Clinical Significance of manuka honey and medical grade honey for antibiotic-resistant infections: A Systematic Review

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Introduction

- The unique antimicrobial and anti-inflammatory properties of honey have been established for millennia (Cremers *et al*., 2020).
- Honey exhibits a broad spectrum of activity, inhibiting a variety of microorganisms .
- Main factors contributing to the antimicrobial activity of honey are methylglyoxal, hydrogen peroxide and bee defensin-1 (Nolan *et al*., 2019).
- Antimicrobial resistance and multi-drug resistant microorganisms have become one of the largest threats to face modern medicine.
- Some of the clinically significant MDR pathogens include *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, *Escherichia coli*, extended-spectrum β-lactamase-producing (ESBL) *E. coli* and vancomycin-resistant enterococci (VRE) (World Health Organisation, 2017).
- New and novel strategies are required to combat these infections.
- This systematic review explores the efficacy of Manuka honey and medical-grade honeys against a variety of drug-susceptible and drug-resistant bacterial pathogens, to determine if honey should be further explored, utilised and implemented as a treatment.

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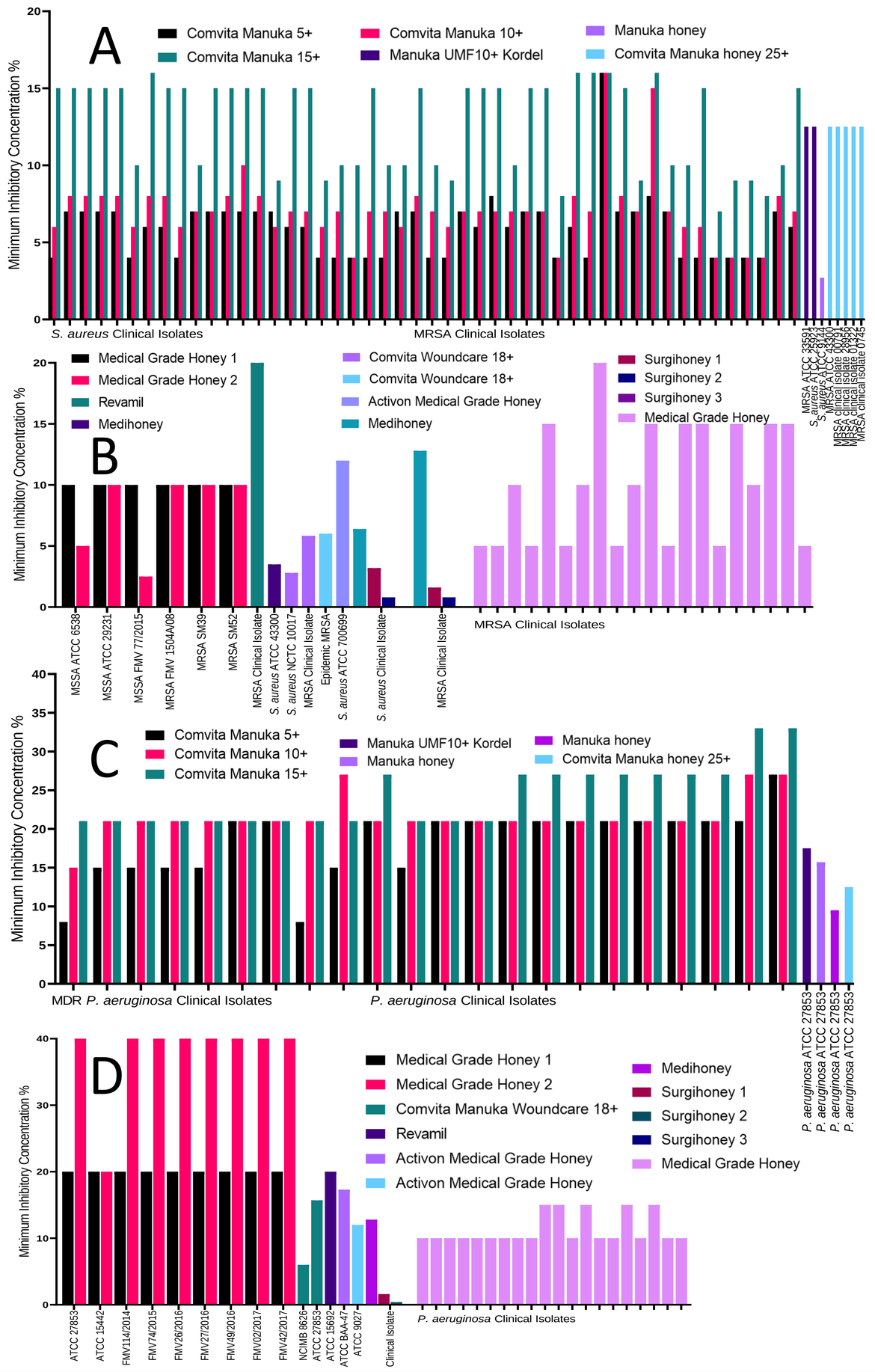
Methods

- To search the literature, PubMed, ScienceDirect, Google Scholar and Web of Science databases were used and searched by two independent researchers.
- Keyword search terms selected were: “Manuka honey”, “medical grade honey”, “Medihoney”, “multidrug resistant”, “multidrug resistance” and “multidrug resistant organism”.
- 3081 publications were identified and 32 articles selected based on title, abstract and type of article. 17 articles were removed due to not reporting antimicrobial activity of manuka or medical grade honey. 20 articles were therefore included in the systematic review.
- Two main methods were used in the majority of the papers, broth dilution and the agar dilution assay. These were used to determine minimum inhibitory concentrations (MICs) as a percentage.
- Manuka honey was defined as a honey originating from *Leptospermum* spp. and did not state any medical-grade classification. Medical-grade honey was defined as any honey stating a medical grade or medical use

Results

- *S. aureus* and *P. aeruginosa* were two of the most tested microorganisms and therefore had a very good representation for honey susceptibility. Both type strains and multidrug resistant isolates were tested against various manuka and medical grade honeys.
- For all *S. aureus* isolates tested, the MIC was 20% or lower. Comvita Manuka 5+ was more effective than Comvita Manuka 10+, 15+ and 25+, regardless of methicillin resistance and the lowest MIC observed was for a non-graded manuka honey (Figure A). Medical grade honeys exhibited a wider range of efficacy, with surgihoney being the most effective and Revamil the least effective (Figure B).
- *P. aeruginosa* exhibited a range of MIC to manuka honey. Comvita Manuka 5+ had the lowest MIC for all the Manuka honeys tested, with the lowest MIC for a multidrug resistant clinical isolate (Figure C). The most effective medical grade honey was Surgihoney followed by Comvita Manuka Woundcare 18+, the least effective was medical grade honey (Figure D).
- A variety of multidrug resistance bacteria were inhibited by both manuka and medical grade honey, with MICs ranging from 5% to 33% (Table 1).

Organism	Antibiotic Resistance	Honey and MIC
MRSA (Glasser *et al.,* 2010)	Clindamycin, erythromycin, levofloxacin and moxifloxacin	Medical-grade honey, 5%
MRSA (Glasser *et al.,* 2010)	Erythromycin, levofloxacin and moxifloxacin	Medical-grade honey, 20%
MRSA (Glasser *et al.,* 2010)	Gentamycin, levofloxacin, tetracycline and trimethoprim	Medical-grade honey, 5%
MRSA (Glasser *et al.,* 2010)	Erythromycin	Medical-grade honey, 15%
P. aeruginosa (Glasser *et al.,* 2010)	Amikacin, gentamycin, tobramycin, ampicillin/sulbactam, cefepime, ceftazidime, pipericillin/tazobactam, levofloxacin, ciprofloxacin, imipenem and meropenem	Medical-grade honey, 10%
P. aeruginosa (Glasser *et al.,* 2010)	Ampicillin/sulbactam	Medical-grade honey, 15%
ABC complex (Glasser *et al.,* 2010)	Amikacin, gentamycin, tobramycin, ampicillin/sulbactam, cefepime, ceftazidime, pipericillin/tazobactam, levofloxacin, ciprofloxacin and meropenem	Medical-grade honey, 10%
ABC complex (Glasser *et al.,* 2010)	Pipericillin/tazobactam	Medical-grade honey, 20%
Multidrug-resistant *P. aeruginosa* (Grima *et al.,* 2019)	Not Specified	Comvita Manuka 5+, <9% Comvita Manuka 10+, 15% Comvita Manuka 15+, 21%
P. aeruginosa (Grima *et al.,* 2019)	No resistance	Comvita Manuka 5+, 27% Comvita Manuka 10+, 27% Comvita Manuka 15+, 33%
E. coli (Lin *et al.,* 2011)	Amoxycillin, Amoxy/Clavulanate, Cefaclor, Trimethoprim, Ceftriaxone, Cefuroxime, Ceprofloxacin, Cotrimoxazole and Gentamicin	Manuka honey UMF16+, 5.08%
***E. coli* ATCC 25923** (Lin *et al.,* 2011)	Not Specified	Manuka honey UMF16+, 6.87%
E. cloacae (Lin *et al.,* 2011)	Amoxycillin, Amoxy/Clavulanate, Cefaclor	Manuka honey UMF16+, 5.88%
E. cloacae (Lin *et al.,* 2011)	Not Specified	Manuka honey UMF16+, 10.65%



Discussion

- Both manuka honey and medical grade honeys exhibited a wide range of efficacy against both Gram positive and Gram negative bacteria.
- Ungraded or lower graded manuka honeys were often more effective than higher grades.
- Surgihoney 3 was the most effective of all medical grade honeys, having the lowest MICs overall.
- Multidrug resistance strains often had lower MICs when compared with non-resistant counterparts, regardless of which honey was being tested.

Conclusions

- Manuka honey and medical grade honey are both effective at inhibiting a variety of microorganisms.
- Drug-resistant status of the organisms tested did not appear to impact the efficacy of the honey
- Honey therapy should be implemented, where possible, regardless of antibiotic resistance.

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