

Introduction

There is growing concern regarding antibiotic resistance, and it is estimated that if no action is taken, antimicrobial drug-resistant diseases could cause 10 million deaths each year by 2050, costing £66 trillion (Interagency Coordinating Group on Antimicrobial Resistance, 2019). As such, clinical studies focused on honey as an antimicrobial are emerging. Honey is a natural and effective therapy with broad-spectrum antimicrobial activity and no risk of resistance, which may potentially reduce use of antibiotics (Yaghoobi et al, 2013). This Made Easy explores the role of natural wound healing remedies, the impact of Medical Grade Honey (MGH) and the range of L-Mesitran® (H&R Healthcare) products.

Author: Sharon Gardner (details on page 4)

L-Mesitran® (H&R Healthcare) is a range of MGH-based products with antioxidants, providing a natural solution for wound management. L-Mesitran comes in a variety of formats to meet wide-ranging clinical requirements, aid patient choice and acceptability and provide a solution to issues that patients find particularly distressing (e.g. pain). L-Mesitran products use naturally occurring agents that are proven to aid wound healing and increase patient compliance, while not contributing to antimicrobial resistance (Zbucnea, 2017; Nair et al, 2020).

Use of honey in wound care

Honey has been used since ancient times in wound care (Figure 1). Honey has antioxidant, anti-bacterial and anti-inflammatory properties (Yaghoobi et al, 2013). It has been shown to be active against a wide range of pathogens, including methicillin-resistant *Staphylococcus aureus* (Yaghoobi et al, 2013). MGH can resolve persistent (multidrug-resistant) infections and biofilms, without risk of developing tolerance (Pleeging et al, 2020).

Honey is a super-saturated solution of sugars with a low water content, which binds water molecules — such as those present in

wound exudate — making them unavailable for the microorganism. The acidity of honey (pH 3.4–6.1) also helps to restrict microbial growth (Stephen-Haynes and Callaghan, 2011). Honey can be used to create a moist healing environment and stimulate epithelialisation. The use of honey leads to improved wound healing in acute cases, decreased inflammatory response and pain relief in burn patients who may be more susceptible to pain.

Differences between MGH preparations

In general, honey can be divided into two different types based on their antimicrobial action: peroxide and non-peroxide (methylglyoxal) based. Manuka Honey has a non-peroxide mode of action and was the first honey extensively investigated for medical use; however, other types of honey, such as MGH, may have similar or stronger antimicrobial activity (Hermanns et al, 2020; Smaropoulos and Cremers, 2021).

MGH follows a strict criteria to guarantee its safety, quality, and efficacy for therapeutic uses (Hermanns et al, 2020; Smaropoulos and Cremers, 2021). MGH is harvested in organic regions and must be sterilised using gamma irradiation. As a result, each MGH performs to the same high standard and conforms to CE and FDA regulations. In wound care, supplemented MGH, such as L-Mesitran, has been shown to enhance antimicrobial activity and can induce faster healing and less scarring compared to non-supplemented MGH (Cremers et al, 2020; Pleeging et al, 2020). This consistent and stronger activity can resolve persistent infections insensitive towards other therapies including antibiotics (Nair et al, 2020; Pleeging et al, 2020). As such, MGH preparations without any enhancement or supplementation may yield slower wound healing.

It is recognised that applying a product containing 100% honey may cause pain and therefore a lower percentage of honey in MGH helps to create a gentle treatment, while still preserving the beneficial properties (Pleeging et al, 2020; Smaropoulos and Cremers, 2020a;

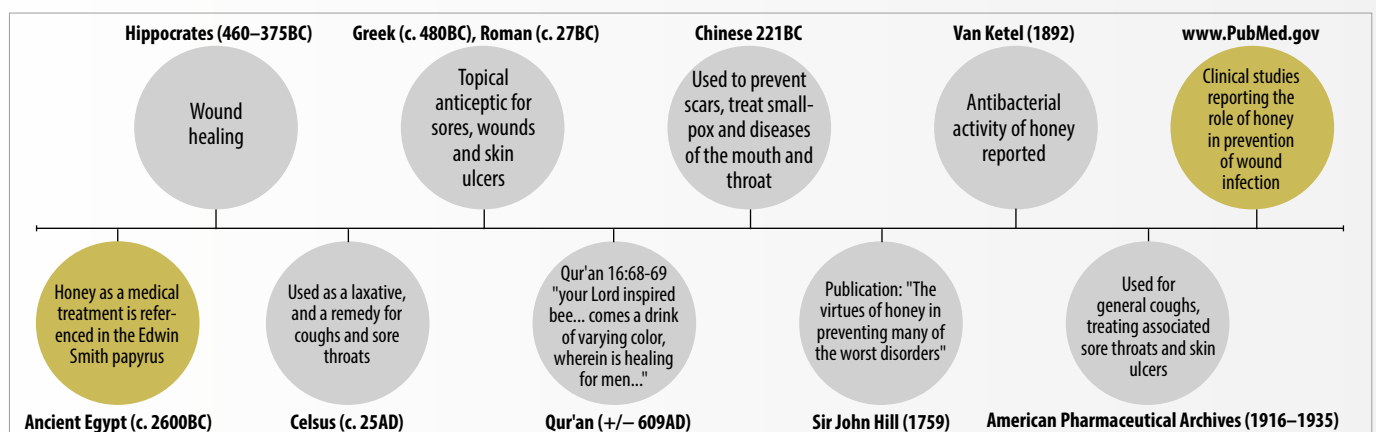


Figure 1. Timeline for use of honey in medicine

2020b). L-Mesitran is comparatively easy to apply, and cost-effective as only a thin layer of product is needed for efficacy compared to products containing 100% honey (Nair et al, 2020).

The L-Mesitran range contains MGH, along with topically applied naturally occurring agents to provide antimicrobial action and facilitate healing, such as medical-grade hypoallergenic lanolin, sunflower oil, cod liver oil, *Calendula officinalis*, *Aloe barbadensis*, vitamin C and E, and zinc oxide — the benefits of these are discussed below. The composition and percentage of MGH vary within the L-Mesitran range.

Natural remedies in wound care

Lanolin is a waxy substance secreted by the sebaceous glands of sheep and has been widely used for thousands of years. Medical-grade lanolin (Medilan®) is ultra-purified and hypoallergenic. It penetrates the skin and can help to retain and release water into the dry stratum corneum when required, causing almost no sensitisation (Stephen-Haynes and Callaghan, 2011; Pleeing et al, 2020).

Sunflower oil contains fatty acids, including linoleic acid, which are necessary for the skin's barrier function. Linoleic acid stimulates cell growth (Silva et al, 2018). Topically applied sunflower oil can help to prevent nosocomial infections (Darmstadt et al, 2005), preserve stratum corneum integrity (Danby et al, 2013) and encourage granulation (Marques et al, 2004).

Cod liver oil is high in omega-3 fatty acids, vitamin A and vitamin D. Cod liver oil accelerates the speed of epithelial and vascular healing (Terkelsen et al, 2000) and increases pro-inflammatory cytokine production (McDaniel et al, 2008).

Calendula officinalis is a natural oil extracted from the marigold flower, which possesses properties conducive to wound healing, particularly relating to inflammation, microbial load and epithelialisation (Leach, 2008).

Aloe barbadensis (*Aloe vera*) is widely used for its antibacterial, anti-viral and anti-inflammatory effects and pro-healing properties (Sahu et al, 2013).

Other natural agents include:

- Vitamin C, a well-known co-factor in the biosynthesis of collagen to improve tensile strength in skin. It is also an angiogenic agent
- Vitamin E, which can modulate cellular signalling, gene expression and help wounds infected with methicillin-resistant *Staphylococcus aureus* to heal (Hobson, 2016)
- Zinc oxide, which forms a protective barrier on the skin and plays a major role in regulating every phase of wound healing (Lin et al, 2018).

What is L-Mesitran?

L-Mesitran combines MGH, along with antioxidants vitamin C and E to help boost the effect of honey (Pleeing et al, 2020; Figure 2).

Both these vitamins exert antimicrobial activity against a wide range of microorganisms, including *Staphylococcal* species (including *Staphylococcus aureus*), *Streptococcal* species, *Proteus vulgaris*, *Escherichia coli*, *Bacillus subtilis*, *Candida albicans*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (Pleeing et al, 2020).

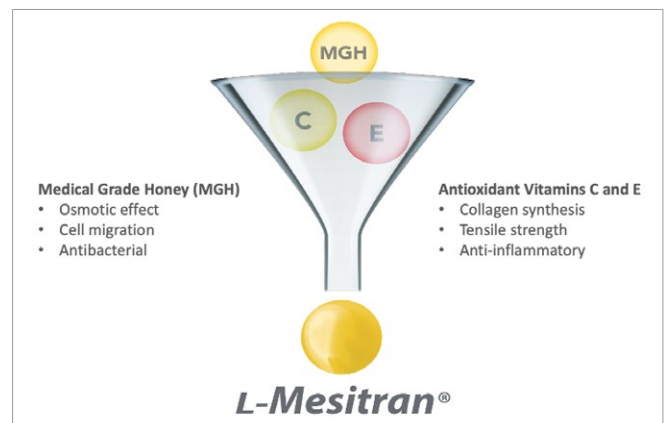


Figure 2. L-Mesitran® — a combination of MGH and antioxidants vitamin C and E

L-Mesitran is indicated for a wide range of wounds including:

- Chronic wounds
- Superficial and acute wounds
- Superficial and partial thickness burns
- Fungating wounds
- Oncology wounds.

L-Mesitran products have been designed to help heal wounds naturally and are available in a variety of different formats in order to meet a wide range of requirements, as selection should be appropriate for the wound and treatment type.

L-Mesitran® Ointment is antibacterial and contains 48% MGH, medical-grade hypoallergenic lanolin (Medilan®), sunflower oil, cod liver oil, *Calendula officinalis*, *Aloe barbadensis*, vitamin C and E and zinc oxide. The ointment draws fluid from the surrounding tissue once in contact with the wound, helping to debride and reduce bacterial colonisation in deep and/or superficial wounds. It is important to note that only a thin layer is required for optimal effect.

L-Mesitran® Soft is antibacterial and contains 40% MGH, medical-grade hypoallergenic lanolin (Medilan®), propylene glycol, PEG 4000 and vitamin C and E. It is indicated for use on patients with sensitivity to honey, due to its reduced honey content. The gel dissolves and removes non-viable tissue to promote healing.

L-Mesitran® Hydro is a hydro-active, antibacterial dressing and contains 30% MGH, an acrylic polymer gel and water with a polyurethane film backing. **L-Mesitran® Border** is identical, but with an adhesive border. These dressings create and maintain a moist environment — the thin honey-hydrogel layer can absorb at least 7 times its own weight in wound fluid. The dressings are suitable for

Table 1. Summary of clinical evidence for the L-Mesitran range		
Study	Method	Results and discussion
MGH for the Treatment of Extravasation-Induced Injuries in Preterm Neonates: A Case Series (Smaropoulos and Cremers, 2021)	Case series of seven preterm neonates (28–36 weeks of gestation) with extravasation injuries secondary to peripheral intravenous administration of total parental nutrition and medication	<ul style="list-style-type: none"> L-Mesitran Ointment effectively debrided necrotic tissue, removed slough and no signs of infection were detected, irrespective of initial wound presentations Following treatment, all wounds progressed to normal epithelialisation and closed in 7 to 67 days L-Mesitran Ointment was safe and successful in treating extravasation-induced injuries, independent of location and severity.
Synergistic antimicrobial activity of supplemented MGH against <i>Pseudomonas aeruginosa</i> biofilm formation and eradication (Pleeging et al, 2020)	Case reports of four wounds predominantly infected with <i>Pseudomonas aeruginosa</i> , including a diabetic foot ulcer, abscess, pressure ulcer and wound on the ankle	<ul style="list-style-type: none"> L-Mesitran Soft has a strong activity on <i>Pseudomonas</i> biofilms, without the need for antibiotics Infections were resolved quickly, and the wound healing trajectory improved L-Mesitran Soft promoted granulation and reduced malodour, pain, necrotic tissue and slough.
MGH kills antibiotic-resistant bacteria and prevents amputation in diabetics with infected ulcers: A prospective case series (Nair et al, 2020)	Prospective case series of six patients with infected diabetic ulcers, of which some were at risk of (further) amputation	<ul style="list-style-type: none"> All treated with one or more MGH formulations of the product range of L-Mesitran (Soft, Ointment, Net, Tulle, or Hydro), which typically reduced malodour in a couple of days and controlled infection within 2–3 weeks L-Mesitran resolves infections and enhances healing by promoting granulation, angiogenesis, and re-epithelialisation, decreasing inflammatory and oxidative stress, and providing nutrients L-Mesitran is safe and cost-effective for treating complicated diabetic wounds with (antibiotic-resistant) infections and at risk of amputation.
Treating severe wounds in paediatrics with MGH: A case series (Smaropoulos and Cremers, 2020a)	Prospective observational study of five paediatric patients of different wound types including an extravasation-induced injury, a haemangioma, a coccyx ulcer, and two with thermal burns	<ul style="list-style-type: none"> L-Mesitran Ointment was easy to apply, did not cause pain or discomfort and helped to prevent possible infections due to its strong antimicrobial activity L-Mesitran Ointment provides a natural and efficient alternative to antibiotics In all cases, treatment was well received, and full wound healing achieved.
MGH for the treatment of paediatric abdominal wounds: a case series (Smaropoulos and Cremers, 2020b)	Prospective observational case series evaluating five young infants with abdominal wounds	<ul style="list-style-type: none"> All wounds rapidly presented granulation and re-epithelialisation Peripheral oedema and inflammation decreased upon initial application Necrotic tissue was effectively debrided, slough removed, and no signs of infection were detected Scar formation was minimal and full range of motion was preserved in all cases.
The pro-healing effects of MGH supported by a paediatric case series (Smaropoulos and Cremers, 2019)	Prospective observational case series of four paediatric patients with wounds of different origin	<ul style="list-style-type: none"> L-Mesitran Ointment prevents pathogen infiltration, has antimicrobial activity, keeps the wound moist and possesses strong pro-healing effects, such as autolytic debridement and restoration of vascular structures Anti-inflammatory and anti-oxidative action of MGH together with vitamin C and E may inhibit scar formation.
Patient education, self-care, and MGH — managing a diabetic ulcer (Nwabudike and Maruhashi, 2017)	Case report of an 85-year-old diabetic patient with multiple comorbidities who presented with a 2-week history of right leg ulceration	<ul style="list-style-type: none"> L-Mesitran Soft may be an affordable and efficacious option for patients with multiple comorbidities and leg ulcers Success of treatment depended on the patient-physician relationship, which improved compliance without reducing efficacy Treatment could be carried out at home, translating into cost savings.

areas that are difficult-to-dress or where mobility is key. The dressing locks away and absorbs exudate, preventing maceration and odour, so is indicated for use on highly exuding wounds.

L-Mesitran® Net is a sterile open-weave mesh dressing coated with a hydro-active hydrogel and contains 20% MGH, an acrylic polymer gel and water on a polyester mesh structure. L-Mesitran Net requires a secondary dressing and can be used in conjunction with L-Mesitran Ointment and Soft. The open-weave net allows passage of exudate from the wound to be absorbed by the secondary dressing, avoiding maceration. This wound contact layer provides a moist wound interface to help promote an ideal healing environment.

In vitro evidence

The synergistic antimicrobial activity of MGH-based wound care products has recently been explored against multidrug-resistant *P. aeruginosa* biofilm (Pleeging et al, 2020). All products in the L-Mesitran range demonstrated significant biofilm inhibitory activity; however, the most potent antimicrobial activity (6.08-log inhibition and 3.18-log eradication) was identified with L-Mesitran Soft.

Its supplementary ingredients such as vitamin C and E were individually investigated. Separately the components of L-Mesitran Soft exert antimicrobial activity, but in combination, a synergistic activity may occur (Pleeging et al, 2020). Several clinical cases from

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Author details:
Sharon Gardner, Clinical Support Nurse Specialist, H&R Healthcare

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Pleeging et al (2020) illustrate the clinical antimicrobial efficacy of L-Mesitran Soft against *P. aeruginosa* biofilms, see Table 1.

Hermanns et al (2019) evaluated the susceptibility of five clinical isolates of *C. albicans* and a control strain to L-Mesitran Soft. Results showed that 50% dilutions of L-Mesitran (with a honey content of at least 20%) eradicated clinical isolates of *C. albicans*, while regular honey (40%) was ineffective and did not show antifungal activity. Similar results were obtained in another study, supporting that the supplements in L-Mesitran Soft strongly enhanced the antifungal activity of the MGH component against several *Candida* species, including *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and the superbug *C. auris* (de Groot et al, 2021).

Cremers et al (2020) investigated the antimicrobial activity of L-Mesitran (40% MGH) and an 80% Manuka Honey product against *Staphylococci* and *Pseudomonas* pathogens. At low bacterial concentration, L-Mesitran and Manuka Honey were similarly effective against *Staphylococci*; however, at high levels, L-Mesitran was more effective. L-Mesitran showed significantly stronger antimicrobial activity against *Pseudomonas* bacteria. Overall, L-Mesitran demonstrated higher efficacy and consistency against *Pseudomonas* and *Staphylococci*, while containing only half of the amount of honey (Cremers et al, 2020).

Clinical studies

A recent case series has demonstrated that MGH should be more frequently considered when treating paediatric wounds (Smaropoulos and Cremers 2020a). MGH helped to keep wounds moist, while the strong osmotic effect promoted autolytic debridement. MGH has also been shown to be safe and effective to treat a variety of abdominal wounds in young paediatric patients (Smaropoulos and Cremers,

2020b). MGH is recommendable as a first-line treatment in paediatric patients and is also safe to be used for preterm neonates with extravasation-induced injuries (Smaropoulos and Cremers, 2021).

The L-Mesitran product range has been shown to be effective, safe, and easy to apply, in different patients and clinical situations (Zbucnea, 2017). See Table 1 for a full summary of clinical evidence.

Promoting patient compliance

L-Mesitran has been found to reduce pain and discomfort for patients, which can contribute to improved acceptability and compliance with treatment. Positive user experiences have been reported, highlighting that effectiveness of L-Mesitran is retained and more importantly, enhanced, compared to other MGH products (Pleeging et al, 2020; Smaropoulos and Cremers, 2020a).

Summary

L-Mesitran wound care products offer the unique formulation of MGH with antioxidants vitamin C and E to boost the antimicrobial effect of the honey. The products use effective, naturally occurring agents to manage bacterial load and encourage healing and patient compliance, without contributing to antimicrobial resistance.

L-Mesitran has provided positive patient experiences and outcomes, helping to manage inflammation, malodour, and pain, promote debridement, stimulate healing, and provide an optimal moist wound environment (Smaropoulos and Cremers, 2019; 2020a). It is a safe and cost-effective approach, suitable for different wound types. The variety of products available means the range is easy to use throughout all stages of the healing process and can help to improve choice and acceptability to patients.

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