REVIEW ARTICLE

Mechanisms of action of manuka honey in an equine model of second intention wound healing: current thoughts and future directions

Authors

Albert S Tsang, Andrew J Dart, Christina M Dart, Leo Jeffcott

Affiliation:
Research and Clinical Trials Unit, University Veterinary Teaching Hospital Camden, University of Sydney, 410 Werombi Road, Camden, New South Wales, 2570, Australia

Correspondence:
Andrew Dart, Research and Clinical Trials Unit, University Veterinary Teaching Hospital Camden, University of Sydney, 410 Werombi Road, Camden, New South Wales, 2570, Australia
Email: andrew.dart@sydney.edu.au
Phone: +61 293511743

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Abstract

Honey has been utilized for the treatment of wounds by ancient civilizations for millennia. In recent times, there has been renewed interest in the use of honey in the treatment of chronic wounds and burns in response to the increased development of antimicrobial resistance to antibiotics. The physical properties of honey enhance wound healing by increasing the release of oxygen from hemoglobin, inactivating bacterial proteases and drawing fluid out of the wound bed initiating autolytic debridement. Honey also has broad spectrum antimicrobial activity. Peroxide or non-peroxide bactericidal activity is derived from phytochemicals drawn from specific plant species. Of the honey varietals, manuka honey, from the manuka tree (*Leptospermum scoparium*) is the most widely studied for its non-peroxide antimicrobial properties and ability to improve wound healing. This review summarizes the known mechanisms of action of manuka honey and the results of 4 experimental studies performed by the authors using an equine model of second intention healing. In addition, the future direction of research investigating the use of different varietals of honey as a therapeutic agent to enhance wound healing is explored.

Key-words: Honey, manuka honey, wounds, second intention healing, horse, equine, wound healing

1. Introduction

Honey has been used for medicinal purposes by the ancient Egyptians, Greeks and Chinese.[1-3] Historical uses of honey include gastrointestinal ailments, pain relief and treatment of infections.[4] However, its most common use was to promote wound healing and for this purpose it was often combined with other substances such as animal fats and lint.[2] However, the use of honey to treat wounds fell out of favour shortly after World War I with the development of modern antimicrobial agents.[5-7]

Recently, with the emergence of antimicrobial resistance in many clinically relevant bacterial species, there has been renewed interest in the medicinal properties of different types of honey.[7,8] The vast majority of recent research has focused on the antimicrobial properties of honey, however, there is a growing body of research that suggests many honey varietals have other mechanisms of action that modulate the process of wound healing.[9-11] Variability in the concentrations and profile of the bioactive components of different honey varietals suggest that different types of honey have varying medicinal properties, or in other words, all honeys do not behave equally.[12-16]

Whilst there are over 300 types of honey found around the world, the majority of studies have been performed on manuka honey which is produced from the manuka tree (*Leptospermum scoparium*) found in New Zealand.[17] The *Leptospermum* species of plants are predominately found in Australia and New Zealand and total approximately 83 different species.[2] Honey derived from the manuka tree has been found to display superior antimicrobial activity compared to many other honey varietals.[12,18] As a result, the increasing public awareness of its health benefits, has seen the cost of raw manuka honey increase 10-fold over the past 20 years.[19]

Wounds in the distal limb of horses occur frequently and are characterized by contamination, excessive skin tension and tissue avulsion that often precludes primary closure.[20] There is often involvement of the underlying bone, tendons and joints so ultimately these wounds are left to heal by second intenion.[20] Wounds involving the distal limb in horses have been found to exhibit a weak and persistent inflammatory phase of healing in the distal limb compared compared to those involving the body.[21] This prolonged low grade inflammation, in combination with the lack of soft tissues and a relatively poor vascular supply, can promote the formation of exuberant granulation tissue which results in a complicated, and often delayed, healing process.[22] There are some similarities between wounds in the distal limb of horses and diabetic ulcers observed in people, including relatively poor blood supply and chronic inflammation.[23] As such, wounds of the equine distal limb may serve as a useful model for experimental studies that are beneficial to multiple species. The purpose of this review is to summarize the current knowledge on the bioactivity of manuka honey, its application and role in second intention wound healing in horses, and highlight areas for future investigation.

2. The properties of manuka honey

2.1. Generic features of honey

A high sugar content and a low pH, generally between 3.2 and 4.5, are physical properties that are common to all varietals of honey.[16] Ripened honey consists of 80% sugars, 18% water and a complex mixture of amino acids, peptides, arabinogalactan proteins, organic acids, polyphenols, carotenoid-like substances, flavonoids, vitamins and minerals.[24,25] The high sugar content produces a high osmotic gradient that leads to bacterial dehydration and shrinkage of the cell wall.[26] This high osmolality also initiates an influx of fluid, lymph and nutrients into the wound bed, creating a moist environment.[27,28] These properties promote autolytic wound debridement and enhance tissue healing. The low pH environment promotes the release of oxygen from hemoglobin and encourages wound contraction,[29] as well as reducing the activity of bacterial proteases.[30] Bacterial proteases contribute to poor tissue healing by

damaging the extracellular matrix and destroying cytokines and growth factors.[31]
Glucose oxidase is an enzyme produced by worker bees and is found in all types of honey in varying concentrations.[16] This enzyme is responsible for oxidizing glucose into gluconic acid and releasing hydrogen peroxide. Hydrogen peroxide is only detected in diluted honey because dilution leads to activation of glucose oxidase.[32] The generation of hydrogen peroxide is greatest when honey is diluted to 30-50%.[33] Hydrogen peroxide is a commonly used disinfectant and its presence contributes to the overall antimicrobial activity of honey. Hydrogen peroxide also acts as a messenger in the activation of nuclear factor-κB (NF- κB), a transcription factor which plays a key role in regulating the immune response to infection.[34]
The activity and concentration of hydrogen peroxide varies substantially between honey varietals and can be related to plant species, environmental conditions and entomological factors, including age of the bee and foraging patterns.[35] The variable antibacterial activity of some honey varietals is also affected by processing and storage conditions, including heat and light, and catalases that are produced by some bacteria and pollen.[24,35-38] It has also recently been shown that the antibacterial activity of late harvest honey (honey aged in the honeycomb for one year) is significantly increased compared with freshly harvested honey.[39]

2.2. Non-peroxide antimicrobial activity of manuka honey

Honey derived from some plant sources has recently been shown to have superior antimicrobial activity even in the presence of high concentrations of catalase which is known to deactivate hydrogen peroxide.[9,15] This has been termed non-peroxide antimicrobial activity because the properties are due to bioactive components of the honey other than the production of hydrogen peroxide. Honey derived from the *Leptospermum* species of plants, including manuka honey, have been shown to exhibit non-peroxide antimicrobial activity and superior antimicrobial activity compared to honey derived from many other plant sources.[40] Methyglyoxal (MGO), an organic compound found in manuka honey, has been shown to be responsible for the majority of the antimicrobial activity.[20,40-42] The mode of action is through its ability to interact with macromolecules such as DNA and RNA.[20,40-42]
Methylglyoxal is produced from the non-enzymatic conversion of a chemical found in high concentrations in the flower of the manuka tree, dihydroxyacetone (DHA).[24].
Methylglyoxal has recently been shown to limit the production of hydrogen peroxide by inhibiting the enzyme glucose oxidase, so hydrogen peroxide does not contribute to the antimicrobial activity of manuka honey.[14,43,44]
The levels of DHA in stored manuka honey slowly decreases over time as it is converted into MGO, which subsequently increases at a similar pace. The concentration of MGO in stored honey plateaus after 3-4 months and maintains a consistent ratio of DHA to MGO of 2:1.[41,42]
Several other bioactive components of honey such as the glycoside, leptosin, and proteins secreted by honey bees, bee defensin-1 and the family of major royal jelly proteins, have all been shown to exhibit antibacterial and anti-inflammatory effects. [45,46] It has been suggested that the antibacterial factors within honey are likely to interact together, thereby creating a synergistic effect and/or regulating the activity of other chemicals.[47]
Unique Manuka Factor (UMF) is a trademarked grading system placed on the label of commercially available Manuka honey by licensed producers in New Zealand.[48] The UMF rating assures the purity and quality of the product and represents a similar zone of growth inhibition in a radial diffusion assay with *Staphylococcus aureus* when compared with a known concentration of an antiseptic (phenol) solution.[24,48] Each individual batch of manuka honey is tested for antimicrobial activity, however, it is worth noting this testing does not demonstrate precisely which components contribute to this property.[24] In general, a UMF

rating of 10-15 is required for the batch to be considered therapeutically useful, whilst a UMF16-30 has superior activity with high antimicrobial efficacy. A UMF rating 5-9 has minimal antimicrobial activity and is not recommended for therapeutic use as an antimicrobial agent, whilst a UMF 0-4 has no detectable antibacterial activity.[49]

The specific actions of MGO have yet to be fully elucidated, but it has been suggested to involve a combination of enzymatic and non-enzymatic processes that involve the ability of MGO to interact with macromolecules such as DNA and RNA.[40,41] The mode of action also appears to differ depending on the micro-organism involved. Exposure of gram-positive organisms to MGO leads to the downregulation of autolysin, an enzyme involved in cell division, and the cleavage of bacterial cell wall components.[50,51] Exposure of gram-negative bacteria to MGO appears to lead to altered gene expression of proteins involved in the structural integrity of the cell wall and cell lysis.[50-53] A decrease in virulence factors of bacteria has also been observed following treatment with manuka honey, including downregulation of flagella-associated proteins,[53] inhibition of siderophore formation,[54] and reversal of antibiotic resistance.[55]

2.3. Effects of manuka honey on bacterial biofilms

Bacterial biofilms are known to impair healing of wounds in both humans and horses due to the ability of biofilms to interfere with the activity of many antibiotics.[56-58] Manuka honey has been shown to inhibit the formation of biofilms and cause detachment of established biofilms, although the exact mechanism of action is currently unknown.[59-61] Exposure of bacteria to manuka honey *in vitro* has demonstrated downregulation of genes coding for surface-binding proteins important in biofilm formation, virulence, and cell to cell communication.[59,61,62] Low concentrations of manuka honey may prevent biofilm maturation by disrupting cellular communications,[10,63] whilst higher concentrations of manuka honey are able to penetrate and detach established biofilms.[58,59,64] The methylglyoxal in manuka honey appears to play a critical role in disruption of biofilms but it not exclusively responsible for this property.[61,65]

2.4. Effects of manuka honey on modulating the immune system and healing

Most of the initial interest in manuka honey focused on its antimicrobial effects. However, there is a growing body of evidence to show that manuka honey can modulate the inflammatory response and guide the healing process by stimulating the production of cytokines that regulate fibroblast production and angiogenesis.[9,66] A 5.8kDa bioactive component of manuka honey has been identified as being responsible for stimulating monocyte activity through activation the toll-like receptor 4 (TLR4).[66] Activation of TLR4 and subsequently the intracellular signalling pathway NF-κB enhances the production of interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) which are important in regulating the inflammatory response and orchestrating tissue repair.[66-68]

It has been speculated that, in general, honey can stimulate the production of inflammatory cytokines (IL-1β and TNF-α) in settings of low inflammation, whilst supressing these same cytokines during settings of infection.[69] This is because honey has demonstrated both pro-inflammatory and anti-inflammatory properties. Initial stimulation of inflammation in a wound is critical to aid resolution of infection and facilitate removal of foreign material and cellular debris.[70] However, if inflammatory cell activity, particularly neutrophils, is prolonged in the wound bed, this can delay healing.[71] It is currently unclear how the bioactive elements of honey display the properties which are required by the wound at a particular point on the continuum of wound healing and which components are responsible for this phenomenon. On top of these characteristics, honey has also exhibited the ability to inhibit cyclo-oxygenase-2 (COX-2) expression and have an antioxidant effect by altering the production of reactive oxygen species (ROS) and a number of phenolic compounds.[72,73] Recently, it has also been observed that cultured human dermal fibroblasts altered production of IL-6 and interleukin-8 (IL-8) in a dose dependent manner when exposed to dilute UMF10 manuka honey. A 0.5% manuka honey solution resulted in a significant increase in IL-8 production, whilst a concentration of 1.0% resulted in a marked decrease in IL-8 production but an increase in IL-6 production.[17,74]

3. Studies investigating topical UMF20 manuka honey on wound healing in the horse

Recently, a series of studies investigating the effects of topical UMF20 manuka honey in an equine model of second intention healing on the lower limb have been reported.[75-79] These studies were conducted using a contaminated and/or non-contaminated surgical wound healing model. Briefly, standardized, full thickness, surgical wounds were created on the dorsal aspect of the metacarpal or metatarsal bones. These were made using a standard, flexible template laid over the skin slightly medial to the extensor tendons. Once the skin was removed, fresh feces retrieved from a horse not involved in the study was applied under a bandage for 24 hours (contaminated model) or saline soaked gauze under a bandage for 24 hours (non-contaminated model). At 24 hours the feces or saline gauze were removed, a standardized template was applied next to the wound as a reference for magnification and the wounds were digitally photographed. Medications were topically applied daily and the bandages were changed daily for 12 days, after which time the wounds were left open to heal. The duration of bandaging was based on a previous study performed by our group that showed surgically created, distal limb wounds bandaged with a semi-occlusive bandage began to show visual evidence of dysregulated healing and excessive granulation tissue around 12 days.[22] If bandages were removed at this time and left open, most wounds would progress to heal normally. Digital photographs were taken weekly out to 6 – 8 weeks and total time to healing was recorded for each wound. Wound photographs were measured using a commercially available software package and wound variables compared statistically.[75-78] Significance was set at $P<0.05$.

3.1. Study 1: Effects of UMF 20 Manuka honey on second intention wound healing in horses: a pilot study[75]

This pilot study involved creation of a single 2.5 x 2.5 cm full thickness wound on the metacarpus of both front legs of 8 Standardbred geldings.[75] Wounds were contaminated with feces for 24 hours under a bandage. The following day, the wounds were rinsed with sterile saline and treated with either UMF20 manuka honey, or left untreated. Bandages were removed daily to allow treatment of the wounds for 12 days. On day 13, bandages were removed, treatment was stopped, and wounds were left open to heal. Wound area was measured weekly for 8 weeks and the overall time to healing was recorded. Treatment with UMF20 manuka honey for 12 days resulted in less retraction of the wound and treated wounds remained smaller than untreated wounds until day 42. There was no difference in overall healing time between treated and untreated wounds. The authors reported that the treated wounds appeared to visually develop a healthier bed of granulation tissue earlier than untreated wounds.

3.2. Study 2: Effects of a 66% manuka honey gel and duration of treatment on second intention healing of distal limb wounds in horses[76]

Manuka honey has a liquid consistency at room temperature and therefore is best applied under a bandage to optimise contact with the wound. However, it has been demonstrated that bandages applied to the distal limb wounds in horses can promote dysregulated healing and the production of exuberant granulation tissue if applied for prolonged periods of time (> 12 days) in the equine distal limb.[22,80] To address the liquid consistency and to improve adherence of the manuka honey to the wound without a bandage, a gel mixture consisting of 66% UMF20 manuka honey and 34% water-based, pH neutral gel was developed.[76]

This study was performed to compare the efficacy of commercially available UMF20 manuka honey to 66% UMF20 manuka honey gel when applied to wounds daily under a bandage for 12 days. The study also set out to evaluate the effect of daily application of the manuka honey gel mixture throughout the process of wound healing compared to untreated control wounds. Five, full thickness wounds (2 x 2 cm) were created on the dorsomedial aspect of both metacarpi. Wounds were assigned to five different treatment groups: (1) UMF20 manuka honey, (2) 66% manuka honey gel applied for 12 days, (3) gel carrier alone applied for 12 days, (4) 66% manuka honey gel applied throughout healing and (5) untreated control. Wounds on one leg were contaminated with feces under the bandage for the first 24 hours, whilst the wounds on the other leg were left non-contaminated. Bandages were removed after 24 hours and the wounds rinsed with sterile saline. For the first 12 days bandages were changed daily and wounds treated as assigned. On day 13, bandages were removed and wounds were left open to heal. Treatment with the manuka honey gel mixture was continued daily on the assigned wound on each leg until the wounds were completely healed. Wound area was measured on day 1 then weekly until day 42. The time to complete healing for each wound was recorded.

Throughout the first 42 days of healing, wounds treated with either of the manuka honey products retracted less than untreated controls and wounds treated with gel alone. The wounds treated with either of the manuka honey products were smaller than untreated controls and wounds treated with gel alone from day 7 until day 35. Wounds treated with the 66% manuka honey gel mixture throughout healing, healed faster than all other wounds. Wounds treated with either the 66% manuka honey gel or UMF20 manuka honey for 12 days healed faster than control wounds and wounds treated with gel alone.

3.3. Study 3: Effect of manuka honey on growth factors, bacterial counts and histomorphology during early healing of distal limb wounds in horses[77]

Growth factors such as transforming growth factor-β1 (TGF-β1) and TGF-β3 are known to play a crucial role in regulating wound healing. An imbalance in the expression of these growth factors have been implicated in the production of excessive granulation tissue and delaying healing of distal limb wounds in horses.[81,82]

This study was performed using 10 Standardbred geldings to investigate the effect of 66% manuka honey gel on the levels of TGF-β1 and TGF-β3, bacterial counts and wound histomorphology during the first 10 days of healing.[77] Wounds (2.0 x 1.5 cm) were created on the dorsomedial aspect of the metacarpi of both forelimbs. Wounds were assigned to 3 groups: (1) wounds contaminated with feces for 24 hours then treated with manuka honey gel, (2) contaminated control wounds and (3) non-contaminated control wounds. All wounds were bandaged for the first 24 hours. In 5 horses, the wounds were bandaged for the entire study whilst the wounds in the other 5 horses were left open after the first 24 hours. Four biopsies were taken from different wounds on days 1, 2, 7 and 10 to evaluate the effects of the manuka honey gel, wound contamination and bandaging on TGF-β1 and TGF-β3 concentrations, aerobic and anaerobic bacterial counts and histomorphology of the wound bed.

The study found that daily application of manuka honey gel had no effect on TGF-β1 and TGF-β3 concentrations within the wound and no effect on wound bacterial counts. Histologically, manuka honey gel decreased wound inflammation (day 7 and 10), increased angiogenesis (days 2, 7 and 10), increased fibroplasia and collagen organisation (day 7) and increased epithelial hyperplasia (day 7 and 10).

The authors noted the number of treatment variables and complexity of the study may have limited the detection of some differences between treatment groups. Furthermore the wound biopsies were taken 24 hours after application of the treatment which may have not truly reflected some of the effects of manuka honey, particularly the antimicrobial effects of manuka honey treatment.

3.4. Study 4: Effects of different grades of manuka honey and generic multi-floral honey on wound healing[78]

The price of manuka honey has substantially increased in the last 20 years, particularly the cost of higher UMF grades of manuka honey.[19] Investigation into the efficacy of less expensive UMF grades of honey and generic honey on equine wound healing is considered warranted. This study was performed to assess the efficacy of UMF 5 manuka honey and a generic, multi-floral honey on wound healing in the equine distal limb. Two full thickness skin wounds (2.5 x 2.5 cm) were created on the metatarsi of both hindlimbs in 8 Standardbred horses. Wounds were assigned to one of four treatments: (1) UMF20 manuka honey, (2) UMF5 manuka honey, (3) generic multi-floral honey and (4) a saline control. Wounds were not contaminated with feces. For the first 12 days, wounds were treated with the assigned treatment and bandages were replaced daily. On day 13, treatment was stopped and wounds were left open to heal. Wound area was measured on day 1 then weekly until day 42. The time to complete healing was recorded.

Wounds treated with UMF20 manuka honey healed in a shorter time frame than wounds treated with generic honey and saline controls. There was no difference in time to complete healing between wounds treated with generic honey and saline controls. Treatment with UMF5 manuka honey resulted in faster healing times compared with generic honey and saline controls, however, this result was not statistically significant.

From the results of this series of studies, it is apparent UMF20 manuka honey has a beneficial effect on second intention healing of wounds on the distal limb of horses. The principal therapeutic effect of manuka honey appears to be in the early stages of wound healing, although daily application throughout healing appears to have some beneficial effect. Despite the proven potent antimicrobial effects of UMF20 manuka honey,[26] topical treatment in the contaminated wounds did not appear to alter bacterial counts in one study,[77] suggesting that it's antibacterial properties may not play the primary role in enhancing wound healing in the equine distal limb.[77] However it is important to note the authors highlighted limitations in that study that may have affected this result. [77] It is likely that in heavily contaminated, naturally occurring wounds in horses the antimicrobial activity wound contribute to improving the overall wound environment. Further studies in this area are warranted.

Treatment with UMF5 manuka honey reduced healing times compared with generic honey and saline controls. Although this result was not statistically significant, it suggests a potential benefit of manuka honey on wound healing even when applying a UMF grade of manuka honey that displays very weak antimicrobial activity.[78] It is interesting to speculate from the results from these two studies on wound healing in horses, [77,78] that the ability of manuka honey to modulate the immune response may play a bigger role in improving healing than previously thought.

There were several limitations to the wound healing models used in the 4 studies.[75-78] Surgically created wounds contaminated with feces are not strictly representative of many naturally occurring wounds which are associated with significant tissue avulsion and heavy and deeper seated contamination. However it might be expected that the effect of daily application of manuka honey, or multiple applications daily, would have a greater effect in naturally occurring wounds. Nonetheless the results using this experimental model are probably more clinically relevant than more traditional wound healing models where wounds are created aseptically and surgically.

4. Future directions for research

The majority of research into the properties of honey has focused on manuka honey. The standardization and grading of the antimicrobial properties, the increased incidence of antimicrobial resistance, and the popularity of natural products in healing have increased the price of manuka honey substantially over the last two decades.[19] However there are approximately 83 species of bushes and trees from the *Leptospermum* (Tea tree) family found in Australia, including the manuka tree (*Leptospermum scoparium*).[2] There is growing interest from the Australian honey industry to market honey produced from Australian plants, such as the jelly bush (*Leptospermum polygalifolium*), jarrah tree (Eucalyptus marginate) and marri tree (Corymbia calophylla), for medicinal purposes. [35,83-85] Limited research has shown that honey produced from these plants show similar antibacterial activity to manuka honey.[83,84] In the case of jelly bush honey, similar or higher levels of MGO than manuka honey has been reported, and this honey exhibits similar non-peroxide antimicrobial activity that was stable for up to seven years in storage.[83] Further research should be targeted at determining whether honey derived from other species of plants have medicinal properties and can be used topically to enhance wound healing.

In the series of studies presented here, a 66% dilution of UMF20 manuka honey in an aqueous, pH neutral gel exhibited the same beneficial properties of pure manuka honey with the added benefit of a consistency that would adhere to wounds without requiring a bandage. [75-78] It is interesting to note in honey varietals that rely on the production of hydrogen peroxide for their antimicrobial properties, that dilution of honey to a concentration of 30-50% maximises the production of hydrogen peroxide.[33] The ancient Greeks used to use a combination of 33% honey to 67% grease or animal fat as a wound dressing.[86] Further dilutions of manuka honey should be evaluated to determine if the therapeutic effects are retained and at what dilution activity is optimized and what dilution activity is lost. This may have relevant economic benefits with respect to reducing the costs of commercial production of wound healing products containing manuka honey while ensuring activity.

Horses are very prone to traumatic lacerations of the distal limb and the treatment of these wounds can be quite expensive. There are no epidemiological data in the veterinary field that demonstrates the exact cost of treating complex wounds, however, in the human literature the cost of managing diabetic foot ulcers was estimated to be $10.9 billion in the USA in 2001.[87] The global incidence of type 2 diabetes and hence the incidence of diabetic foot ulcers has increased dramatically in that time and continues to rise.[87] With the rising costs of treating problematic complex wounds in both human and veterinary medicine, it would be prudent to find ways to optimize the cost effectiveness of treatment. Determining which types, grades or dilutions of honey would be most beneficial at different time points along the continuum of wound healing could improve the quality and cost of care.

A recent Cochrane systematic review (2015) into the use of honey as a topical treatment for wounds found "high quality evidence" that honey dressings healed partial thickness wounds faster than conventional dressings. However, the reviewers noted that there was "low quality evidence" on the ability of honey to control infection.[88] *In vitro* work demonstrates that manuka honey develops a synergy with different types of antibiotics, increasing their efficacy, and has also shown the ability to make previously resistant strains of bacteria sensitive to common antibiotics.[55,89] It would be interesting to investigate whether the synergy between manuka honey and antibiotics transfers into an *in vivo* setting and may have application in a clinical setting.

There are limited studies on the safety of manuka honey. In the Cochrane review the authors reported there was "very low quality evidence" on the incidence of adverse effects following the use of honey.[88] This is supported by human clinical trials that have reported very few adverse effects when honey has been ingested, when it is used as a sinus flush or used topically on wounds.[90-92] More information on the rate and type of adverse effects is important as the use of honey as a therapeutic agent continues to increase, particularly if the use of honey spreads beyond topical application and into other modes of therapy. Intra-peritoneal administration of honey was shown to prevent post-operative peritoneal adhesions in rats,[93] and if the synergy between manuka honey and antibiotics can be transferred into a clinical setting there could be the potential for honey products to be applied in a parenterally or into joints or synovial structures.

5. Conclusions

The use of honey in wound healing has been described since ancient times and the evidence for its use continues to expand. While more unbiased information, particularly large randomised clinical trials, is required, the majority of the literature that has accumulated over the last few years supports the properties that can be medically beneficial in a human and veterinary setting. As the evidence continues to expand it is possible that the use of honey based products therapeutically will also increase benefit human and veterinary patients.

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