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Honey in the Management of Infections

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ABSTRACT

***Background*: Honey, a natural product of bees of the genera *Apis* and *Meliponinae*, has been recognized for medicinal properties since antiquity. Honey has demonstrated antimicrobial properties. These effects are variably ascribed to the pH, hydrogen peroxide content, osmotic effect, and as yet unidentified compounds putatively described as inhibines.**

***Materials and Methods*: This review will explore the use of honey in necrotizing soft tissue infections, postsurgical wound infections, wounds other than postsurgical infections, *Helicobacter pylori* of the stomach and duodenum, and burns. Throughout, the *in vitro* evidence that exists and the explanations that can be offered for the purported benefits of honey will be reviewed. Most of the reports are either uncontrolled case series or *in vitro* observations. As such, detailed critique of statistical methods will not be undertaken.**

***Conclusion*: The purpose of this paper is not to debunk honey therapy as a myth, but to stimulate thought among surgeons interested in surgical infection and perhaps serve as the nidus for future research. The use of honey should be considered when more conventional therapies have failed.**

And your Lord revealed to the bee: Make hives in the mountains and in the trees and in what they build. Then eat of all the fruits and walk in the ways of your Lord submissively. *There comes forth from their bellies a beverage of many colors, in which there is healing for mankind*. Verily in this is a sign for those who give thought.

—The Koran, Surah Al-Nahal, verse 68 & 69

HONEY HAS BEEN RECOGNIZED for medicinal properties since antiquity. It is mentioned for healing purposes in the Bible, the Koran, and the Torah. It is mentioned in the Edwin Smith Papyrus dating from the 17th century B.C., and is again referred to by Hippocrates and Democritus in ancient Greece, Galen in ancient Rome, and Avicenna in medieval times. In the past century there have been sporadic reports of its use in the treatment of various wounds and infections, which will be reviewed here.

HONEY AS A SUBSTANCE

Honey is a natural product of bees of the genera *Apis* and *Meliponinae*. The bees collect nectar from flowering vegetation. The nectar is

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subjected to enzymatic processing *in vivo* in both the collecting bee and in a processing bee inside the hive. The processing bee then deposits the nectar into a wax cell in the hive, where due to relative warmth and fanning by bees, the water content is reduced by evaporation to 17%. The sugars in the nectar are converted enzymatically into glucose and fructose. Glucose oxidase then converts the glucose into gluconic acid and hydrogen peroxide. The antimicrobial effects of honey are variably ascribed to the pH, the hydrogen peroxide content, the osmotic effect, and as yet unidentified compounds putatively described as inhibines. Various researchers have neutralized the hydrogen peroxide with catalase *in vitro* in order to exclude the activity of hydrogen peroxide, with varying results. For the bee's purposes, the antimicrobial effect is very useful; honey can feed a hive through a long winter, and likewise, has a shelf life of many years for human consumption. Commercial processing involves heating of the honey to inactivate enzymes that may facilitate crystallization of the honey, making it less attractive commercially. Honey can be purchased commercially in both unprocessed and processed states.

The use of honey as an anti-infective agent was limited until recently to wounds, including burns, pressure ulcers, other ulcers of the skin, and traumatic or surgical wounds [1–4]. With the recognition in recent years that peptic ulcer disease is in large part an infectious disease (*Helicobacter pylori*), there has been attention to the use of honey in its eradication [5–10], as application to the gastric and duodenal mucosa would be both simple and pleasant for the patient. This review will explore the use of honey in necrotizing soft tissue infections, post-surgical wound infections, wounds other than post–surgical infections, *Helicobacter pylori* of the stomach and duodenum, and burns, including *in vitro* evidence and possible explanations for the purported benefits of honey. Most of the reports are either uncontrolled case series or *in vitro* observations. As such, a detailed critique of statistical methods will not be undertaken. The purpose of this paper is not to debunk honey therapy as a myth, but to stimulate thought among surgeons interested in surgical infection and perhaps serve as the nidus for future research.

NECROTIZING SOFT TISSUE INFECTIONS

Spencer E. Efem of the University Teaching Hospital in Calabar, Nigeria, has published a series of papers on the antimicrobial and wound healing effects of honey. He first published a series of 59 patients with wounds and nonhealing ulcers, 80% of which had failed to heal with conventional therapy for periods of one month to two years [11]. He showed that wounds which initially cultured positive for a variety of organisms were sterile at one week, and that 58 of the wounds went on to heal rapidly, with separation of eschar, diminished edema, and rapid reepithelialization. His method was to apply 15–30 mL of unprocessed honey to the wound daily, after cleaning the wound with normal saline. One ulcer was due to a mycobacterial infection and did not respond to honey. Although Efem did not provide data to support the following impressions, he described the effects of honey to be "debridement of wounds by a chemical or enzymatic action; absorption of oedema fluids around wounds; inactivation of bacteria; deodorization of offensive wounds; promotion of granulation tissue formation and epithelialization; and improvement of nutrition." Efem noted the low pH (3.6) and hygroscopic (osmotic) effects of honey and their probable role in its antibacterial effect, but he also noted the effect of inhibine, a previously described thermolabile bactericidal substance. As mentioned earlier, hydrogen peroxide is produced by the action of glucose oxidase, and Efem considered the "inhibine" to be hydrogen peroxide, although there is not universal agreement on this [12,13]. In 1993, Efem published his experience with twenty consecutive cases of Fournier's gangrene managed with systemic antibiotics (amoxicillin/clavulanic acid and metronidazole) and topical unprocessed honey [14]. He compared these patients to 21 similar cases managed by other physicians in the same institution, in which the standard approach of sur-

gical debridement and systemic antibiotics was used. The patients treated with honey had their wounds cleaned with saline upon presentation, then dressed with topical unprocessed honey or packed with gauze soaked in honey, with the wounds inspected and the honey reapplied daily after cleansing with normal saline. At seven days after the start of treatment all wounds were swabbed and found to be sterile, after having grown the usual expected mix of organisms recovered by a surface swab upon initial presentation. Although not analyzed statistically, there were more operations and re-operations required in the orthodox group, although the length of stay was shorter, on average, by 0.5 weeks in this group (Table 1). In the group treated with honey, foul odor, edema, and discharge resolved within 1 week of the commencement of therapy, and all necrotic tissues had separated. Efem concluded that honey is superior to standard therapy and that it may revolutionize the treatment of this disease. Later reports from other authors show that some have indeed adopted honey as an adjunct in the treatment of Fournier's gangrene. Hejase et al. reported on a series of 38 patients with Fournier's gangrene, all of whom had surgical debridement and systemic antibiotics followed by topical application of unprocessed honey on gauze pads three times a day, with one death in the series. They provided neither data for the effects of honey nor controls in their series, but presented the cases as a series. They credited honey with local cleansing and improved healing of the wounds [15].

INFECTED SURGICAL WOUNDS

Support for the use of honey in the treatment of infected surgical wounds is anecdotal, but interesting nonetheless. In both reported series (two patients and nine patients, respectively), honey was used as a salvage maneuver, and therefore there were no controls.

Armon [16] reported on the use of locally produced honey for the treatment of infected wounds at his center in Tanzania. The first was a 20-cm sacral pressure ulcer to the level of bone. The treatment described was application of a "thin layer" of "pure honey" three times a day, followed by a dry dressing. Armon stated that the wound was suitable for surgical closure by day 9, but other complications precluded surgery and the wound went on to heal nonoperatively in 70 days. The second was an infected laparotomy wound after hysterectomy, with pus emanating from the wound and the vagina. The patient had been referred to him for lack of response to partial opening of the wound and several courses of antibiotics. In addition to removing the surgical sutures to allow for drainage, he treated the wound with honey and reported that the wound was granulating by the tenth day and healed by the fourteenth day, without the use of any antibiotics. It is not clear what portion of the good outcome was due to the application of honey, and what part was due to the application of the basic surgical technique of adequate drainage.

Vardi et al. reported on a series of nine infants with infected surgical wounds treated

Table 1. Honey vs. Orthodox Therapy of Fournier's Gangrene, after Efem [14]

	No. of patients	*No. of operations*	*No. of re-operations*	*Length of stay*	*Deaths*
Orthodox treatment	21	21	19 delayed primary closure, 2 flap reconstruction of scrotum	4.0 weeks	3
Honey treatment	20	1 (delayed primary closure)	0	4.5 weeks	0

with honey [17]. This series developed from one patient in whom honey was used as a salvage therapy for a sternal wound infection with *Pseudomonas aeruginosa* and mediastinitis with *Staphylococcus aureus*. After this patient did well, they created a standard protocol wherein if a patient had failed conventional treatment of 14 days of intravenous antibiotics and wound cleansing with chlorhexidine solution and fusidic acid ointment, honey therapy was begun. Unprocessed, non-pasteurized, non-irradiated, commercial honey was applied twice daily after cleaning the wound with normal saline. Six of the patients had systemic antibiotics discontinued at the commencement of honey therapy; three continued to receive systemic antibiotics. All wounds were closed by day 21 of the twice-daily application of fresh unprocessed honey. The authors commented on the theoretical risk of introduction of spores of *Clostridium botulinum* and resulting infection. They pointed out that this is a risk known only for the ingestion of non-pasteurized honey by neonates due to the relatively non-acidic milieu of their stomachs, but that no case of *clostridial* infection of a wound from honey has ever been reported. Although this case series is promising, the lack of appropriate controls makes it impossible to determine if the good outcomes were the result of the benefits of honey, the detriments of standard therapy, or just good fortune.

HELICOBACTER PYLORI

Ali et al. reported in 1991 that natural honey had an inhibitory effect on *Helicobacter pylori in vitro*, at solutions of both 10% and 20% honey, and proposed that clinical studies on the treatment of *H. pylori* infection be undertaken [5]. Al Somal et al. performed *in vitro* experiments to determine what concentrations of honey would be inhibitory for *H. pylori*, what the active component of the honey is, and whether it was merely an osmotic effect that inhibits *H. pylori*. They found that Manuka honey from New Zealand, at concentrations as low as 5% v/v, completely inhibit the growth of *H. pylori*, and that 2.5% v/v partially inhibits the growth of *H. pylori*. The authors also found that non-Manuka honey, and an artificially prepared solution mimicking the physical properties of honey, had no inhibitory effect on *H. pylori*. The authors stated that although the active property in Manuka honey has not been identified, they know it is a hydrophilic molecule of a weight of 500 Daltons that is stable at a pH of 1. They proposed clinical trials, and the possibility that an extract of the Manuka tree or Manuka honey could be used in the eradication of *H. pylori* [6]. Although no such large-scale trial has been undertaken, McGovern et al. reported on a small series of volunteers with *Helicobacter pylori* infection by ^{14}C urea breath tests, treated with Manuka honey or Manuka honey and omeprazole. After two weeks of treatment, all 12 of the patients remained positive for *H. pylori* by ^{14}C urea breath test. The authors concluded that, if Manuka honey is effective against dyspepsia, it is not due to eradication of *H. pylori* [9].

Osato et al. revisited the topic in 1999; they compared Manuka honey to honeys obtained commercially from Texas and Iowa, and to an artificially prepared solution mimicking honey (Table 2). They found that at concentrations >15% v/v, all honeys and the artificial solu-

Table 2. *H. Pylori* Isolates Inhibited by Various Solutions, after Osato et al. [7]

	% inhibited		
	5% v/v	*10% v/v*	*≥15% v/v*
U.S. honey	33%	78%	100%
U.S. honey + catalase	33%	78%	100%
Manuka honey	60%	100%	100%
Manuka honey + catalase	60%	100%	100%
Glucose	Not reported	Not reported	100%
Fructose	Not reported	Not reported	100%
Glucose/fructose	Not reported	Not reported	100%

tion inhibited growth of all *H. pylori* isolates tested. Additionally, when catalase was added to the honeys concentrated >15% v/v, the honeys retained their ability to inhibit all *H. pylori* isolates; therefore, the anti–*Helicobacter pylori* activity was interpreted to be due to the osmotic effect, as opposed to hydrogen peroxide content. At the lowest concentration tested, 5% v/v, the Manuka honey inhibited 60% of the isolates tested, whereas the U.S. honeys inhibited only 33% of the *Helicobacter pylori* isolates tested. This difference was not statistically significant. The authors concluded that nonoxidant effects are important in bacterial killing, and that paramount among these effects is the osmotic effect. They also concluded that since 15% v/v honey was needed to inhibit all *Helicobacter pylori*, that honey would not be a feasible treatment for *Helicobacter pylori*, as it would probably not be possible to maintain this concentration at the gastric mucosa [7]. In fairness, they probably should have concluded that the Manuka honey deserved further investigation for its non-oxidant, non-osmotic killing property, due to the intriguing, if not statistically significant finding of differences in *H. pylori* inhibition at 5% v/v concentrations.

Finally, Booth suggested in a letter to the editor that if there is so much interest in the role of honey eradicating *Helicobacter pylori*, and *Helicobacter pylori* has been postulated to have a role in the pathogenesis of gastric lymphoma, that there should be interest in the use of honey as a possible cure for a form of gastric cancer [8].

BURNS

The use of alternative treatments for common ailments is particularly attractive in developing countries. Subrahmanyam has conducted a series of clinical trials on the use of honey and other alternative treatments for burn wounds in India. He compared honey to silver sulfadiazine in two randomized trials. The second trial differed from the first in that histological specimens were taken to corroborate clinical impressions. In the first trial, 104 patients with superficial burns < 40% total body surface area were randomized in two groups, to receive topical therapy with either silver sulfadiazine or unprocessed honey. The wounds treated with honey had earlier eradication of bacteria and shorter time to closure, with 45 of the 52 patients achieving wound closure by the fifteenth day as opposed to only five of the silver sulfadiazine-treated patients achieving wound closure by the fifteenth day [18]. Subrahmanyam revisited this subject in 1998, this time also obtaining histological specimens [19]. In addition to reporting the subjective benefits in the honey-treated burns, he also reported that 100% of the honey-treated wounds were closed by day 21 as opposed to only 84% of the conventionally treated burns ($p < 0.001$). The histological specimens essentially corroborated his clinical findings in terms of the presence of granulation, inflammation, and epithelialization. Additionally, in the silver sulfadiazine-treated group, four patients whose burns were assessed initially as superficial and not in need of operation, converted to full thickness and required excision and grafting. Subrahmanyam interpreted this as a bacteriological failure of silver sulfadiazine. He did not consider the possibility of a failure of randomization. In other papers, Subrahmanyam compared honey to potato peels [20], amniotic membranes [21], and OpSite® polyurethane film [22]; honey was superior in each study. However, honey is not always the answer. Subrahmanyam found in his most recent study that early excision and grafting, the modern standard of care, was superior to honey in the treatment of burns [23]. He performed a prospective, randomized trial with 25 patients in each arm, randomized to early excision and grafting or expectant management with topical unprocessed honey applied on alternate days, with delayed grafting after the separation of slough. The only advantage seen in the honey group was that they required less blood transfusion (21% of blood volume vs. 35% of blood volume). There were three deaths, all from sepsis, in the honey group versus one death, from status asthmaticus, in the excision group. Ninety-two percent of the excision patients had a good functional and cosmetic outcome, whereas only 55% of the honey-treated group had a good outcome.

EVIDENCE FOR THE ANTIMICROBIAL PROPERTIES OF HONEY

The text of this section is summarized in Table 3. In 1984 Obaseiki-Ebor and Afonya, from the University of Benin in Nigeria, reported on the anti-candidal effects of a distillate of honey *in vitro* [24,25]. They showed that 72 isolates of *Candida albicans* were all susceptible to the HY-1 fraction of honey distillate, whereas 10% of the isolates were variably resistant to nystatin, miconazole nitrate, or clotrimazole. Minimal inhibitory concentrations (MIC) were determined for this compound as well as for commercial antifungals as v/v%. The MIC $_{90}$ for HY-1 was 2 v/v%, as compared to mycostatin suspension with an MIC $_{90}$ of 0.5 v/v%. They did not elaborate on the chemical nature of the distillate or on the mechanism of action. They also did not comment on the osmotic activity of the solutions, but a 2 v/v% solution of a distillate of honey is not likely to have as great an osmotic effect as honey.

Willix et al. of the University of Waikato in New Zealand reported on the antibacterial activity of Manuka honey as opposed to other honeys [26]. They stated that the antibacterial effects of honey are due in large part to hydrogen peroxide derived from an enzymatic system intrinsic to unprocessed honeys. However, they cited a systematic review of commercially available honeys in New Zealand by Allen et al. [27], using an assay that controlled for the osmotic effects of honey and negated the effect of hydrogen peroxide by adding catalase to the assay. They found that the antibacterial effect of honey (tested against *Staphylococcus aureus*) varied widely among honeys, comparable to a range of between 2% and 58% w/v of phenol, in an almost Gaussian distribution. They proposed that an unidentified factor in a local honey, Manuka honey, was responsible for this effect. Descriptions of the chemical nature or proposed mechanism of action of this factor have not been published. Manuka honey is a variety of honey that comes only from New Zealand, from bees fed on the nectar of the Manuka bush, *Leptospermum scoparium*. Similar antibacterial activity has also been found in honey from bees fed on the nectar of *Leptospermum polygalifolium*, which is found in the wilds in Australia. Willix et al.

Table 3. Summary of Findings of Various Studies on the Antimicrobial Properties of Honey

Author	*Principal findings*
Obaseiki-Ebor et al. [24]	1. 72 isolates of *Candida albicans* were susceptible to the HY-1 fraction of honey distillate, whereas 10% were variably resistant to pharmacologic antifungals 2. MIC_{90} for HY-1 fraction 2 v/v%, MIC_{90} for mycostatin, 0.5 v/v%
Allen et al. [27]	1. Antibacterial effect of various honeys was comparable to phenol 2% to 58% w/v in a Gaussian distribution.
Cooper et al. [3]	1. Non-Manuka honey at 25% w/v, with catalase, had no antibacterial effect against *Staphylococcus aureus*. 2. Manuka honey at the same concentration, with catalase, had no loss of antibacterial activity. 3. Compared sugar solutions to honey a. Lowest concentration of sugar with antibacterial activity against *S. aureus* is 29% v/v b. MIC for Manuka honey 2–3 v/v% c. MIC for non-Manuka honey 3–4 v/v% d. Concluded that non-osmotic effect must be responsible for antibacterial effect.
Efem [28]	1. Tested honey vs. sugar solutions against clinical microbiology isolates 2. Honey effect *in vitro* against broad range of organisms, including fungi 3. Sugar effective only against *Streptococcus pyogenes*, but was not tested against anaerobes or fungi
Waldhan et al. [29]	1. Honey vs. sugar syrup against 21 bacteria and 2 fungi 2. At full strength, no difference in bacteriostatic effect, but honey more bactericidal 3. At lesser dilutions, honey more bacteriostatic and bactericidal at all concentrations.

MIC = minimal inhibitory concentrations.

tested Manuka and non-Manuka honey against a variety of wound-infecting species of bacteria. They found that the relative sensitivities of various organisms varied between the Manuka honey and other honeys, but that overall both types of honey can completely inhibit bacterial growth at concentrations below 11% v/v. Manuka honey, with catalase added to neutralize hydrogen peroxide, could still inhibit completely the growth of *Staphylococcus aureus* at a concentration of 1.8% v/v. The sugar content of the two honeys was the same, so they ascribed the different relative antibacterial effects of the honeys to a different, unknown activity in Manuka honey. Another comparison of Manuka and non-Manuka honey was undertaken in 1999 [2], this time against *Staphylococcus aureus* isolates from clinical wound infections, at various dilutions and with the addition of catalase to inactivate hydrogen peroxide. The non-Manuka honey at a 25% v/v dilution, in the presence of catalase, had no detectable antibacterial activity, whereas the Manuka honey under these conditions had no loss of antibacterial activity in the presence of catalase. The authors noted also that the lowest concentration of sugar that has antibacterial activity against *S. aureus* is 29% v/v, and that the MIC values for Manuka honey (2–3% v/v) and non-Manuka honey (3–4% v/v) are well below the concentration at which osmolarity could be credited with the antibacterial activity.

Efem addressed the question of the osmotic effect of honey in 1992 by testing *in vitro* the antibacterial effect of honey and the effect of a sugar syrup with physical properties similar to honey [28]. He used a wide variety of bacterial and fungal isolates from clinical infections (*Streptococcus pyogenes*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas spp.*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Clostridium welchii*, *Clostridium tetani*, *Clostridium oedematiens*) and incubated them on appropriate culture media with wells of the honey or sugar cut into the media. Zones of inhibition were measured. Honey was inhibitory against all bacteria tested except *Pseudomonas aeruginosa* and *Clostridium oedematiens*. The sugar syrup was ineffective against any of the bacteria tested, with the exception of moderate activity against *Streptococcus pyogenes* (the anaerobes were not tested against the sugar syrup). The fungi tested were all uniformly suppressed by honey at 100% concentration, but, when diluted to 50% and 20%, the honey lost efficacy against the fungi. The fungi were not tested with sugar solution.

In 1998, Wahdan et al. compared the antimicrobial activity of honey and a sugar syrup with the same sugar content as honey against 21 bacteria and 2 fungi [29]. They found that there was no difference in bacteriostatic activity between full-strength honey and sugar syrup, but that the honey was statistically significantly more bactericidal. At dilute concentrations, the honey was always more bactericidal and bacteriostatic. Because of these differences when concentration was controlled for, the authors invoked some other properties of honey as at least partially responsible for its antimicrobial activity. They also point out multiple references from the apiary literature describing "inhibines," which are suspected to be hydrogen peroxide and phenolic acids, among which caffeic and ferulic acids were identified in honey for the first time in their laboratory.

In conclusion, honey has been shown to be clinically useful in various settings involving soft tissue infections and non-healing wounds, and there appear to be some properties of honey that are controlling infection other than via the strictly osmotic effect. The caveat is that all of the data are generated from small studies, generally without rigorous statistical analysis. It is unlikely that the large studies with elaborate monitoring of protocol and professional statistical analysis will ever be done, as the expense of such studies is unlikely to ever be rewarded with the proceeds of honey sales to make such research financially feasible. The applicability of *in vitro* studies of antibacterial effects is unknown *in vivo*, but the clinical evidence suggests that honey may be useful in certain circumstances. Its use should be considered when more conventional therapies have failed. The usefulness in the management of *Helicobacter pylori* is less compelling, and in light of the other effective and safe treatments available, is probably not worth further investigation.

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