



Skin & Wound

TECHNICAL REVIEW



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EXECUTIVE SUMMARY

Here at Mānuka Vet® our philosophy is to drive change in the world of animal healthcare. With concerns from all over the globe about resistance to antibiotics and the threat that this poses to both human and animal health we believe New Zealand can lead the way in developing innovative and sustainable medicinal Mānuka honey products.

Mānuka Vet® is a partnership between Maori landowners and experienced Veterinarians. Achieving a balance between science, nature and medicine is at the heart of everything we do. We are as active in managing our Mānuka plantations and creating sustainable opportunities for our stakeholders, as we are in leading edge veterinary research.

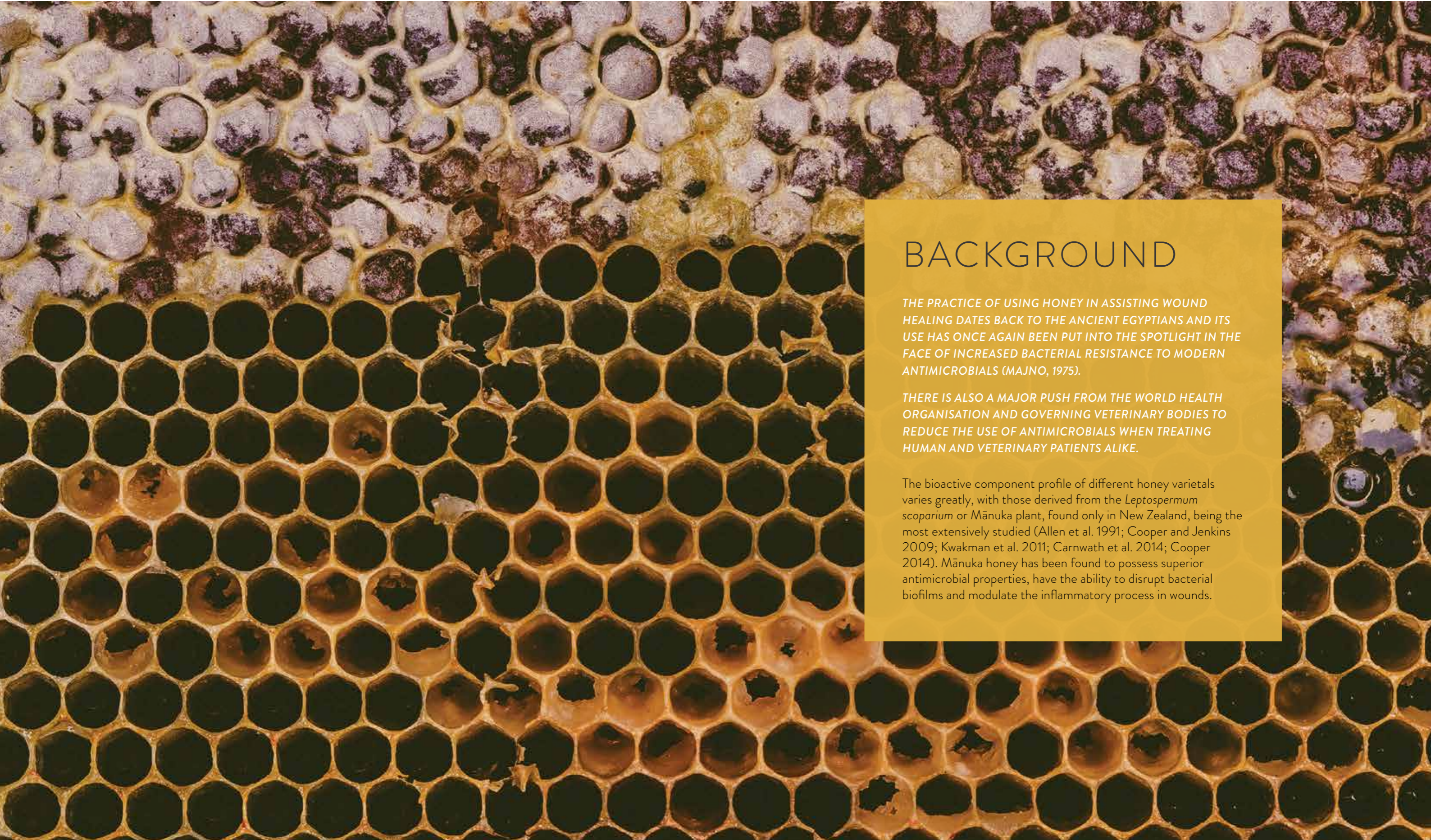
Our products meet the rigorous requirements for quality and assurance and are the best nature can offer. After all, when treating wounds on our much loved animals only the best will do!

This technical booklet summarises how Mānuka honey has been shown to heal wounds and provides information about Mānuka Vet® and our products.

- We are New Zealand owned and operated.
- We control the entire supply chain from the hives to the finished product, so we can ensure our products are of the highest quality.
- We use 100% pure New Zealand *Leptospermum scoparium* (Mānuka) honey, which is the authentic Mānuka honey that research has shown aids in wound healing.
- All of our products are ultra-filtrated to remove potentially harmful contaminants and laboratory tested to ensure product sterility. Therefore, they are safe to use on large open wounds.
- Mānuka Vet® products are all independently certified (MGO 350+ or MGO 500+) and therefore may reduce the level of scarring and speed up the wound healing process by stimulating cells that help repair damaged tissues.
- For substance testing in horses and racing dogs, our products are non-swabbable so they can be used safely at home and while out competing/ at the races.
- The products have been formulated and tested by veterinarians.



MĀNUKA HONEY &
WOUND HEALING



BACKGROUND

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 (MAJNO, 1975).

THERE IS ALSO A MAJOR PUSH FROM THE WORLD HEALTH ORGANISATION AND GOVERNING VETERINARY BODIES TO REDUCE THE USE OF ANTIMICROBIALS WHEN TREATING HUMAN AND VETERINARY PATIENTS ALIKE.

The bioactive component profile of different honey varieties 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.



GENERAL FEATURES OF MĀNUKA HONEY

Mānuka honey consists of approximately 80% sugars, mainly fructose and glucose, with the remainder being tightly bound water molecules that are unavailable to micro-organisms (Cooper 2014; Kwakman and Zaat 2012). Mānuka honey contains large levels of gluconic acid which 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 (Molan

1999, 2011). This creates a moist, nutrient-rich wound environment, which promotes autolytic debridement, enhanced wound healing, and osmotic stress and shrinking of bacteria (Molan 1999, 2006).

The low pH created by the Mānuka honey 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).

FEATURES UNIQUE TO MĀNUKA HONEY

Mavric et al. (2008) has shown that Mānuka honey contains methylglyoxal (MGO) and that it is responsible for a majority of the antimicrobial activity seen in Mānuka honey. 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. Levels below 350mg/kg are not recommended for therapeutic use (Molan 2001).

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 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 of many honey varieties that don't contain MGO (Serralta et al. 2001; Freeman et al. 2009; Merckoll et al. 2009).

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 has been shown by Tonks et al. (2001, 2003, 2007) to activate toll-like receptor 4 on monocytes, that leads to increased production of IL-1 β , IL-6 and TNF-alpha from monocytes, which are integral to tissue repair and regeneration.

FOR HORSES



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, more severe and contaminated, the effects of Mānuka honey may be more potent in these cases (Dart et al. 2015).

Bischofberger et al. (2015) 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.



THE PRACTICAL USE OF MĀNUKA HONEY IN SECOND INTENTION HEALING

Contaminated or traumatised wounds should have necrotic tissue and debris removed to augment wound healing (Theoret and Wilmink 2008).

Mānuka honey should be applied within the first 24 hours of wounding and using that which has MGO levels >500mg/kg (Bischofberger et al. 2013). Dart et al. (2005) recommends to use 30ml (approximately 20g) per 10x10cm area with a bandage applied over the wound, that is initially changed every day, with increasing intervals between changes occurring as exudate levels decrease over time (Matthews and Binnington 2002).

Bandaging should continue for 12 days or until a healthy bed of granulation tissue has formed (Dart et al. 2009) 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 (Bischofberger et al. 2013; Dart et al. 2015).

If excessive granulation tissue develops, this should be excised and Mānuka honey application should be continued thereafter.

FOR DOGS & OTHER ANIMALS



STUDIES DEMONSTRATING THE EFFICACY OF MĀNUKA HONEY ON WOUND HEALING IN OTHER SPECIES

There is substantial evidence of the potential efficacy of honey accelerating wound healing in other species. Many studies have provided evidence of the beneficial effects of honey on excisional and burn wounds in rabbits, rats, dogs and guinea pigs (Kundu 2005, Lusby 2006, Jalali 2007, Sukur 2011, Zohdi 2012, Aljady 2000, Schencke 2011) which include a reduction of bacterial counts, enhanced wound closure, accelerated rate of re-epithelialisation and significantly reducing the expression of pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6).

In a recent study by Lacopetti et al (2020), Mānuka honey used to treat wounds created on the backs of sheep, promoted cell proliferation and neovascularisation ultimately enhancing

the healing process. Mānuka honey also increased the tensile strength of treated wounds (Rozaini, 2004), increasing the collagen concentration and stabilisation of fibres.

Maruhashi et al (2016) used medical grade honey treatment which promoted rapid clinical progress in 70% of dogs with otitis externa, with over 90% resolved by day 21. In this study, in vitro assays showed activity against all bacterial isolates, including methicillin-resistant strains of Staphylococcus and Pseudintermedius (MRSP). This is supported by further studies, substantiating the efficacy of Mānuka honey against resistant bacteria (Cooper 2010, Roberts 2015) providing a way to reduce antibiotic use at a time of increasingly prevalent antibiotic resistant bacteria.



THE PRACTICAL USE OF MĀNUKA HONEY IN SECOND INTENTION HEALING IN OTHER SPECIES

The antimicrobial, anti-inflammatory and autolytic debridement properties of Mānuka honey, make it best suited to necrotic, infected and contaminated wounds (Curtis, 2018). All wounds and peri-wound tissues should be thoroughly cleaned which includes meticulous debridement and copious irrigation (Stanley 2012).

Due to the osmotic action of Mānuka honey, exudate levels are likely to increase, and an absorbent secondary 3-layer dressing is required (Curtis 2018). Dressings are generally changed every 1-3 days. Hollis (2017) reports that as long

as there is Mānuka honey available on the dressing in contact with the wound, and there is no exudate soaking through the overlying bandage, the dressing can be left in place as long as five days.

The use of a suitable barrier cream around the wound will help to prevent maceration of the surrounding healthy tissue if exudate levels are high (Hollis, 2017).

Bandaging should continue until a healthy bed of granulation tissue has formed (Dart, 2009), and at this point bandaging may no longer be necessary.

WHAT IS UMF?

UMF stands for Unique Mānuka Factor and is a quality trademark that relates to the level of methylglyoxal (MGO) in the Mānuka honey.

The rating 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* (Mavric et al. 2008; Adams et al. 2009; Atrott et al. 2012).

At Mānuka Vet® all our products are tested and certified to contain minimum levels of MGO as stated on the label.

FOR YOUR REFERENCE PLEASE FIND BELOW A TABLE WHICH SHOWS HOW THE UMF AND MGO RATINGS CORRELATE

UMF RATING	MINIMUM MGO* METHYLGLYOXAL
-	30
UMF 5+	83
UMF 10+	263
UMF 12+	354
UMF 15+	514
UMF 18+	692
UMF 20+	829



WHY USE
MĀNUKA VET®
PRODUCTS?





WHY MĀNUKA VET®?

Mānuka Vet® is an entirely New Zealand owned and operated company that aims on being a world leader in producing veterinary medicines, with sustainability and nature at the core of its principals. Our products have been formulated

and tested by veterinarians and are backed by scientific evidence and we have control over the entire supply chain so we can ensure that the quality of our products are second to none.

MĀNUKA HONEY - RISK MANAGEMENT & QUALITY ASSURANCE SOURCING

Honey is initially extracted and batched under approved Risk Management Plans in accredited export processing facilities before being sent to our GMP approved animal products manufacturer

for formulation and packaging. At each step the honey is tested to maintain the highest consistent standards in our Mānuka Vet® products including QA, shelf life and stability testing.

AT VARIOUS STAGES MĀNUKA VET® MĀNUKA HONEY IS TESTED FOR THE FOLLOWING:

- Methyglyoxal (active ingredient)
- Dihydroxyacetone (precursor compound)
- Forecasted activity
- Hydroxymethylfurfural (excessive heat exposure)
- C4 Sugars (adulteration)
- Tutin (toxic compound)
- Parabens (toxic compound)
- Pfund (colour)
- Conductivity (mineral content)
- Pollen count
- Bacterial CFU (Colony Forming Units)
- Particulates
- Sterilisation QA

All Mānuka honey supply is traceable to the origin of production and producer and is sourced directly from selected landowner producers, which secure ongoing consistency and quality. All supplied Mānuka honey must be harvested, logged and extracted in export Risk Management Plan approved facilities.

Producing land sources should encompass large stands of Mānuka (in excess of 100ha) and far from potential sources of chemical pollutants (eg. manufacturing or intensive horticulture). We have a preference of working with Maori landowners for the social and cultural benefits that can be generated alongside good business.

TESTING

All Mānuka Vet® Mānuka honey are sample tested for selection by independent laboratories and

certified to meet the following minimal standards for labelling and medical grades.

NZ MINISTRY OF PRIMARY INDUSTRIES INTERIM LABELLING GUIDE FOR MĀNUKA HONEY

MĀNUKA - TYPE HONEY HAS THE FOLLOWING, NATURALLY PRODUCED, CHARACTERISTICS:

- A colour greater than 62 mm pfund.
- A conductivity range of 347-867 $\mu\text{S}/\text{cm}$.
- A flavour typical of Mānuka-type honey (mineral, slightly bitter).
- An aroma typical of Mānuka-type honey (damp earth, heather, aromatic).
- Presence of dihydroxyacetone (DHA) and methylglyoxal (MG).

MĀNUKA VET® MEDICAL GRADE HONEY MEETS THE ADDITIONAL FOLLOWING CRITERIA;

- A minimum methylglyoxal level of 360mg/kg (12.1 NPA), or higher (as determined by the branded grade of product being produced), for the shelf life of the Mānuka Vet® product.
- Is ultra-filtrated.
- Is hermetically sealed and sterile.

ADDITIONALLY, MĀNUKA VET® SAMPLE TESTS ALL BATCHES FOR PESTICIDES OR OTHER AGRICULTURAL/HORTICULTURAL CHEMICALS INCLUDING;

- Tutin (The maximum level of tutin allowed is now 0.7 milligrams per kilogram. This came into effect in New Zealand law on 12 March 2015)
- b) Parabens



PROCESSING

- All honey movements are under the NZ Electronic Documentation system to ensure chain of custody to the animal product manufacturing facility.
- All batched honey supplied to the manufacturing facility for formulation and packaging is accompanied with a Certificate of Analysis stating the laboratory results for the supplied batch.
- Quality control of all batched honey by an independent laboratory ensures all Manuka Vet® products are sterile prior to distribution.
- Randomised product quality checks of each batch is completed prior to release and distribution of any batched product.
- Mānuka Vet® completes annual independent audits of its Origin, Quality and Processing policies and systems.



A SUMMARY
OF MĀNUKA VET®
PRODUCTS

Mānuka Vet[®] Skin & Wound

GEL

AVAILABLE IN 20G AND 100G TUBES

- Consists of 100% *Leptospermum scoparium* (Mānuka plant) honey from New Zealand
- >500 MGO
- Sterile
- Filtered
- Can be safely applied to a wound under a bandage or applied directly onto an open wound

For the management of wounds in the early stages of healing that may be traumatised and/or contaminated.

The 20g tube is designed for smaller wounds or as a single 20g application to cover an area of 10 x 10cm in larger wounds. The 100g tube is designed to be a multiple use container for larger or more complicated wounds. See product insert for use recommendations.



Mānuka Vet[®] Skin & Wound

CRÉME

AVAILABLE IN 100G TUBES

- Consists of 80% *Leptospermum scoparium* (Mānuka plant) honey from New Zealand
- >350 MGO
- Sterile
- Filtered
- Can be applied directly onto an open wound (not to be applied under a bandage).

Mānuka Vet[®] Skin & Wound Creme is 80% genuine Mānuka honey with added emollients and natural oils to help repel insects.

The creme is designed to complement medical grade Mānuka Vet[®] Skin & Wound Gel by being able to be used in the later stages of wound healing or in the initial stages of healing minor wounds and abrasions.

The 100g tube is designed as a conveniently sized multiple use container for all wound sizes.



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Mānuka Vet

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*Mānuka Vet® products are proudly produced using genuine New Zealand mānuka honey.
Developed by nature – tested by veterinarians – proven by science*
