REVIEW

CURRENT RESEARCH INTO SECOND INTENTION EQUINE WOUND HEALING USING NEW ZEALAND MĀNUKA HONEY.

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Mānuka Vet®

INTRODUCTION

The practice of using honey in assisting wound healing dates back to the ancient Egyptians and its use has once again been put into the spotlight in the face of increased bacterial resistance to modern antimicrobials (Carter *et al.* 2016). There is also a major push from World Health Organisation and Governing Veterinary bodies to reduce the use of antimicrobials where necessary when treating human and veterinary patients alike.

The bioactive component profile of different honey varietals varies greatly, with those derived from the *Leptospermum Scoparium* or Mānuka plant, found only in New Zealand, being the most extensively studied (Allen *et al.* 1991; Cooper and Jenkins 2009; Kwakman *et al.* 2011; Carnwath *et al.* 2014; Cooper 2014).

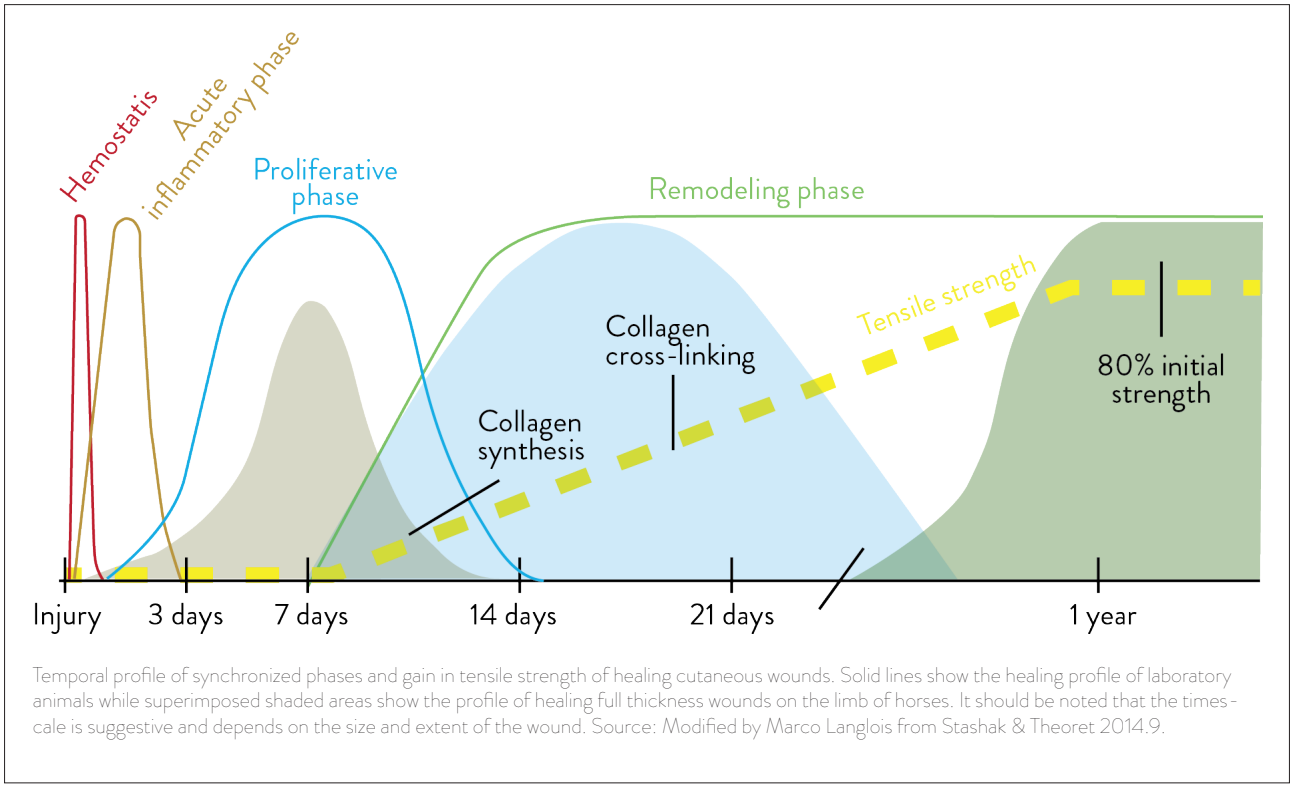
Mānuka honey has been found to possess superior antimicrobial properties, have the ability to disrupt bacterial biofilms and modulate the inflammatory process in wounds (Dart 2015).

PHYSIOLOGY OF WOUND HEALING

Veterinarians must understand the biology of wound healing so that the best approach at the best time can be implemented, "healing is a matter of time, but it is sometimes also a matter of opportunity" (Hippocrates).

The objective of wound healing is to re-establish an epithelial cover and repair the integrity, strength and function of an area. Figure 1. depicts the various phases and timings of wound healing and identifies the four phases wherein lie the biggest opportunities for effective wound management.

Figure 1. Physiology of Wound Healing. Theoret and Schumacher, 2016.
(Solid lines = laboratory animals, Shaded areas = horses)



Temporal profile of synchronized phases and gain in tensile strength of healing cutaneous wounds. Solid lines show the healing profile of laboratory animals while superimposed shaded areas show the profile of healing full thickness wounds on the limb of horses. It should be noted that the time-cale is suggestive and depends on the size and extent of the wound. Source: Modified by Marco Langlois from Stashak & Theoret 2014.9.

FEATURES UNIQUE TO NEW ZEALAND MĀNUKA HONEY

Mānuka honey in general consists of approximately 80% sugars, mainly fructose and glucose, with the remainder being tightly bound water molecules that are unavailable to microorganisms (Cooper 2014; Kwakman and Zaat 2012). Mānuka honey contains large levels of gluconic acid that creates a pH range from 3.2 to 4.5 (Molan 1992).

The high osmotic gradient of the honey creates a fluid shift from adjacent tissues and circulatory system into the wound. This creates a moist, nutrient- rich wound environment, which promotes autolytic debridement, enhanced wound healing, and osmotic stress and shrinking of bacteria (Molan 2006).

The low pH created by the Mānuka honey also reduces the activity of bacterial proteases (Gethin 2008), which can destroy cytokines, growth factors and the extracellular matrix; all of which contributes to non-viable soft tissues and poor wound healing (Tarnuzzer and Schultz 1996).

New Zealand Mānuka honey also contains methylglyoxal (MGO) that it is responsible for a majority of the antimicrobial activity seen. MGO is produced from dihydroxyacetone, a substance found in high concentrations in the Mānuka bush (Kwakman and Zaat 2012).

The level of MGO determines the antimicrobial efficacy of the Mānuka honey, with levels greater than 350 (mg/kg) being therapeutic and levels exceeding 500 (mg/kg) showing superior activity with high antimicrobial efficacy. MGO levels below 350 (mg/kg) are not recommended for therapeutic use (Molan 2001; Tsang *et al.* 2017).

UMF stands for Unique Mānuka Factor and it relates to the level of methylglyoxal in the Mānuka honey. The rating of UMF refers to the percentage concentration of phenol with the same antimicrobial activity as the honey when tested in a radial diffusion assay with *Staphylococcus aureus* (Atrott *et al.* 2012).

As with any antimicrobial, it is therefore essential to consider the total concentration of active MGO in the total product when assessing what therapeutic benefits it may offer the patient.

Furthermore, a recent study examining the antibacterial activity of a variety of honeys against common equine wound isolates found that 18 of 29 samples tested were contaminated with either bacteria or fungi (Carnwath *et al.* 2014).

Multiple brands of honey purchased from a local supermarket and UMF5 Mānuka honey were among the contaminated samples. This study reaffirmed the general recommendation that only Mānuka honey above 12UMF has therapeutic benefits and that sterility of the product should be a consideration before administering it to wounds (Carnwath *et al.* 2014).

HOW DOES IT WORK?

The action of MGO can be attributed to both enzymatic and non-enzymatic processes that have the ability to disrupt the nucleophilic centres of macromolecules (Mavric *et al.* 2008; Adams *et al.* 2009). In Gram-positive organisms MGO down-regulates autolysin, causing disruption to cell wall cleavage and cell division (Jenkins *et al.* 2011a, b) and in Gram-negative organisms MGO disrupts gene expression of proteins involved in cell wall stability, causing cell lysis (Henriques *et al.* 2011; Jenkins *et al.* 2011a, b). Additionally, MGO was shown by Jenkins *et al.* (2011a, b) to downregulate a protein that limits the ability of methicillin-resistant *Staphylococcus aureus* to withstand exposure to stress.

MGO has also been shown to downregulate genes coding for surface-binding proteins and this can lead to prevention of biofilm formation and disruption of established biofilm (Jervis-Brady *et al.* 2012a, b; Maddocks *et al.* 2012). This is significant as biofilms are associated with delayed healing and chronic infection of wounds, and can interfere with antimicrobial effects (Serralta *et al.* 2001; Freeman *et al.* 2009; Merckoll *et al.* 2009).

Furthermore, New Zealand Mānuka honey has also been shown to modulate the inflammatory

response in wounds by enhancing the production of cytokines that regulate fibroblast production and angiogenesis (Molan 2006; Tonks *et al.* 2007). Mānuka honey was been shown by Tonks *et al.* (2001, 2003, 2007) to activate toll-like receptor 4 on monocytes, that leads to increased production of IL-1ß, IL-6 and TNF-alpha from monocytes, which are integral to tissue repair and regeneration.

STUDIES DEMONSTRATING THE EFFICACY OF MĀNUKA HONEY ON WOUND HEALING

Bischofberger *et al.* (2011) showed that wounds created on the dorsal aspect of cannon bones in horses that were treated with Mānuka honey retracted less, remained smaller than untreated wounds and developed a healthier bed of granulation tissue than untreated controls.

Bischofberger *et al.* (2013) was also able to demonstrate the benefits of adding Mānuka honey to a wound for the duration of wound healing. This study compared wounds managed without topical pharmaceuticals, and those with Mānuka honey that was applied either for 12 days only or for the entire duration of wound healing.

Bischofberger *et al.* (2013) found that wounds treated with either protocol of applying Mānuka honey healed faster than controls and interestingly wounds treated with Mānuka honey for the duration of healing healed faster than all others.

These wounds were created surgically and as naturally occurring wounds are often traumatic in origin, and as a result more severe and contaminated, the effects of Mānuka honey may be even more potent in these cases (Dart *et al.* 2015). Bischofberger *et al.* (2015) also showed that Mānuka honey, when used in contaminated wounds, was able to decrease inflammation, increase angiogenesis, increase fibrosis and collagen organisation and increase epithelial hyperplasia. These effects resulted in a more organised bed of granulation tissue in the early stage of wound healing.

Recently, Tsang *et al.* (2017) also showed that treatment of wounds with UMF20 reduced overall wound healing time compared with wounds treated with generic honey and UMF5 honey. Using a contaminated wound model, it was demonstrated that wounds treated with high grade Mānuka (20 UMF) had decreased wound inflammation (days 7 and 10), increased angiogenesis (days 2,7,10) increased fibrosis and collagen organisation (day 7) and increased epithelial hyperplasia (days 7,10) compared with control wounds. This suggests the action of high grade Mānuka honey is to enhance

Figure 2. Wound at Days 0, 1 and 3 (left to right in photos) on a 7-year-old TBX treated with surgical debridement and topical sterile Mānuka honey (500+ MGO). Photos courtesy Dr Rebecca Penman.

the early inflammatory process and to promote a more mature granulation bed earlier compared to untreated wounds (Tsang *et al.* 2017).

THE PRACTICAL USE OF MĀNUKA HONEY IN SECOND INTENTION HEALING

These and other studies have now enabled practical suggestions to be made for the use of Mānuka honey in treating wounds [Table 1]. Contaminated or traumatised wounds should have necrotic tissue and debris removed to augment wound healing.

Mānuka honey should be applied within the first 24 hours of wounding and using Mānuka honey which has MGO levels >500mg/kg.

It is recommended to use 30ml (approximately 20g) per 10x10cm area with a bandage applied over the wound, which is initially changed every day, with increasing intervals between changes occurring as exudate levels decrease over time. Bandaging should continue for 12 days or until a healthy bed of granulation tissue has formed and at this point bandaging may no longer be necessary. When applying to an open wound only a thin film applied 2-3 times daily is necessary and should be applied for at least 21 days or until the wound is healed completely (Dart *et al.* 2015). If excessive granulation tissue develops, this should be excised and Mānuka honey application should be continued thereafter. Aligning the cost of high grade medical Mānuka honey to the key benefits of wound healing, and to match specific honey and product characteristics at the specific time points of wound healing (first 12 to 21 days), may be beneficial.

CONCLUSION

The rising cost of high activity honey has led owners and even veterinarians to use or recommend lower UMF Mānuka honey or generic table honey, but when it comes to wound healing all honeys do not behave equally. New Zealand Mānuka honey specifically appears to represent a step forward in the area of equine wound healing and reducing antibiotic use. It has been found to possess superior antimicrobial properties, have the ability to disrupt bacterial biofilms and modulate the inflammatory process in wounds to speed healing and reduce scarring. Choosing Mānuka honey that exceeds therapeutic concentrations (MGO > 350mg/kg) and is sterile is a critical consideration when using or recommending a product.

DECLARATION OF INTEREST

The authors are both consultants to Manuka Vet NZ Limited, New Zealand.

Table 1:	Optimal Treatment Plan using Mānuka honey topically to treat equine distal limb wounds left to heal by second intention (Dart, *et al.*, 2015).
1	Surgically debride wounds to remove contaminated, necrotic and devitalised or infected tissues.
2	Apply > 500MGO Mānuka honey, room temperature within 24 hours of injury or debridement
3	Apply 30ml honey to each 10x10cm dressing area
4	Change bandage each day and reapply the honey for up to 12 days
5	Remove bandage at 12 days and leave wound open
6	Apply a thin film of Mānuka honey to the wound 2-3 times daily for at least 21 days

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