wound exudate and still prevent bacterial growth) to be 2–3% for *Staphylococcus aureus*,<sup>15</sup>  
132 3.3–4% for coagulase-negative staphylococci,<sup>16</sup> 5.5–9% for Pseudomonads,<sup>17,18</sup> 2.7–3% for  
133 MRSA,<sup>19</sup> and 3.8–5% for VRE.<sup>19</sup> The antibacterial potency of the honeys used in the various  
134 honey wound-care products now on sale manufactured from *Leptospermum* honey (Manuka  
135 honey and Jellybush honey) is higher than that of the honey used these studies, but there are  
136 other wound-care products manufactured from honeys not selected to have high levels of  
137 antibacterial activity.<sup>20</sup>

138  
139 Another consideration is the type of antibacterial activity in honey. Most honeys owe their  
140 antibacterial activity (beyond that just due to the osmotic effect of the high sugar content) to the  
141 production of hydrogen peroxide by an enzyme that the bees secrete into the nectar harvested  
142 to make honey.<sup>13</sup> But some Manuka and Jellybush honeys have also a high activity due to a  
143 phytochemical antibacterial component which comes from the nectar of some varieties of  
144 *Leptospermum*. Although in laboratory testing the MIC values recorded are near the same for  
145 mid-range honeys of either type, this would not be the case on a wound. There is in wound fluid,  
146 and more so the cells in wound tissues, the enzyme *catalase* which rapidly breaks down  
147 hydrogen peroxide, so honeys other than the *Leptospermum* ones would have their antibacterial  
148 activity greatly decreased. Also to be noted is that all types of honey vary from batch to batch in  
149 their antibacterial potency. Much of the Manuka and Jellybush honey on sale as a food item has  
150 little or none of the phytochemical antibacterial component, but the *Leptospermum* honey on  
151 sale as medical products has standardised high levels of it.

152

### 153 **Why honey works well on diabetic ulcers**

154 A wound will not heal if it is infected. Toxins produced by bacteria can stop the growth of cells  
155 which repair the wound. Bacterial proteases can digest away the matrix necessary for tissue

156 replacement, and digest cell growth factors. Also, components of the outer coat of the bacteria  
157 can stimulate a strong inflammatory response and the resultant inflammation then prevents  
158 healing and if severe can activate proteases to cause ulceration. Foot infections are a serious  
159 complication of diabetes and a leading cause of diabetes-related hospitalizations. Amputation  
160 may be needed when infections fail to respond to therapy. The development by bacteria of  
161 resistance to antibiotics has become a major global problem. Methicillin-resistant  
162 *Staphylococcus aureus* (MRSA) has become a major cause of infections, including diabetic foot  
163 infections. Initially it was associated only with hospital-acquired infections, but now is also a  
164 problem in the community. The effectiveness of honey in clinical usage in clearing infection with  
165 MRSA<sup>12, 21-24</sup> and VRE<sup>12</sup> has been reported. As well the antibacterial action, there have been  
166 many reports of honey having a rapid debriding effect, which painlessly lifts off slough and  
167 necrotic tissue (which are reservoirs of bacteria on the wound), making surgical debridement  
168 unnecessary.<sup>25</sup>

169  
170 Diabetic ulcers, instead of going through the normal four overlapping stages of healing,  
171 hemostasis, inflammation, proliferation and remodelling, seem instead to be arrested in the  
172 inflammatory/proliferative process.<sup>1</sup> This allows for infection and inflammation, which preclude  
173 healing. The potent anti-inflammatory action of honey is likely to play an important part in  
174 overcoming this impediment to healing in diabetic ulcers. The anti-inflammatory action of honey  
175 was noted by Dioscorides two millennia ago, who wrote of honey being good for sun-burn,<sup>4</sup> and  
176 since then a large amount of clinical and histological evidence for it has accumulated, which has  
177 been reviewed.<sup>26</sup> The anti-inflammatory action of honey would decrease the excessive activity  
178 of collagenase and elastase, a feature of inflammatory conditions and which causes the  
179 premature degradation of collagen and growth factors in chronic wounds.<sup>1</sup> A characteristic of  
180 the extracellular matrix in wounds in diabetes is the presence of advanced glycation and  
181 lipoxidation end products which stimulate oxidative stress and inflammation in wounds.<sup>1</sup> The

182 excellent antioxidant properties of honey would be beneficial in counteracting these effects. It is  
183 of note in this respect that another advantage of using active Manuka honey instead of other  
184 types of honey is that it does not generate hydroxide free radicals like honey with antibacterial  
185 activity due to hydrogen peroxide does, and rapidly quenches any formed by the Fenton  
186 reaction.<sup>27</sup>

187

188 The good results achieved on diabetic ulcers with honey may also be due to honey directly  
189 moving the wounds on from the arrested state of healing. It has been observed that honey  
190 promotes tissue regeneration through stimulation of angiogenesis and the growth of fibroblasts  
191 and epithelial cells.<sup>25</sup>

192

193 The slow healing rates seen in diabetic wounds could also be due to lack of insulin or lack of  
194 responsiveness to insulin. As well as regulating the uptake of glucose into cells, insulin  
195 functions as a growth hormone, and it has been shown that intravenous infusion or topical  
196 application of insulin improves the rate of wound healing.<sup>28-30</sup> Honey has an insulin-mimetic  
197 effect: when administered by inhalation as an aerosol, honey significantly reduced random  
198 blood glucose (measured 30 min after inhalation), significantly reduced the fasting blood  
199 glucose level (3 hours after inhalation), and the intensity of hyperglycemia was significantly  
200 lowered in the glucose tolerance test after honey inhalation.<sup>31</sup>

201

202

### 203 **Modern developments in the usage of honey**

204 In the “rediscovery” of the use of honey for wound care there has been a lack of awareness of  
205 some ancient wisdom. Four millennia ago the Ancient Egyptians mixed cotton fibres and fat into  
206 honey to create a dressing that would hold the honey on a wound.<sup>32</sup> It is necessary to create a  
207 retentive dressing of some sort, because at body temperature honey becomes very runny and



208 flows off a wound. It takes very little dilution of honey with wound exudate to make the honey  
209 very watery. The water content of honey is bound up on the sugar molecules in honey, so it  
210 does not easily wet absorbent dressing materials. This means that if honey is applied to a  
211 wound, whether directly or placed on an absorbent dressing, when the dressing is held on the  
212 wound the honey tends to be squeezed out laterally. To get the honey to be retained well on the  
213 wound it needs to be soaked into the absorbent dressing before it is applied. Various sorts of  
214 such honey-impregnated dressings are now available as sterile medical products.<sup>20</sup>

215  
216 In our initial work on clinical use of honey dressings we used a Gamgee type of dressing  
217 impregnated with honey. We found that with heavily exuding wounds it was necessary to  
218 change the dressing up to three times a day, as the exudate flushed the honey from the side of  
219 the dressing facing the wound to the outside of the dressing pad or even right through it and into  
220 the secondary dressing. This left no honey in contact with the wound bed, with the consequence  
221 that healing was slow, adhesion of the dressings occurred, and maceration of skin around the  
222 wound occurred. This situation was greatly improved when we changed to using a honey-  
223 impregnated alginate fibre dressing pad instead, as the alginate fibres transform to a gel when  
224 wound exudate is absorbed into them. (This also has the advantage of the hemostatic  
225 properties of alginate.) Thus the honey is held in a soft gel in contact with the wound bed rather  
226 than being flushed into the secondary dressing, so less frequent changes of dressings are  
227 needed. By keeping sufficient honey in contact with the wound bed, by changing the dressings  
228 frequently enough to cope with the level of exudate, the level of exudate will decrease because  
229 of the anti-inflammatory activity of honey. Less frequent dressing changes will be needed then.  
230 However, if dressings are not changed frequently enough and the honey is washed away, then  
231 the anti-inflammatory activity will also be washed away and the wound will remain highly  
232 exudative. Another form of dressing has been developed in which the honey is combined with  
233 sodium alginate to gel it, giving a rubbery material which swells as it absorbs exudate.<sup>33</sup> This

234 has a massive capacity to absorb exudate without the honey being flushed from the wound bed.  
235 Commercialisation of this dressing is proceeding, and it is expected to be available for clinical  
236 evaluation soon.

237

238 By updating the ancient wisdom of using a honey selected as the best for medical use (we use  
239 active Manuka honey with a high level of the non-peroxide antibacterial activity that is unique to  
240 *Leptospermum* honey, processed with minimal heating to avoid damaging its therapeutic  
241 properties) and creating a dressing material to hold the honey in place on the wound (we use  
242 alginate dressings pads impregnated with this honey) we have been able to get very good  
243 results with diabetic ulcers. We use honey dressings on neuropathic foot ulcers where despite  
244 pressure off-loading healing is inhibited by the presence of *Pseudomonas* and *Staphylococcus*  
245 *aureus*. We use these dressings to debride the ulcers and reduce the bacterial burden. Good  
246 healing rates are then achieved. With ischaemic foot ulcers, where healing cannot occur  
247 because of lack of tissue viability, we use honey dressings to prevent infection of these ulcers  
248 whilst waiting for re-vascularisation to be carried out. We find that if there is enough blood flow  
249 then diabetic ulcers which are due to a combination of ischemia and neuropathy will heal with  
250 off-loading of pressure. We find that honey is particularly useful for diabetic ulcers that are  
251 otherwise difficult to debride particularly where bacterial loading may be a confounding factor in  
252 the creation of slough.

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