Research Article

Synergism between manuka honey and penicillin antibiotics against *Escherichia coli*

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Abstract

Previous studies have suggested synergistic effects between manuka honey and different antibiotics against *Staphylococcus* aureus. In the present study we have tested *in vitro* the antibacterial efficacy against *Escherichia coli* of manuka honey with or without ampicillin and penicillin using the disc diffusion method. Similar synergistic effects of manuka honey with ampicillin and penicillin were observed, particularly in early phases of treatment. Overall, these results support the potential use of natural antimicrobials such as manuka honey either alone or in combination with synthetic agents to lower their therapeutic dose and prevent antibiotic resistance.

Keywords: Antibiotics; Antibiotic resistance; Natural; Synthetic; Manuka honey

1. Introduction

Although the therapeutic properties of honey have been known for centuries, its antiseptic and antimicrobial properties have been discovered recently. Consisting mainly of carbohydrates, honey also contains several enzymes, proteins, aminoacids, vitamins, lipids, minerals, and phytochemicals which vary considerably by type of honey and are believed to exert health benefits [1, 2]. The antibacterial activity of honey has been attributed to different factors, including hydrogen peroxide, low pH, high osmolarity, and methylglyoxal (MGO) [3-6]. Among the different types of honey, manuka honey has attracted attention for its antimicrobial effects in numerous bacterial pathogens [7] receiving regulatory approvals for clinical use as a wound care agent in the European Union, the USA, New Zealand and others. Of particular interest is that, despite attempts to induce bacterial resistance to manuka honey in the laboratory, there has been no such report which may be due to the complex composition of honey and the multiple active components [8]. Furthermore, multi-resistant bacterial strains have been shown to remain sensitive to manuka honey suggesting a broad spectrum of action and highlighting its potential clinical usefulness [9]. With increasing concerns over antimicrobial resistance worldwide [10], there has been much focus on the potential use of natural antimicrobials [11, 12]. The objective of this study was to compare the antibiotic activity of manuka honey with commonly used synthetic antibiotics, specifically ampicillin and penicillin, as well as to explore any synergistic effects.

2. Materials and Methods

2.1 Inoculum and plate preparation

Commercially available agar plates were spread-plated with approximately 200 µl suspension from an overnight liquid culture of *Escherichia coli* (E. coli) incubated at 37°C for 48 hours.

2.2 Antimicrobial susceptibility test

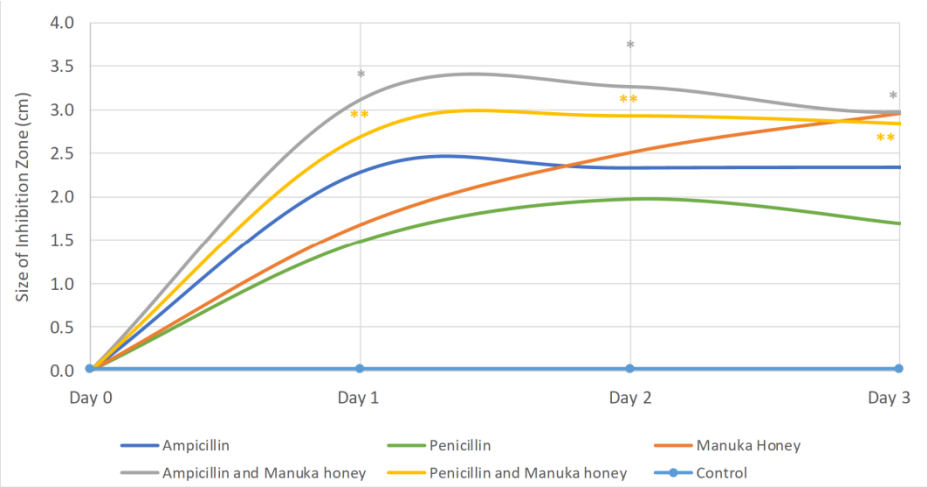
Antimicrobial susceptibility test was done using the disc diffusion method as previously described [13]. In each plate six discs were placed, one each containing ampicillin (10 µg), penicillin (10 units), and manuka honey (1 drop), two containing manuka honey with ampicillin or penicillin, respectively, and an empty disc (negative control). The plates were then incubated immediately at 37°C and the diameters of the inhibition zones were measured every 24 hours.

2.3 Data analysis

Data-driven simulation was used to generate 100 observations per treatment group at each timepoint using the SAS procedure PROC SIMNORMAL and the parameters of the input data set. Subsequently, mixed models with repeated measures taking into consideration the correlation of iterations over time were used to compare the antimicrobial activity of ampicillin, penicillin, manuka honey and their combinations. The least square mean estimates were plotted against time. Statistical analyses were performed using SAS version 9.4.

3. Results and Discussion

Using the disc diffusion method all tested treatments exhibited significant ($p<0.0001$) antibacterial activity against *E. coli* (Figure 1). By Day 1, the antibacterial effects exerted by ampicillin were more potent, as demonstrated by larger inhibition zones, compared to the effects of penicillin ($p<0.0001$) or manuka honey ($p<0.0001$), while penicillin and manuka honey had comparable efficacy. On Day 2, ampicillin and manuka honey had comparable antibacterial activities which were significantly higher than penicillin ($p=0.0103$ and $p=0.0011$, respectively). Whereas, on Day 3, Manuka honey was most potent, followed by ampicillin and penicillin.



*p<0.0001 compared to ampicillin alone; **p<0.0001 compared to penicillin alone

Figure 1: Antimicrobial activity of manuka honey, synthetic antibiotics and combinations thereof.

In regard to combination treatments, on both Days 1 and 2, combination of manuka honey with ampicillin (manuka honey + ampicillin) or with penicillin (manuka honey + penicillin) resulted in significantly greater inhibition of bacterial growth compared to ampicillin alone ($p<0.0001$), penicillin alone ($p<0.0001$), or manuka honey (both $p<0.0001$). By Day 3, the antibiotic activity of all treatments had reached a plateau with maximal effects observed with manuka honey alone, manuka honey + ampicillin, and manuka honey + penicillin which were comparable. Overall, these results suggest a synergistic effect of manuka honey with ampicillin and penicillin, particularly in early phases of treatment. Similar synergistic effects *in vitro* were previously reported for manuka honey with antibiotics from the same class (oxacillin) and different classes (tetracycline, imipenem, mupirocin, rifampicin) against *Staphylococcus aureus* increasing the external validity of our findings [14, 15]. Further investigation will be needed to confirm whether the combinations identified here are effective against clinical isolates and biofilms. In the context of recommended antibiotic stewardship programs, aimed at improving antibiotic use to conserve effectiveness and reduce emergence of resistant strains [16], the results of our study suggest that use of manuka honey either alone or in combination with synthetic agents to lower their therapeutic dose in *E. coli*-related infections, merits further consideration.

Acknowledgments

Not applicable

Declaration of Interest Statement

None declared

Appendices

Not applicable

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