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Letter to the Editor

The post-antibiotic effect of manuka honey on gastrointestinal pathogens

Sir,

An increasing number of studies have shown that honey has substantial antimicrobial activity [1]. This has mostly been demonstrated by minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) tests in which microorganisms are exposed to a constant level of honey for a long period. However, the efficacy of honey taken orally would be greatly affected by dilution in large amounts of body fluids and water from food and drink as well as by a short period of contact with bacterial cells owing to rapid peristalsis in the gastrointestinal tract. We therefore investigated how long it would take manuka honey to eliminate microorganisms and whether or not honey has a post-antibiotic effect (PAE) similar to other common drugs.

Manuka honey (SummerGlow Apiaries Ltd., Hamilton, New Zealand) used in this work had non-peroxide antibacterial activity equivalent to that of 16.5% (w/v) phenol when tested by the method described by Allen et al. [2]. Artificial honey [3] consisting of sugars and distilled water was included as a control. *Escherichia coli* ATCC 25922, *Salmonella* serotype Typhimurium Phage Type 104 (ESR, Christchurch, New Zealand), *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Shigella flexneri*, *Shigella sonnei* (Waikato Hospital, Hamilton, New Zealand), *Salmonella* serotype Enteritidis and *Yersinia enterocolitica* (Medlab, Hamilton, New Zealand) were tested using Mueller–Hinton broth (MHB) (BD, Sparks, MD). Before exposure to the honey solution, it was ensured that the bacterial culture was in log phase at a density of ca. 10^6 colony-forming units/mL.

The MICs and MBCs of manuka honey for the microbes were determined (five independent repeats) as described previously [4]. To conduct time–kill assays, the inoculum was added to 20% (v/v) honey solution and viable counting was conducted hourly during overnight incubation at 37 °C. The presence of a PAE of 20% (v/v) manuka honey was determined by the method described by Craig and Gudmundsson [5]. Bacterial solution exposed to fresh MHB was included simultaneously in the assay as a control. Results of the MIC, MBC and pharmacodynamics assays are placed side by side for comparison in Fig. 1.

All microbes had a lower MIC value with manuka honey than with artificial honey (data not shown). Manuka honey at a concentration <8% (v/v) could inhibit most of the tested bacteria, and the MBC/MIC ratios of ca. 1:1 suggested that it acts primarily in a bactericidal manner. For most of the species, 20% (v/v) manuka honey solution was capable of killing the majority (1 $\log_{10}$) of organisms within 2–6 h (Fig. 1). The manuka honey showed a PAE of ca. 2–2.5 h against most of the species. *Pseudomonas aeruginosa* and *Y. enterocolitica* revealed a surprisingly long PAE of >3.5 h and >4.5 h, respectively (Fig. 1). The overall Spearman correlation coefficients (ρ) for all nine species for MIC–PAE and MBC–PAE were −0.033 ($P = 0.932$) and −0.208 ($P = 0.592$), respectively.

The pharmacodynamic studies appeared to reveal some hidden information that was not observed in the MIC and MBC studies. It is generally considered that a higher MBC means the bacteria are more tolerant to the antimicrobial agent and it may take some time for the agent to have a full effect on the metabolism of the cells.

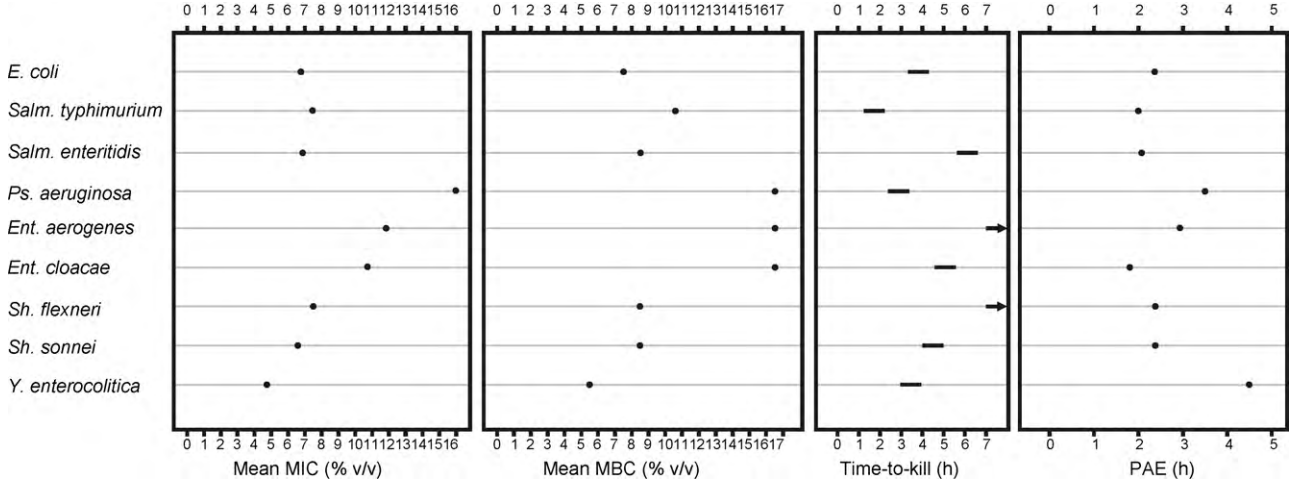

Fig. 1. Dot–plot of data from the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), time–kill and post-antibiotic effect (PAE) tests with manuka honey. Time–kill data are shown with bars instead of dots to demonstrate the approximate range of time the manuka honey (20%, v/v) takes to kill 90% of bacteria; results outside the detectable range are shown with arrows.

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However, it was observed that bacterial species with high MIC or MBC values were not necessarily able to survive in the honey for a long time. For instance, *P. aeruginosa* completely lost its viability within as short a time as *S.* Typhimurium, regardless of it being a notoriously difficult organism to control [6]. This suggests that some bacterial species might actually not be as hardy as suggested by the high MIC and MBC values and it may be possible to eradicate some difficult microbes as readily as other general species as long as the honey concentration is sufficiently high.

Similarly, there is no evidence of a correlation between the PAE and MIC or between the PAE and MBC. It is possible that the multidisciplinary activities in manuka honey [1,7] have different modes of bactericidal action on different species. The activities in the honey may be especially effective against some species (*P. aeruginosa* and *Y. enterocolitica*) and moderately effective with most other species (*E. coli*, *Salmonella*, *Enterobacter* and *Shigella*) used in this study. This hypothesis needs to be investigated further in the future.

In summary, whilst manuka honey did not show rapid bactericidal activity, it demonstrated a PAE of $\geq$2 h against the microbes tested in this study. This observation may help the community to understand further the properties and utility of manuka honey as an antibacterial when its fluidity and the possibility of the absorption/dilution of its antibacterial components are a concern. This study also provides information that MIC and MBC values are not necessarily correlated with pharmacodynamic profiles and therefore it may not be sufficient to evaluate efficacy solely by MIC and MBC testing.

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Ethical approval: Not required.

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