The Inhibitory Effects Demonstrated by Manuka Honey on Biofilms: How Manuka Honey May Soon Replace Conventional Antibiotic Therapy
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Introduction
The surge of antibiotic-resistant bacteria has raised substantial concerns over how to effectively and efficiently control antibiotic-resistant bacteria capable of secreting biofilms. A biofilm can be defined as a self-producing extracellular matrix (Carter, et al., 2016). Manuka honey, an alternative to conventional antibiotics, has proven successful in inhibiting planktonic cells and killing bacteria living under the protection of biofilms (Brudzynski & Sjaarda, 2015).

Formation of Biofilms
When the structures and functions of various biofilms were assessed, their mechanisms of resistance appeared to be dependent upon multicellular strategies. First, the higher the number of cells present in a given area increases the resistance of these cells to conventional antibiotics (Lin, et al., 2010). In addition, biofilms contain persister cells, requiring minimal amounts of energy in order to survive for long durations (Cundell & Wilkinson, n.d.). Therefore, as the surface level cells die, they offer a protective layer of impenetrability for persister cells in the center of the biofilm (Cundell & Wilkinson, n.d.). Finally, in order for biofilms to be present, an initial adherence to a physical material is required (Lin, et al., 2010).

The Origins of Manuka Honey
Manuka honey is produced by select Leptospermum species native to New Zealand and Australia, and is colonized by the honey bees, Apis mellifera (Brudzynski & Sjaarda, 2015). Levels of antimicrobial components contained in different batches of Manuka honey can range from 100ppm to greater than 1200ppm (Carter, et al., 2016). Therefore, antibacterial activity of Manuka honey has to be tested individually.

Medical-grade Manuka honey is subjected to gamma radiation in order to ensure its sterility (Carter, et al., 2016). The medical community developed the phenol-equivalent scale as a standard to express the potency of antibacterial activity.

Anti-Microbial Properties of Manuka Honey
Methylglyoxal: Unique Manuka Factor (UMF)
Methylglyoxal and its derivatives are known to have antibacterial activity (Lin, et al., 2010). In addition, methylglyoxal is commonly referred to as Leptospermone, a glycoside found exclusively in Leptospermum, was found to be stored near Manuka honey (Marcucci et al., 2009). This finding provides a unique mechanism for Manuka honey against ethanol-induced gastric ulcers in rats. When experimentally induced, the anti-ulcer effect of Manuka honey was demonstrated by decreased gastric secretion and increased gastric tissue weight (Marcucci et al., 2009).

Osmotic Stress, Leptosin, and Phenolic Components
Carter, et al., (2016) successfully demonstrated that the combination of a high sugar content and low pH, which promotes osmotic stress, inhibits microbial growth, even when the honey has been subjected to more than 30-40% (Kwakman & Zaat, 2012). Methyl syringate-4-O-D-glucoside, commonly referred to as Leptosin, a glycoside found exclusively in Leptospermum, was found to have a positive correlation with the UMF value. This indicates that levels of leptosin may be linked to the modulation of antimicrobial activity (Carter, et al., 2016). Marcucci (1995) concluded in an experiment that phenolic acids including flavonoids derived from propolis and present in Manuka honey, exhibited weak antibacterial activity, have potentially contributed to the observed non-peroxide antibacterial activity (NPABA).

Isolation of a 5.8-kDa Component
Tonks, et al. (2007) discovered a 5.8-kDa component in Manuka honey that stimulates human immune cells via TLR4, or the cytokine induction in human monocytes. This component was determined to be directly involved in the mechanism which stimulates innate immune cells to respond. While it is unknown whether this moiety is unique to Manuka honey or universally present in all honeys, it does appear to play a role in the anti-inflammatory activity observed in Manuka honey (Tonks, et al., 2007).

Anti-Biofilm Activity in Manuka Honey
Manuka honey has been proven to inhibit in-vitro biofilm experiments. More specifically, Gentamicin and Manuka honey produced an additive interaction against P. aeruginosa biofilms and a synergistic interaction with vancomycin against S. aureus biofilms (Campeau & Patel, 2014). When Manuka honey dressings were utilized in conjunction with oxacillin, tetracycline, imipenem, and mupirocim, a synergistic effect was achieved against MRSA (Carter, et al., 2016). The findings suggested that the combined therapeutic intervention of Manuka honey wound dressings and antimicrobials could lower the dosage of antimicrobial medications required to inhibit the biofilm as well as prevent the development of resistance.

Manuka honey’s bactericidal action is associated with non-peroxide antibacterial activity (NPABA). In-vitro isolates with multi-drug resistant phenotypes have not demonstrated any reduction in their susceptibility nor generated any resistant strains to Manuka honey when administered at inhibitory levels under normal laboratory conditions (Carter, et al., 2016). While bactericidal effects were seen in both planktonic cultures and biofilms, a higher concentration of Manuka honey was required to inhibit sessile bacteria, compared to its counterpart, free-living bacteria (Hammond, et al., 2014). Test strains of well-known pathogenic bacteria were inhibited at lower concentrations in a liquid medium compared to on agar well diffusion plates (Hammond, et al., 2014). This finding may be attributed to the ability of the components of Manuka honey to diffuse more readily and uniformly in a liquid medium due to the osmotic effects.

Further Applications
Gastrointestinal Ulcers
Almasauda et. al. (2016) has performed experiments to assess gastroprotective effects associated with Manuka honey against ethanol-induced gastric ulcers in rats. After experimentation, the researchers were able to conclude that Manuka honey substantially lowered the rats’ ulcer index, indicating that it protected the gastric mucosa from lesions and preserved gastric mucosal glycoproteins. Further research and experimentation is still needed in order to determine if Manuka honey is able to produce similar anti-ulcer outcomes in humans.

Anti-Cancerous Properties
Vallianou, Evangelopoulos, Skourtis, and Kazazi (2017) have confirmed with in-vitro experimentation, the anti-cancerous properties of Manuka honey via apoptosis. Scientists believe that Manuka honey induces caspase-9, which in turn, activates the caspase-3 executor proteins. These caspese enzymes are directly involved in the death receptor signaling pathway, which ultimately induces apoptosis (Vallianou, et al., 2017). This contributes to the immune-protective and immune-mediator activity, which is closely associated with anti-cancerous properties. In vivo testing has yet to be conducted. Therefore, Manuka honey’s interaction in the human body is unknown and may inhibit or alter some of the anti-cancerous properties observed.

References