Honey

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Executive Summary

Honey is a carbohydrate-rich syrup produced by bees, primarily from floral nectars. Fructose and glucose are the major components but a large number of other chemical compounds are present in small quantities. Moisture content and water activity are low. The British Pharmacopeia (1993) provides a monograph for purified honey.

Four aspects of the composition of honey have been identified to contribute to its antibacterial activity. The low water activity inhibits microbial growth, particularly bacterial growth. Its low pH, a result of the formation of gluconic acid, also has a mild antibacterial effect. When diluted with water, hydrogen peroxide is formed by the action of the enzyme glucose oxidase. Finally, some honeys contain other compounds, largely uncharacterised, that have antimicrobial activity.

Antibacterial activity can be easily measured *in vitro*, by the use of established microbiological techniques, such as agar well diffusion assays. Studies using this, and other related techniques, have shown that antimicrobial activity varies widely according to the source of the honey, but that most honeys have significant activity against a range of pathogens. These pathogens include those commonly implicated in gastric and skin ulcers.

A number of studies have been carried out on animal models of wound and burn healing in which honey is used as a treatment. These studies compare the use of topical honey to other treatments including saline and silver sulfadiazine.

Honey has an extensive history of traditional human medicinal use, in a large number of societies. It may be used alone or in combination with other substances, and has been administered both orally and topically.

The few clinical trials of honey in human therapeutic use are summarised. These studies evaluated the use of honey to treat partial thickness burns to less than 40% of the body surface area and compared honey to other treatments such as sterile gauze, silver sulfadiazine, amniotic membrane and boiled potato skins. Honey compared favourably to these treatments, in terms of reducing healing time and in limiting infections during healing.

There are a considerable number of clinical reports of the use of honey to treat ulcers, burns, surgical wounds and gastric ulcers and as a carbohydrate source in oral rehydration therapy. Many of these studies showed beneficial effects of honey use.

As a widely consumed food, honey has a very long history of safe use, its low water activity protecting it from microbial spoilage. The majority of clinical reports of honey use indicate few if any adverse effects, the most common complaint being a burning sensation with topical application. ADRAC has no adverse reports associated with honey. Nevertheless there are three areas of potential safety risk associated with honey: toxic honey, allergy to honey, and infant botulism. Production of toxic honey is controlled largely through limiting honey production from areas where toxic honey has been produced in the past, and through blending different batches of honeys. Honey allergy is not common but is well recognised and can result in anaphylaxis. Allergy may be to both plant and bee proteins found in the honey. Infant botulism is a rare condition caused by contamination of honey with spores of *Clostridia*. Australian health authorities recommend that honey not be eaten by infants.

Assessment

Honey is a substance with a long history of traditional use as an active medicinal compound. In modern pharmaceutical practice it is widely used as an excipient ingredient and a monograph exists in the BP93 that adequately defines the substance and is already used by the TGA for this purpose.

The mechanism of antimicrobial action of honey is most likely a combination of a number of different factors. Its low water activity is likely to play a major role when honey is applied topically, but studies comparing its effect to sugar syrups of the same concentration have shown that honey has superior activity. Hydrogen peroxide is produced within honey by the action of the bee-derived enzyme glucose oxidase and has known antimicrobial activity. Chromatographic studies have shown that honey contains a wide range of compounds, many of which have not been identified. In some honeys such as manuka honey, removal of peroxide does not destroy all antimicrobial activity, suggesting that some other compounds in honey also play a role in inhibiting microbial growth.

There are many reports of the traditional medicinal use of honey in a large number of cultures. Both the Bible and the Koran recommend its use. It has been used in a wide range of conditions, including skin, eye, respiratory and gastrointestinal illnesses.

Animal studies have shown that topically-applied honey can be effective in accelerating wound healing and in controlling infection in wounds in some circumstances. The number of animal studies is small and several of these are poorly designed and have major inadequacies in result reporting. For example, authors generally do not indicate the severity of the wounds applied to test animals, making it difficult to extrapolate the findings to wounds observed in humans. Poor design and reporting limit the worth of two animal studies supplied in the application of the use of honey to treat experimentally-induced gastric ulcers.

Human clinical trials of honey use are scarce. One Indian researcher has conducted a number of trials of the use of topically-applied honey in patients (50 to 100 per trial) with partial thickness burns covering less than 40% of their body surface area. The trials compared honey to a range of modern and traditional remedies, with patients randomly assigned to treatments. Honey treatment was more effective than sterile gauze/film, silver sulfadiazine, potato skins and amniotic membrane, with more rapid healing, fewer infections and some evidence of reduced inflammation in healing tissue.

There are a considerable number of observations in the medical literature of the use of honey to treat human burns, ulcers and surgical wounds. Most of these reports are of honey's use in developing countries, where it provides major advantages in terms of its low cost and ease of use. Many of the wounds treated had already been treated conventionally with little success and within this context, honey was found to be an effective treatment in accelerating healing and reducing the incidence of infection. However one study of long-standing leg ulcers, predominantly varicose ulcers, found that honey had limited efficacy.

Incomplete information suggests that honey has the potential to be incorporated into products used for skin infections, gastrointestinal conditions, eye infections and to treat nappy rash. Only one study is provided to support the use of honey to treat gastric ulcers. This study is poorly designed and reported and little weight can be given to its findings, which claimed that

honey was an effective treatment in cases of moderate-severe ulceration. Similarly, the only study examining honey for opthalmic use is also poorly designed and of little use. There is no evidence presented to support the use of honey in nappy rash ointments, although the studies of honey and skin ulcers suggest that honey may be effective for the treatment of minor rashes.

This paper is an evaluation of the safety of honey for use in listable medicines. These medicines must only be used for minor, self-limiting conditions and promoted in accordance with the Therapeutic Goods Advertising Code. Ointment style products for the treatment of minor cuts and burns, and oral products for the relief of symptoms of indigestion are the types of products that would be acceptable as listable goods. If sponsors wished to produce goods to treat conditions such as varicose or gastric ulcers, Registration would be required and sponsors would be required to produce evidence of efficacy. The evidence presented in this paper would be insufficient to establish efficacy for uses such as gastric ulcer treatment.

Honey was incorporated into an oral rehydration solution and compared to the standard World Health Organisation (WHO) solution in the treatment of dehydrated infants. The honey solution was of comparable efficacy to the standard treatment. Oral rehydration products must undergo Registration and therefore any honey-containing products proposed for use would undergo thorough evaluation of efficacy and label claims. The evidence presented in this paper would be insufficient to establish efficacy or safety for oral rehydration products.

Oral rehydration products are generally targeted to infants and young children as these are two of the population groups most susceptible to the effects of dehydration. However honey has been known to induce infantile botulism as a result of the presence of spores of *Clostridia*. For this reason, honey is not recommended for use as a food for infants in Australia. Any listable goods containing honey and recommended for oral use should be required to carry a warning that they are not suitable for use by infants without medical supervision.

Allergy to honey is known to occur and can result in anaphylaxis, although such allergic reactions are not common. One source suggests that approximately 2% of people with food allergies may be allergic to honey. The allergenic components in honey may be derived from either bee or plant proteins. When presented as a food, honey is not required to carry a warning statement about allergenic potential. There is no evidence available in Australia to indicate that any therapeutic goods containing honey have caused severe allergic reactions.

Honey can contain toxic compounds when produced by bees foraging on toxic plants or on the poisonous nectar produced by some sap-sucking insects. Deaths from toxic honey consumption have been recorded throughout history. This problem is generally controlled by prohibiting honey production in certain areas and by blending different batches of honey to reduce concentrations of any particular toxins that may be present.

Conclusion

Honey is a substance suitable for use as an active ingredient in listable therapeutic goods in Australia. It is likely to find use in products such as ointments for the treatment of minor burns, cuts and skin infections. While it may be suitable for use in oral rehydration products

and to treat more severe burns and wounds, such treatment would require medical supervision and products for these uses would require Registration.

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1. Composition and production of honey

Honey is prepared by bees from plant nectars, from plant secretions and from excretions of plant sucking insects ("honeydew"). The Food Standards Code defines it as "the nectar and saccharine exudations of plants gathered, modified and stored by the honey bee". The British Pharmacopeia (1993) defines purified honey as being "obtained by purification of the honey from the comb of the bee, *Apis mellifera* L, and other species of *Apis*.

The chemical composition of honey varies depending on plant source, season and production methods. Storage conditions may also influence final composition, with the proportion of disaccharides increasing over time (White et al 1960). Fructose (approximately 38% w/w) and glucose (~31%) are the two major sugars present in honey, with lesser amounts of sucrose (~1%), other disaccharides and oligosaccharides. Gluconic acid, other acids and small amounts of proteins, enzymes (including glucose oxidase), amino acids and minerals may also be present. Potassium is the major mineral present. Honey is mildly acidic with a pH around 3.9. Moisture content is low (~17%), as is water activity (0.562 – 0.62) (White 1975).

The British Pharmacopeia (BP) 1993 includes a monograph for purified honey although this monograph is omitted from the 1998 BP. The 1993 monograph describes the production and physical characteristics of honey and establishes limits for chlorides, sulphates and ash. Limits for density and optical rotation are also specified. It does not establish any honey-specific limits for microbial contamination, heavy metal content or residues of agricultural chemicals. As for all food-derived substances, however, contaminants may be present in honey. The Food Standards Code establishes a maximum level of 0.01 mg/kg for the agricultural chemical phosphine but does not establish any other specific compositional or contaminant requirements for honey when used in foods.

2. Antimicrobial activity of honey

2.1 Mechanism of action

Honey has been demonstrated in many studies to have antibacterial effects, attributed to its high osmolarity, low pH, hydrogen peroxide content and content of other, uncharacterised compounds.

The low water activity of honey is inhibitory to the growth of the majority of bacteria, and to many yeasts and moulds. When applied topically to wounds, osmosis would be expected to draw water from the wound into the honey, helping to dry the infected tissue and reduce bacterial growth. Even when diluted with water absorbed from wounds, honeys would be likely to retain a water activity sufficiently low to inhibit growth of most bacteria. *Staphylococcus aureus* is one bacterium that is tolerant of low water activities, being observed to grow when water activity is as low as 0.86. It has been found to survive treatment on infected skin treated with concentrated solutions of pure sugars, but to be sensitive to the other antibacterial components of honey of the same water activity (Molan 1995). Honey's low water activity is not the only explanation for its antimicrobial activity. Some studies, summarised in Molan (1992), have studied sugar syrups of the same water activity as honey and found them to be less effective than honey at inhibiting microbial growth *in vitro*.

Honey is mildly acidic, with a pH between 3.2 and 4.5. Gluconic acid is formed in honey when bees secrete the enzyme glucose oxidase, which catalyses the oxidation of glucose to gluconic acid. The low pH alone is inhibitory to many pathogenic bacteria and, in topical applications at least, could be sufficient to exert an inhibitory effect. When consumed orally, the honey would be so diluted by body fluids that any effect of low pH is likely to be lost (Molan 1995).

Hydrogen peroxide was identified as the major source of antibacterial activity in honey in 1963 by White, Hubers & Schepartz. Hydrogen peroxide is produced by the action of glucose oxidase on glucose, also producing gluconic acid. Glucose oxidase operates most effectively when honey is diluted. When honey is undiluted, the gluconic acid produced lowers the pH to a point where it inhibits further enzymic activity, and hence further peroxide production. Excessive heat (>50^{o}C) may also reduce glucose oxidase activity (White & Subers 1964).

There are a range of other, largely uncharacterised, substances present in some honeys that have antibacterial effects. Some compounds that have been identified include syringic acid (3.5-dimethoxy-4-hydroxybenzoic acid), methyl syringate, 3,4,5-trimethoxybenzoic acid, 2-hydroxy-3-phenylpropionic acid and the flavonoid pinocembrin. Wootton et al, in 1977, identified a range of volatile substances in Australian honeys although their report does not note whether or not these substances are believed to contribute to honey's antibacterial activity. Volatiles identified included acetoin, acetone, acetic acid, furfural, valeric acid, ethyl salicylate, benzyl alcohol and hydroxymethylfurfural. Tan et al (1989) demonstrated by gas chromatography that manuka honey contained an array of acidic and phenolic substances, the most dominant being 2-hydroxy-3-phenylpropionic acid.

2.2 Measurement of antmicrobial activity

The antimicrobial activity of honey has been measured most commonly by the use of agar well diffusion techniques. This technique takes large plates of agar mixed with cultures of particular bacteria, *Staphylococcus aureus* being the most commonly used. Wells are cut into the agar and solutions of the test material applied. Solutions of varying concentrations of known antibacterial agents, commonly phenol, can be used for comparison. The diameter of the zone of bacterial growth inhibition is measured after incubation of the plates.

2.3 In vitro studies of antimicrobial activity

Allen, Molan & Reid (1991) conducted a major study of the antibacterial activity of New Zealand honeys, categorised according to their floral source. The mean antibacterial activity of undiluted honey was found to be equivalent to a 14% solution of phenol in water. There was a tremendous range of activities observed, however, depending on the floral source. Some honeys had no detectable antibacterial activity, while others had activities up to the equivalent of 42% phenol. For most honeys tested, destruction of peroxide-generating ability by the use of catalase was associated with loss of antibacterial activity. Honey derived from manuka (*Leptospermum scoparium*) and vipers bugloss (*Echium vulgare*) were the only honeys tested that retained significant antibacterial activity.

Further *in vitro* research on manuka honey by the same group of NZ workers (Willix et al 1992) highlighted the pathogen-specific effects of different types of honey. Different concentrations of honeys were incubated aerobically with a range of pathogens to determine the minimum concentration required for 100% growth inhibition over an 8 hour period at 37^{o}C. For some pathogens (eg *S. aureus*, *E.coli*), manuka honey was considerably more

effective at inhibiting growth than other honeys. Complete inhibition of growth of *S. aureus* was achieved at a manuka honey concentration of 1.8% v/v compared to 4.9% for other honeys. The opposite finding was observed for complete inhibition of *Proteus mirabilis*, where a concentration of 7.3% v/v manuka honey was required, compared to 3.3% for other honeys. Despite the differences observed with different pathogens and honey types, the study demonstrated that a range of honeys have bacteriostatic effects at concentrations likely to be achieved when honey is applied topically to wounds.

The same group of researchers has also studied the inhibitory action, *in vitro*, of manuka honey against *Helicobacter pylori*, the bacterium believed causative of human gastric ulcers. Using techniques described previously, Somal et al (1994) found that the growth of a range of isolates of *H. pylori* was inhibited by a 5% v/v concentration of manuka honey. Ali et al (1991) also studied *in vitro* inhibition of *H. pylori* growth in the presence of honey of unstated origin. They found that a honey concentration of 20% was sufficient to inhibit growth of a range of clinical isolates.

The antibacterial effect of a number of Sudanese honeys was studied by Farouk et al (1988) and compared to that of five antibiotics (30 µg/mL) – ampicillin, cephradine, chloramphenicol, gentamicin and oxytetracycline. Undiluted honey (0.2 mL) was tested against the pathogens *Bacillus subtilis, S. aureus, E. coli, Klebsiella aerogenes* and *Pseudomonas aeruginosa*. All honeys tested were inhibitory against all these bacteria but gentamicin was the only antibiotic effective against *P.aeruginosa*. The other antibiotics were more effective at inhibiting bacterial growth than were the honeys, measured in terms of the zone of inhibition on agar plates. For example, antibiotics had a zone of inhibition against *B. subtilis* of 16.8 – 26.5 mm compared to a range of 14.7 – 19.0 mm for honeys.

Enteropathogens common in Nigeria were tested for *in vitro* sensitivity to honey in research by Obi et al (1994). Filter paper disks impregnated with honey of varying concentrations were placed on agar plates innoculated with clinically-isolated strains of a range of pathogens including *Salmonella typhi, Vibrio cholerae* and *Yersinia enterocolitica*. The diameter of the zone of inhibition was measured. Honey concentrations of 40% and above reduced bacterial growth, with undiluted honey having the greatest effect. Concentrations of 30% and lower did not inhibit pathogen growth.

Fungi also show some susceptibility to honeys, demonstrated *in vitro* by the NZ researchers Brady, Molan & Harfoot (1996). These researchers studied the concentrations of manuka honey and another non-manuka honey required to inhibit the growth, in agar, of a range of clinical isolates of fungi responsible for tinea. The non-manuka honey concentration required to inhibit fungal growth around agar wells ranged from 5 - 20% v/v. For manuka honey, concentrations of 10 – 50% v/v were required to inhibit growth, concentrations substantially higher than those found to inhibit bacterial growth. Fungi tend to be more tolerant of low water activities than the majority of bacteria.

3. Efficacy studies - animals

3.1 Animal studies of honey and surface wound healing

Twenty-four male mice underwent skin excision (10x10 mm) from the nape of the neck, to the depth immediately above the first layer of muscle, in a study by Bergman et al (1983). Half the animals had pure honey applied in a thin layer to the wounds, twice daily, while the control group had saline applied at the same frequency and time of day. Four animals from

each group were killed at 3, 6 and 9 days after wounding and the damaged tissue excised completely. Depth and quality of granulation tissue was determined microscopically and the degree of epithelisation measured as the distance from the skin border to the wound centre. The honey-treated tissue underwent more rapid and more extensive epithelisation than did the saline-treated control. After 3 days, the honey-treated tissue had 58% more skin growth ($P<0.001$), after 6 days it had 114% more ($P<0.001$) and after 9 days, 12% more ($P<0.01$) than the controls. Honey-treated mice had a greater thickness of granulation tissue in the centre of the wounds ($P<0.001$) compared to the control mice. No bacterial infections were detected in any of the wounds, which may reflect hygienic standards in the original surgical procedure. This experimental model therefore may not be representative of wound healing in infected tissue.

Several papers by Egyptian and Indian researchers, have claimed that orally-administered honey was more effective in treating surface wounds than was topically-applied honey (Suguna et al 1992 and 1993, El-Banby et al 1989, Kandil et al 1987). These studies all used rats given surgical wounds. The studies suffer from several major defects in design, reducing their worth. Nevertheless they are mentioned for the sake of completeness due to the consistent outcomes reported, although these outcomes would appear to be unexpected. Wounds applied were either excision of a 4 cm^2 area of skin (Suguna et al 1992 and 1993) or by making a 10 mm incision (Kandil et al 1987, El-Banby et al 1989). None of these studies reported the depth of the wounds although the studies of excised skin reported the excision to be "full thickness of skin". The excised skin studies used only 6 rats per group. Kandil et al (1987) did not report the number of rats in each group and did not present a statistical analysis of the results. El-Banby et al (1989) used a slightly larger group of rats (10) and presented some statistical analyses of results. The amount of honey administered orally was small in each study (0.5 – 1.0 mL per day, to rats weighing 125 – 150 g) and concurrent feeding practices were not described. The same amount of honey was used for topical treatment.

Gupta et al (1992) studied the effect of topical natural honey on the healing of infected skin wounds in buffalo calves, and compared this effectiveness to that of ampicillin ointment, and ampicillin mixed with honey. Although this study was of a superior design to those of Suguna et al (1992 and 1993), El-Banby et al (1989) and Kandil et al (1987), with wound production being well-defined, a large number of wounds being studied (90) and histological observation being undertaken, the report suffers from a major defect in that no tabulated results are provided. The authors present only three photographs as evidence in support of their conclusions. The authors claim that honey was significantly more effective than ampicillin (2.5% ampicillin sodium in petroleum jelly) or 2.5% ampicillin sodium in honey in accelerating wound healing. The amount of ointments applied was not stated. The authors report that honey-treated wounds showed less neutrophilic infiltration and more formation of angioblasts and fibroblasts. Without presentation of numerical results it is difficult to assign much weight to this paper, beyond the anecdotal.

Deep skin burns were applied in twelve places on the flanks of three pigs in a study by Postmes et al (1996) that compared the efficacy of honey to sugar solutions, both of very similar carbohydrate composition and concentration, and silver sulfadiazine (1% cream) in healing burn tissue. Burn tissue was examined histologically on days 7, 14, 21, 28, 35 and 42 post-burn. Honey and sugar both produced more rapid healing than did silver sulfadiazine, with wounds closing within 21 days for honey and sugar, but requiring 28-35 days for silver sulfadiazine. Burns treated with sugar solution produced thicker new skin (mean 7.1 mm

after 28 days), with evidence of inflammation, than was found on the burns treated with honey, which showed little inflammation (mean dermal thickness after 28 days: 5.1 mm). The mechanism by which honey produced a more rapid and effective healing than either sugar or silver sulfadiazine was not identified, although tissue treated with sugar showed more myofibroblasts than did the honey-treated tissue.

3.2 Honey and gastric ulcers

Oral administration of honey significantly accelerated the healing of indomethacin-induced gastric ulcers in rats, in a study by Ali (1994). The effect of honey, administered twice daily at a rate of 312 mg/kg, was comparable to that of the drug sucralfate (500 mg/kg) administered with the same frequency, and both treatments were more effective than no treatment. The dose of sucralfate used in this study was far in excess of that recommended for human use. Forty rats were included in each treatment group. The healing effect of honey was measured in terms of the severity of dissected lesions, extent of diarrhoea, and weight loss over time. The author speculated that the healing effect of honey in this study may be due to five factors: its viscosity, so that it provides a protective covering over the affected area; its hygroscopic properties enabling it to absorb oedema fluids; promotion of the formation of granulation tissue; antibacterial activity; and the presence of enzymes such as catalase.

Acetyl salicylic acid (50 mg/kg body weight) was used to induce gastric ulcers in 60 rats in a study by Kandil et al (1987b). Twenty four hours after administration of acetyl salicylic acid, 0.5 mL of either floral honey, honey produced by bees feeding on sugar, or saline was administered to each rat for 3 days. The dose of test substance would be approximately equal to 4 g/kg bodyweight. Rats were then sacrificed and the number of gastric ulcers estimated. 80% of rats consuming floral honey were classed as healed, compared to only 47% of rats consuming sugar honey. This study had some major deficiencies, such as failure to describe the effect of honey consumption on other food intake, the absence of a definition of "healed" and poor data reporting (eg the results reporting only the number of ulcers rather than the size of ulcers).

4. Efficacy studies - human

4.1 Traditional medicinal uses

Honey has a long history of use as a medicinal substance. It was used by the ancient Greeks and Sumerians (Molan 1995). In ancient Egypt it was used as a wound treatment, mixed with grease and fibre, and for gut conditions. Hippocrates recommended honey and vinegar for pain, water and honey for thirst and a mixture of honey, water and other substances to treat acute fevers, as well as recommending its use to treat ulcers (Beck & Smedley 1944, Zumla & Lulat 1989). Its use is referred to in the Koran, which specifically refers to its role in treating diarrhoea (Kandil et al 1987, Salem 1981). The Bible mentions the use of honey in eye problems (Beck & Smedley 1944). In Ayurvedic medicine, honey is described as the nectar of life and its use is recommended for various conditions (Subrahmanyam 1996). Russian soldiers in World War 1 used it, apparently successfully, for wound healing purposes (Bergman et al 1983). Honey, lime leaves and palm kernel are traditional medicines for wound healing in Ghana (Ankra-Badu 1992) and among the Bambara of Mali, honey is a traditional treatment for measles, both via the oral route and as an eye ointment (Imperato and Traore 1969).

Beck & Smedley summarised the traditional uses of honey as follows: "… its main employment was as a helpful remedy for gastric and intestinal disorders, especially as a pleasant laxative. Respiratory troubles were next in order. The sedative and soporific power of honey is often emphasized. The diuretic effect of honey was well known and it was a favoured remedy for all kinds of inflammation of the kidneys, for gravel and for stones. The antiseptic property of honey made it a desirable gargle, expectorant and a valuable adjunct in mouth hygiene. In inflammation of the eyes and eyelids honey was extensively used. In surgical dressings and skin diseases it was a remedy of first choice. The smallpox patients were anointed with honey. It was also employed as a vehicle for nauseous or bitter medicines."

4.2 Clinical trials - wound healing

The Indian researcher Subrahmanyam conducted a number of studies of the topical use of honey to treat burns. In all studies, patients had partial thickness burns to less than 40% of their body surface area. In 1991, he reported on a trial comparing honey with silver sulfadiazine (SSD) with a total of 104 patients randomly allocated to receive one of the two treatments. After the burns were washed with saline, half the patients were treated with 15 – 30 mL honey spread over the wound each day, the amount applied depending on the size of the burn. The burn was then covered with dry, sterile gauze. Remaining patients were treated with gauze impregnated with SSD, the gauze being replaced daily. Age, sex and injury characteristics of both groups were similar. Among patients treated with honey, healthy granulation tissue appeared at a mean of 7.4 days, compared to 13.4 days for SSD patients. Wounds healed more rapidly in the honey group (33/52 patients within 10 days and all within 40 days) compared to the SSD group (35/52 patients within 30 days and all within 60 days). Four honey-treated patients showed infection at the burn site after 7 days of treatment, compared to 38 of the SSD patients.

In 1998 Subrahmanyam reported another study comparing topical honey with topical SSD in the treatment of burns. After saline washing within 6 hours of the burn occurring, 50 patients received either 16-30 mL unprocessed honey every 2 days or a covering of gauze impregnated with SSD, replaced daily. Characteristics of the treatment groups did not differ substantially and patients had a mean burn area of 15% of the body surface. Satisfactory epithelisation was achieved within 7 days in 84% for honey-treated patients and within 10 days for all, compared to 72% and 84% respectively for SSD. Histological examination of tissue showed that the honey-treated tissue underwent earlier subsidence of acute inflammation.

In 1993, Subrahmanyam reported a comparison of the use of topical honey to that of sterile, moisture permeable polyurethane film (OpSite). Trial participants were treated in hospital within 6 hours of the occurrence of the burn. Burns were washed with normal saline and then patients were randomly allocated to receive treatment with either OpSite (the control group) or sterile gauze impregnated with untreated honey. In both groups, cultures were taken from the wound surface on admission, day 8 and day 21 and the time required for complete healing was noted. The author did not compare the characteristics of the two groups, however, so it is unclear whether patients were age-matched and had burns of comparable severity. Wounds healed more rapidly in the patients treated with honey (mean healing time 10.8 days) compared to the control group (15.3 days) ($P<0.001$). Fewer burns became infected in the honey treated group (8 vs 17 patients).

The same author (Subrahmanyam 1996) conducted a similar trial comparing honey to boiled potato peel for the treatment of partial thickness burns. According to the author, potato peels are commonly used as burn dressings in developing countries. Fifty patients were randomly allocated to each treatment group, within 6 hours of the occurrence of the burn and after washing the burn with normal saline. Depending on the burn size, between 15 – 30 mL honey was applied every 2 days and the wound covered with sterile dry gauze. All wounds were observed until healing was complete. The characteristics of the two groups were reported and did not differ substantially in age, mechanism of injury or burn area. Burns healed more quickly in the honey-treated group (mean 10.4 days vs 16.2 days) ($P<0.001$) and granulation tissue appeared sooner (mean 6.8 days vs 9.2 days). Among honey-treated patients, only 4 had pathogens in the wound after 7 days compared to 42 in the potato peel group.

Amniotic membrane, prepared from fresh caesarian or vaginal deliveries, was used in another of Subrahmanyam's trials of the use of topical honey to treat partial thickness burns. Sixty four patients were randomised to receive either honey-impregnated gauze every 2 days until healed (40 patients), or to have their burn covered with amniotic membrane (24 patients). Patient characteristics were similar in the two groups. The burns treated with honey healed faster compared to those treated with amniotic membrane (9.4 vs 17.5 days, $P<0.001$) with less scarring (8% vs 17%, $P<0.001$).

4.3 Clinical observations - wound healing

There have been a number of reports on the clinical use of honey to treat skin wounds. These studies are not double-blinded, placebo-controlled studies. Nevertheless they provide an overview of the ways in which honey has been used successfully in humans. Much of this work has been conducted in developing countries, where the low cost of honey treatment is a major incentive for its use.

Topical application of honey has been used successfully to treat infected wounds resulting from radical vulvectomy due to carcinoma of the vulva. Cavanagh et al (1970) used household honey (floral source not stated) in 12 patients who developed infected wounds following surgery. Undiluted honey was poured into the wound twice daily and the wound covered loosely with gauze. Wound cultures were taken from the wound at time of tissue breakdown, and at subsequent time intervals. Contaminating bacteria included *Proteus mirabilis, Pseudomonas aeruginosa, Escherichia coli, Enterobacter* species, *Streptococcus faecalis, Staphylococcus aureas* and *Clostridium perfringens*. All wounds were found to be free of bacteria within 3 to 6 days of treatment. Complete healing occurred within 8 weeks for all patients, and within 3 weeks for one patient. While the study did not use control patients for comparison purposes, the author notes that the wound from radical vulvectomy is known to present problems with healing, often requiring skin grafts. Two adverse effects were noted with this treatment. Infection with the yeast *Candida* near the edge of the wounds, where the concentration of honey was reduced, was noted in 3 patients. Excessive use of honey overly-dehydrated the wounds, which could be remedied by the use of saline packs at night.

In two African studies honey was used successfully to treat ulcers and wounds (Efem 1988) and Fournier's gangrene (gangrene of the scrotal area) (Efem 1993). In the first of these studies, 59 patients (47 male, 12 female, aged 2 months to 78 years) with various wounds and ulcers (including Fournier's gangrene, burns, tropical, diabetic and traumatic ulcers, cancrum oris, cancerous sores and bed sores) were treated with topical honey application. Most of the

patients' ulcers and wounds had failed to respond adequately to conventional treatment including antibiotics in some cases. With one exception, all non-cancerous ulcers responded to a treatment regime of washing with saline and the topical application of 15-30 mL honey daily. Pathogens isolated at the commencement of the study included *Pseudomonas pyocyanea* (35 cases), *Escherichia coli* (31), *Staphylococcus aureus* (15), *Proteus mirabilis* (9), coliforms (9), *Klebsiella* species (7), *Streptococcus faecalis* (3) and *Streptococcus pyogenes* (1). In all successful cases, no pathogens were detected when cultures were taken after 1 week of treatment. In the case of the non-responding patient, *Mycobacterium ulcerans* was isolated from the wound and intravenous antibiotic therapy commenced. Patients with malignant ulcers underwent surgical treatment once a diagnosis of malignancy was reached. In the study of Fournier's gangrene (Efem 1993), 20 cases treated with topical honey (15 – 30 mL, dose frequency not stated) combined with oral amoxicillin and metronidazole, were compared to 21 cases who underwent surgical management of the infection together with various oral antibiotics. Patients were not matched for age or for other complicating conditions, therefore reducing the value of the study but nevertheless providing interesting results. Both groups of patients had comparable hospitalisation times, but three of the group treated surgically died, with no deaths in the honey group.

Honey was reported (Phuapradit & Saropala 1992) to be successful in aiding the healing of abdominal wounds that had broken down following caesarian section. Honey was applied daily in a thin layer (amount not specified) and the wounds taped with micropore tape. The paper was published in the *Australia NZ Journal of Obstetrics & Gynaecology*, with an editorial comment indicating a number of flaws with the study, but suggesting nevertheless that topical honey application may have occasional uses in treating caesarian wounds.

Thirty three Burundian patients with wounds of diverse origin were treated by daily topical honey application (Ndayisaba et al 1993). The wounds were first washed with saline on day 1 and then covered with a dry sterile dressing. The initial mean wound size in these patients was 57 cm^2 and healing was successful within 5 – 6 weeks in 29 cases. Where necessary, additional treatments such as the removal of necrotic tissue were administered. Burns were reported to respond more rapidly to honey treatment than did infected wounds, although data were not provided to support this claim.

A Sudanese study of the use of topical honey in 11 wound patients found that honey applied daily to cleaned wounds (amount applied stated as 'generous') was an effective treatment in all but one case (Farouk et al 1988). Application of honey to large septic wounds was reported to be commonplace in Kenyan bush hospitals in the 1970s by Branicki (1981), who reports "the application of undiluted honey in a thin layer 2 – 3 times daily gave excellent results. Honey rendered the wounds bacteriologically sterile in 3 – 6 days and encouraged the formation of healthy granulations. Before application any pockets of pus present were drained." Armon (1980) presented two case reports of the successful use of topical honey to treat large abscesses in African patients.

In contrast to these African studies, a recent small (10 patients, 11 ulcers) NZ trial of honey in the treatment of leg ulcers provided equivocal results. Patients (median age 61.5 years) with predominantly varicose ulcers of duration approximately one year, and average ulcer size of 9 cm^2, had honey applied once daily for 8 weeks. The ulcers were covered with gauze after honey was applied. There was little change in the bacterial flora other than a slight reduction in coliforms (not quantified in the paper). Four ulcers showed healing over more

than 25% of their surface area, six ulcers did not change and one worsened. Two patients withdrew after 5 weeks due to the presence of infections (Wood et al 1997).

4.4 Clinical observations - gastrointestinal conditions

Two tablespoons of honey (30 mL) given before meals three times daily was used to treat male and female patients (20 – 40 years) suffering from gastritis, duodenitis and duodenal ulcers. The study, by Salem (1985) was poorly designed and reported and of little value beyond the anecdotal. Although a placebo was used (composition not stated), there was no comparison of results between the two groups. The author claimed that two-thirds of patients recovered following treatment, that the haemoglobin levels of most patients increased and that faecal blood loss decreased. Salem also notes that he has used honey in the form of enemas to treat ulcerative proctitis.

4.5 Use in oral rehydration products

Oral rehydration products are widely used to treat acute diarrhoea, typically in infants and young children. They are mixtures of sugars, typically glucose, and electrolytes, in concentrations designed to promote movement of water across the gastrointestinal tract into the body, to balance fluid and electrolyte losses. Haffejee and Moosa (1985) prepared an oral rehydration solution using honey as the carbohydrate source, and compared it to the standard WHO oral rehydration mixture (glucose, sodium, potassium, chloride) prepared with the same electrolyte concentration. Children aged 8 days to 11 years (total patients=169), suffering from gastroenteritis, were studied under close medical supervision. Children were assigned to one of the two study groups, those receiving the WHO solution being somwhat older (mean age 19 months vs 14 months for the honey group). Where possible, the cause of the gastroenteritis was identified. Mean recovery time (64 hours) was comparable for both groups of patients. When only patients with bacterial gastroenteritis were considered (36 patients), those receiving honey recovered more quickly (58 vs 93 hours, $P<0.05$). No other differences in indicators of recovery were noted between the two groups.

4.6 Use in opthalmic conditions

Anecdotal evidence is provided by Emarah (1985) about the use of honey, topically applied, to treat a range of opthalmic conditions in Egypt. Conditions treated included chronic, non-specific conjunctivitis and persistent blepharitis. Honey was applied directly to the damaged tissue, 2 to 3 times daily. No patients worsened following treatment, and the majority of patients improved. The paucity of objective data provided in this paper (eg quantities of honey used, objective measures of improvement, details of patients participating in the trial and the use of concurrent treatments) limits its usefulness.

5. Safety of honey

5.1 Food use

Honey has a very long history of low-risk food use. It is often consumed alone, as a spread, or may be mixed with a wide range of other foods. Daily intake as a food could easily reach 100 g in some individuals, a dose far higher than is likely to be achieved when honey is consumed in therapeutic forms.

5.2 Current Australian therapeutic goods

There are over 300 products in the ARTG that contain honey, predominantly as an excipient. Some grandfathered goods contain honey as an active ingredient. However ADRAC does not contain any reports of adverse reactions associated with these products.

5.3 Reactions following topical use

Efem's African studies (1988 and 1993) of the treatment of serious ulcers with daily application of honey, did not reveal any allergies or other adverse effects over the several weeks of treatment. Phuapradit & Saropala's 1992 report of the use of honey in abdominal wounds found no adverse effects, including allergies. Subrahmanyam, in his 1991, 1993 and 1996 studies reported no adverse effects, such as allergies, from the use of honey. Ndayisaba et al (1993) studied the topical use of honey in 40 patients with major wounds. In one case, a patient discontinued treatment due to a burning sensation on application of the honey. These authors note that several others have reported occasional patient complaints about burn-type pain. Wood et al (1997) reported that some patients with leg ulcers experienced a burning sensation when honey was applied. This presented a significant problem for 3/10 of the participants in this small trial and necessitated the withdrawal of one patient. Emarah (1985) reports that when honey was used to treat eye conditions, patients experienced transient stinging and redness of the eye, which was not severe enough to warrant cessation of the treatment. No reasons for the burning sensations were reported by the authors of these reports.

5.4 Honey allergy

While apparently uncommon, allergies to honey have been reported and can involve reactions varying from cough to anaphylaxis (Kiistala et al 1995). The incidence of honey allergy was reported (in Bauer et al 1996) to be 2.3% of a group of 173 patients with food allergies. Among patients with confirmed honey allergy, 17% had suffered anaphylaxis and 30% asthma (Bauer et al 1996). Bauer et al (1996) report that the proteins responsible for honey allergy are derived from proteins secreted by bees and from proteins derived from plant pollens. Individuals with inhalational allergies to particular plants (eg members of the Compositae family) may sometimes demonstrate allergies to honeys produced by bees foraging on these plants (Bousquet et al 1984, Hebling et al 1992).

Kiistala et al (1995) studied 8 commercially available honeys in Finland and found, by RAST inhibition and immunospot methods, evidence of both pollen and insect allergens. They then challenged 46 pollen-allergic patients (mean age 25 years) with 30 g honey, and 32 patients with a placebo syrup. Minor symptoms were reported by 26% of those receiving honey and by 41% of those receiving the placebo. Symptoms reported included itching in the throat, nose, eyelid and skin, feeling of oedema in the throat or lips, runny nose, headache and redness of the skin. The pattern of symptom distribution was similar between both groups. Although all participants had a history of atopy, including rhinitis and asthma, none had a history of bee or wasp venom allergies.

5.5 Toxins in honey

Plant toxins may in some cases be transferred to honey produced from their nectar. Honeys produced by bees feeding on flowers of the Ericaceae and Solanaceae families are known to have caused toxicity (White 1975, Palmer-Jones 1965), as have those produced from tansy ragwort (*Senecio jacobaea* L.) (Deiner et al 1977). Patterson's Curse has been reported to produce toxins in Australian honeys. Deaths from the ingestion of large quantities of honey derived from *Rhododendron* species have been reported in the Caucasus region, and deaths were reported among Maori and settlers on the NZ North Island (Palmer-Jones 1965). Non-fatal poisoning was widespread in NZ until the 1920s, when honey production in the North Island was stopped. The source of poisoning was identified as being a combination of the plant *Coriaria arborea* (tutu) and the production of honey dew from the passion vine hopper

(*Scolypopa australis)*. Some areas of the North Island have now been closed to honey production and in other areas of NZ beekeepers are advised not to collect honey at certain times of the year when vine hoppers are prevalent (Palmer-Jones 1965). Palmer-Jones also identified a range of other plants that have been implicated in the production of toxic honeys – *Kalmia latifolia, Tripetalia paniculata, Ledum palustre*.

Symptoms of honey poisoning vary depending on the toxin, but include dizziness, nausea, vomiting, convulsions, headache, palpitations and deaths in some cases. Toxins identified include hyenanchin (in the case of the NZ poisonings), euphorbic acid, acetylandromedol and ericolin (Palmer-Jones 1965). These toxins are apparently heat resistant. In the NZ poisoning cases, as little as 5 – 10 g could cause severe poisoning in humans.

5.6 Infantile botulism

Infantile botulism is a rare form of food poisoning caused by ingestions of spores of the bacterium *Clostridium botulinum*. It occurs only in infants less than 12 months of age, with 95% of cases found in the first 6 months of life (Vanderbilt Medical Centre 1998). Honey appears to be one commonly-implicated dietary source of *Clostridium* spores. The condition is rare and only affects infants. Because of the severity of the illness, Australian health authorities recommend that infants do not ingest honey.

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