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Review

Manuka Honey as a Bioactive Antimicrobial System against ESKAPE and Fungi

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Abstract: Manuka honey (MH) has been established as an antimicrobial agent with potent activity against a diverse range of multidrug-resistant pathogens, including the ESKAPE group. The antimicrobial effect is based on a multimodal mechanism of action involving methylglyoxal (MGO), hydrogen peroxide, polyphenols, osmotic pressure, and bee-derived antimicrobial peptides. It inhibits bacterial cell division, compromises membrane integrity, induces oxidative stress, and modulates gene expression related to virulence, including quorum sensing and biofilm maturation. MH exhibits consistent efficacy against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other recalcitrant organisms, with a remarkably low propensity for the development of stable resistance. MH has also augmented the efficacy of various antibiotics for effectively sensitizing resistant strains and enhancing biofilm eradication. Its antifungal activity against *Candida* species, further broadens its therapeutic spectrum. Together, these properties position MH as a clinically relevant adjunct or alternative to conventional antimicrobials, particularly in chronic wound care.

Keywords: Manuka honey; methylglyoxal; antibacterial; antifungal; ESKAPE; antibiotic adjuvant

1. Introduction

Monofloral Manuka honey (MH) is primarily derived from the nectar of *Leptospermum scoparium*, a species native to New Zealand. Unlike regular honeys, where antibacterial efficacy is largely peroxide-dependent, MH demonstrates significant non-peroxide antimicrobial activity that remains stable following peroxide neutralization. The antimicrobial profile of MH is attributed to a chemically complex matrix of bioactive constituents rather than a single dominant component [1]. Compositionally, MH is defined by high concentrations of methylglyoxal (MGO), which originates from the non-enzymatic conversion of dihydroxyacetone (DHA) during the maturation process. Besides MGO, various phenolic acids and flavonoids contribute to the overall antimicrobial synergy. Medical-grade MH exhibits potent activity against both Gram-positive and Gram-negative bacteria, including multidrug-resistant strains [2].

Antibacterial effects and associated morphological alterations are species-dependent and vary across honey varieties [3]. Clinical evidence further supports the therapeutic application of medical-grade GH in the management of infected wounds, including those colonized by MRSA and *P. aeruginosa* [4]. The exposure of *P. aeruginosa* to MH disrupts membrane potential, global gene expression, and cellular bioenergetics, reinforcing the paradigm that honey exerts multi-targeted, system-level stress [5].

MH functions through a combination of osmotic stress, chemical toxicity, membrane destabilization, and disruption of the proton motive force. This multi-modal mechanism accounts for its efficacy against highly recalcitrant pathogens and its observed synergy with specific antibiotic classes. In clinical practice, this multifactorial activity is precisely what enables MH to remain effective against diverse microbial communities, including those embedded within chronic wound biofilms. While MH is recognized as a safe dietary product, its

antimicrobial and cytotoxic effects are fundamentally concentration dependent. Therefore, its clinical utility necessitates the identification of application-specific therapeutic windows that maximize microbial inhibition while maintaining host tissue biocompatibility.

This framework positions MH as a model for system-level antimicrobial stress, using *P. aeruginosa* and other ESKAPE pathogens as primary benchmarks. Furthermore, its potential as a novel class of antifungal agents warrants significant consideration (Figure 1).

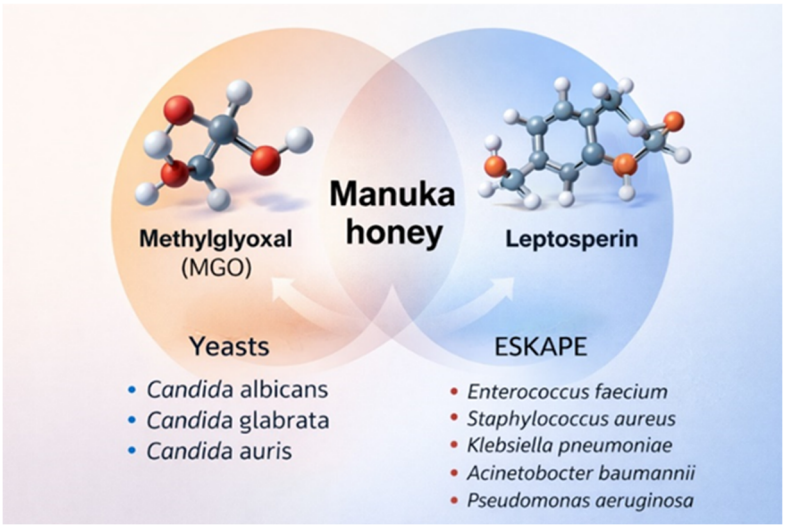

Figure 1. Key chemical markers of MH: methylglyoxal (MGO), the primary non-peroxide antimicrobial compound, and leptosperin, a stable *Leptospermum*-specific glycoside utilized as a definitive authenticity marker for monofloral MH.

2. Major Antimicrobial-Responsive Constituents of Manuka Honey

Although MH contains numerous identifiable chemical entities, only a specific subset has been consistently associated with antimicrobial efficacy across independent analytical and biological investigations. This perspective focuses on the primary compound classes with demonstrated antimicrobial relevance rather than providing an exhaustive chemical inventory. Comprehensive analyses utilizing HPLC, HPLC–MS/MS, GC–MS, and targeted metabolomics have established that the antimicrobial activity of MH arises from the synergistic action of reactive carbonyls, selected phenolic acids, flavonoids, organic acids, and enzyme-derived components, all of which operate alongside inherent osmotic stress. These constituents are present at concentrations sufficient to elicit biological effects and have been repeatedly identified across various MH grades and geographic origins (Table 1).

Table 1. Major antimicrobial-relevant constituents of MH; identified via advanced analytical methods.

Compounds	Key Representatives	Analytical Methods	Antimicrobial Relevance	References
Reactive carbonyls	MGO, DHA	HPLC–UV, HPLC–MS/MS	Non-peroxide antibacterial activity; protein and enzyme modification	[1,6]
Phenolic acids	Gallic, caffeic, *p*-coumaric, and ferulic acids	HPLC–DAD, HPLC–MS/MS	Membrane perturbation, redox modulation, and antibiofilm activity	[1,7]
Flavonoids	Pinocembrin, chrysin, and quercetin	HPLC–MS/MS, LC–ESI–MS	Membrane interaction, metabolic interference, and antioxidant/redox effects	[1]
Organic acids	Gluconic acid, acetic acid	HPLC, ion-exclusion chromatography	Acidification, metabolic stress, and potentiation of other agents	[4]
Enzymatic components	Glucose oxidase, bee defensin-1	Enzymatic assays, proteomics	Controlled H_2O_2 generation; innate antimicrobial peptide activity	[4]

Only compound classes with consistent antimicrobial relevance across multiple studies are included; minor or sporadically reported constituents are excluded. Briefly, MGO (100–1000 mg/kg) serves as the primary antibacterial agent; it is derived from DHA (100–4000 mg/kg) found in the nectar (Figure 2).

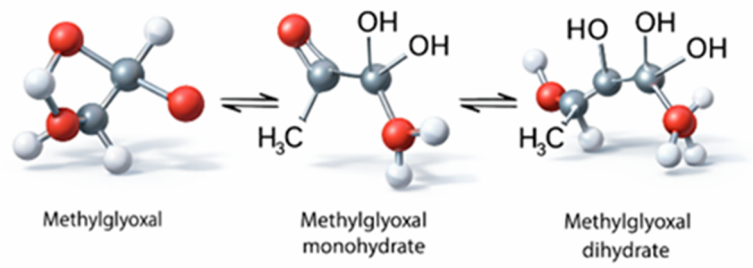

Figure 2. MGO (CH_3COCHO) exists in aqueous systems as an equilibrium mixture of three species: reactive dicarbonyl, monohydrate, and dihydrate. In aqueous or biological environments, rapid hydration of the carbonyl groups shifts the equilibrium toward monohydrate and dihydrate forms, which predominate under physiological conditions. The relative abundance of these species is governed by pH and solvent polarity, influencing MGO's chemical reactivity, stability, and biological effects. This equilibrium favors hydrated forms under physiological conditions, which is highly relevant to glycation and oxidative stress pathways.

Leptosperin (~30–50 mg/kg) serves as a unique chemical marker for Manuka authenticity, whereas methyl syringate (10–50 mg/kg) contributes to antioxidant and antibacterial activities. Flavonoids (including pinobanksin, pinocembrin, and chrysin), typically present at concentrations ranging from trace amounts to tens of mg/kg, also exhibit antioxidant and antimicrobial properties. Variable concentrations of hydrogen peroxide (H_2O_2) further contribute to honey's antimicrobial profile. Conversely, only trace amounts of amino acids and proteins are detected in Manuka honey, and these biomolecules offer negligible nutritional value.

Early investigations of MH relied primarily on HPLC with UV detection, which facilitated the identification of dominant phenolic acids and reactive carbonyls. More recently, HPLC–MS/MS and targeted metabolomics have confirmed the persistence of these compounds while clarifying their relative abundance and variability across samples. Although high-resolution techniques can detect numerous minor constituents, their individual contributions to antimicrobial activity remain either unclear or quantitatively negligible.

Medical-grade MH is distinguished from food-grade MH by its requirement for sterilization, standardization, and clinical approval. Unlike food-grade honey, which may contain natural spores and exhibits high compositional variability, MGH undergoes gamma irradiation to ensure sterility, is strictly tested for consistent MGO activity, and is formulated into specialized wound dressings or gels. These protocols ensure safety and reproducibility, facilitating their use in clinical settings for the management of burns, ulcers, and surgical wounds. MGO is widely recognized as the principal antibacterial component of MH, a role established through the analytical work of Adams et al. (2008) [6], who characterized the active antibacterial fraction. Phenolic compounds further augment this activity through their antioxidant and membrane-active properties, as evidenced by early compositional analyses [7]. Organic acids and osmotic stress represent critical physicochemical contributors to the overall antimicrobial efficacy of MH in the wound microenvironment [4].

3. Eskape Resistance Mechanisms

The exceptional resilience of ESKAPE pathogens is mediated by a sophisticated network of molecular resistance mechanisms that synergistically compromise the efficacy of conventional antimicrobial therapies. These adaptations transcend single-gene modifications, encompassing complex processes such as enzymatic drug degradation, target site modification, upregulated efflux activity, reduced membrane permeability, robust biofilm maturation, and horizontal gene transfer. Notably, these resistance profiles exhibit significant heterogeneity across species and environmental niches, influenced by intrinsic genomic properties and the acquisition of mobile genetic elements.

Table 2 delineates the primary resistance mechanisms observed in ESKAPE pathogens, correlating each with representative examples and seminal literature to provide a comprehensive and integrated synthesis of their clinical significance. Because MH targets multiple cellular systems simultaneously, it bypasses many resistance mechanisms as summarized in Table 2, offering a therapeutic advantage over single-target antimicrobials.

Antimicrobial resistance in ESKAPE pathogens is underpinned by a multifactorial and adaptive framework in which multiple mechanisms operate concurrently. The synergy between enzymatic degradation, target site modification, reduced membrane permeability, and active efflux systems is further compounded by biofilm maturation and horizontal gene transfer. The recognized role of environmental reservoirs extends the scope of resistance beyond clinical boundaries. This integrated resistance landscape emphasizes the inherent limitations of monotherapy and underscores the imperative for combination strategies, innovative antimicrobial platforms, and robust global surveillance.

Table 2. Key resistance mechanisms in ESKAPE pathogens.

Resistance Mechanism	Description	Pathogens	References
Enzymatic inactivation	β-lactamases (ESBLs, carbapenemases) hydrolyze antibiotics	*K. pneumoniae, A. baumannii, Enterobacter spp.*	[8,9]
Target modification	Alteration of antibiotic targets (PBP2a, D-Ala-D-Lac)	*S. aureus* (MRSA), *E. faecium* (VRE)	[3,10]
Efflux pumps	Active extrusion of antibiotics	*P. aeruginosa, A. baumannii*	[9,10]
Reduced permeability	Porin loss limits antibiotic entry	*K. pneumoniae, P. aeruginosa*	[8,10]
Biofilm formation	Protective microbial communities	*P. aeruginosa, S. aureus, A. baumannii*	[8,10]
Horizontal gene transfer	Spread via plasmids/integrons	All ESKAPE	[8,9]
Environmental reservoirs	Persistence in aquatic systems	All ESKAPE	[9,11]

4. Mechanisms of Antimicrobial Action

MH exerts antimicrobial activity through multiple, partially overlapping mechanisms, which helps explain why conventional resistance has not yet been convincingly documented despite its broad use *in vitro* and in wound care. Unlike a single drug-like target, MH combines physicochemical stress, reactive carbonyl chemistry, phenolic/bioactive metabolites, and biofilm disruption in a concentration-dependent fashion, as shown in Figure 3 (Maddocks and Jenkins, 2013) [2].

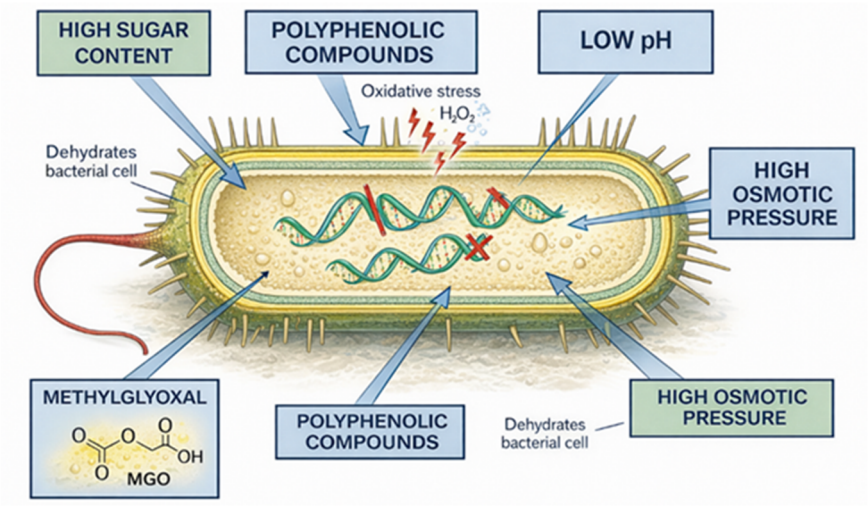

Figure 3. MH with multifactorial antimicrobial mechanisms encompasses osmotic stress, acidity, methylglyoxal reactivity, oxidative injury, and biofilm disruption.

4.1. Physicochemical Stress

The antimicrobial activity of MH is partly due to osmotic stress and acidity. These properties are well described in broader honey studies, including work by Almasaudi (2021) [12], demonstrating the inhibition of bacterial growth via dehydration and metabolic disruption. In MH, MGO can suppress hydrogen peroxide generation by inhibiting glucose oxidase [13], thereby shifting activity toward non-peroxide mechanisms. Honey exhibits potent antibiofilm effects against clinically relevant wound pathogens [14].

4.2. MGO and Dicarbonyl Stress

Reactive α-dicarbonyl MGO can modify both proteins and enzymes. The antibacterial properties of MGO, attributable to its capacity for protein modification and bacterial inactivation, have been demonstrated by Adams et al. (2008) [6].

4.3. Phenolics and Secondary Metabolites

Polyphenols and 3-phenyllactic acid significantly enhance MGO-mediated antibacterial effects [15]. Similarly, membrane-active phenolics, such as gallic acid can disrupt proton gradients and bacterial membranes [16].

4.4. Cell Division, Intracellular Targets, and Biofilms

MH induces morphological changes and loss of viability in *S. aureus* [17], whereas the inhibition of cell division through disruption of FtsZ ring formation in MRSA was demonstrated [18]. Importantly, Cooper et al. (2010) [19] showed no stable resistance development following repeated exposure. Biofilm disruption is a critical feature as Manuka-type honeys can eradicate established *S. aureus* biofilms [20], whereas gene expression studies by Kot et al. (2020) [21] revealed downregulation of biofilm-associated genes. However, adaptive responses have been observed under certain conditions as Camplin and Maddocks (2014) [22] reported increased tolerance following repeated exposure in *P. aeruginosa* biofilms. MH retains activity against multidrug-resistant organisms as it exhibits broad-spectrum efficacy and low likelihood of resistance development [23].

5. Manuka Honey against MRSA

5.1. Manuka versus MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most clinically significant multidrug-resistant pathogens, responsible for persistent wound infections, biofilm-associated complications, and increased morbidity in both hospital and community settings. The rapid emergence of antibiotic resistance of this Gram-positive pathogen necessitated alternative strategies. MH exhibits multifactorial antimicrobial effects, including oxidative stress induction, membrane disruption, inhibition of cell division, suppression of virulence, and biofilm inhibition. These mechanistic effects translate into measurable clinical benefits, particularly in MRSA-colonized wounds where conventional antibiotics often fail. It also enhances antibiotic sensitivity and shows synergistic activity with conventional agents (Table 3).

Table 3. Antimicrobial effect of MH on MRSA.

Mechanism/Effect	MIC (%)	Description	Key Findings	References
Direct bactericidal activity	~5–10	Broad-spectrum killing	Effective vs. MRSA clinical isolates	[24–26]
Oxidative stress	~5–10	Hydrogen peroxide generates ROS	Causes cellular damage	[27]
Cell division inhibition	~5–10	Disrupts septum formation	Growth arrest observed	[18]
Membrane damage	~5–15	Alters cellular structure	Protein expression affected	[17,28]
Virulence suppression	~5–10	Downregulates virulence genes	Reduced pathogenicity	[29,30]
Biofilm inhibition	~10–30	Prevents biofilm formation	Reduces viability	[31]
Synergy with antibiotics	~5–10	Enhances antibiotic action	Restores sensitivity	[32–34]

MH demonstrates potent, multi-target antimicrobial activity against MRSA. Reported MIC values are generally low (~5–10%), supporting its strong intrinsic activity. Its ability to disrupt biofilms, suppress virulence, and synergize with antibiotics further supports its role as an adjunct therapy in resistant infections.

5.2. MH against Pseudomonas aeruginosa

P. aeruginosa is a highly adaptable Gram-negative opportunistic pathogen and a major contributor to chronic wound infections, particularly due to its intrinsic resistance mechanisms and strong biofilm-forming capacity. This is particularly relevant because *P. aeruginosa* biofilms represent some most treatment-refractory microbial structures encountered in chronic wound care. The pathogen exhibits high tolerance to antibiotics through efflux systems, low membrane permeability, and quorum sensing–regulated virulence. MH has emerged as a promising alternative antimicrobial agent with activity against both planktonic and biofilm-associated *P. aeruginosa*. Unlike conventional antibiotics, MH exerts multifactorial effects, including disruption of cell structure, inhibition of motility, suppression of virulence genes, interference with quorum sensing, and inhibition of iron acquisition systems. MH demonstrates significant antibiofilm activity and acts synergistically with other antimicrobial approaches (Table 4).

Table 4. Antimicrobial effect of MH on *P. aeruginosa.*

Effect/Mechanism	MIC (%)	Description	Key Findings	References
Bactericidal activity	~20–30	Direct killing of planktonic cells	Effective killing with MIC50 ≈ 21% and MIC90 ≈ 21–27%	[35,36]
Structural damage	~20–30	Cell wall and membrane disruption	Alteration of cell morphology and integrity	[36]
Gene regulation	~20–30	Alteration of gene expression	Downregulation of oprF and algD virulence genes	[37]
Motility inhibition	~20–30	Suppression of flagella-associated genes	Reduced bacterial motility and spread	[38]
Iron metabolism inhibition	~20–30	Reduced siderophore production	Limits iron acquisition essential for growth	[39]
Quorum sensing inhibition	~15–30	Interference with communication pathways	Reduced biofilm formation and virulence signaling	[40]
Biofilm inhibition	~16–32	Prevention and disruption of biofilms	Significant reduction in biofilm mass and viability	[41,42]
Biofilm resistance adaptation	variable	Adaptive response under prolonged exposure	Emergence of reduced susceptibility in some isolates	[22]
Transcriptomic effects	~20–30	Global metabolic disruption	Broad changes in metabolic and stress-response pathways	[5]

Overall, MH exhibits strong antimicrobial and antibiofilm activity against *P. aeruginosa*, although higher concentrations are generally required compared to Gram-positive pathogens such as MRSA. Its ability to disrupt multiple cellular pathways, including virulence regulation, motility, quorum sensing, and iron metabolism, makes it particularly effective against biofilm-associated infections. While some adaptive responses have been observed, resistance development remains limited. These findings support the use of MH as a complementary or alternative strategy in managing chronic *P. aeruginosa* infections, especially in wound care settings.

5.3. MH Activity against Gram-Negative ESKAPE Pathogens

Unlike Gram-positive pathogens, e.g., *S. aureus*, Gram-negative ESKAPE pathogens, including *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Escherichia coli*, exhibit substantially higher intrinsic resistance to antimicrobial agents due to the presence of an outer membrane barrier, efficient efflux systems, and diverse enzymatic defense mechanisms. These structural and functional features significantly limit the penetration and efficacy of many conventional antibiotics, particularly in multidrug-resistant, extended-spectrum β-lactamase (ESBL), and carbapenem-resistant strains. Within this context, MH has emerged as a promising alternative or adjunct antimicrobial agent, demonstrating broad-spectrum activity against Gram-negative pathogens despite their inherent resistance mechanisms. However, compared with Gram-positive bacteria, these pathogens generally require higher concentrations of MH, typically in the range of 20–30% (*w*/*v*), to achieve inhibitory or bactericidal effects. This difference reflects both the protective role of the outer membrane and the complex adaptive responses of Gram-negative bacteria under antimicrobial stress. MH exerts its antibacterial activity through multiple complementary mechanisms, including membrane disruption, interference with metabolic and respiratory pathways, inhibition of virulence-associated gene expression, and impairment of biofilm formation.

Emerging evidence indicates that MH retains activity against clinically relevant resistant phenotypes, such as mcr-1–positive *E. coli* and *K. pneumoniae*, as well as carbapenem-resistant *A. baumannii*, and may exhibit enhanced efficacy when used in combination with other antimicrobial agents or natural products. These findings underscore the potential of MH as a versatile antimicrobial strategy that can target highly resistant Gram-negative pathogens. Table 5 summarizes representative minimum inhibitory concentrations (MICs), key mechanistic insights, and supporting literature for MH activity against selected Gram-negative ESKAPE organisms. Although higher concentrations of MH are required for Gram-negative pathogens, these levels are readily achievable in topical wound applications and remain clinically practical.

Table 5. MH activity against selected Gram-negative ESKAPE organisms.

Pathogen	MIC (% *w*/*v*)	Key Remarks	References
K. pneumoniae (ESBL/MDR/mcr-1+)	~18–25%	*Enterobacteriaceae* require ~20–30%. mcr-1+ strains: MIC ≈ 22%, MBC ≈ 25%. Strong inhibition at ≥40% MH.	[43–46]
Enterobacter spp.	~20–30%	MIC_{50} ≈ 21%, MIC_{90} ≈ 21–27%. Low MIC claims (~6–12%) inconsistent.	[8,43]
A. baumannii (CRAB)	~20–30%	Active against carbapenem-resistant strains. Combination enhances efficacy.	[8,47,48]
E. coli (incl. mcr-1+)	~20–30%; 18–22%	MIC_{50} ≈ 21%, MIC_{90} ≈ 21–27%. mcr-1+: MIC ≈ 18%, MBC ≈ 22%.	[43,44,49]
Enterococcus faecalis	~6–12%	Higher susceptibility vs. Gram-negative.	[8,23]
Other pathogens	~20–30%	Broad-spectrum activity.	[43,50]

Footnote: CRAB, carbapenem-resistant *Acinetobacter baumannii*; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration; MIC_{50}, concentration inhibiting 50% of tested isolates; MIC_{90}, concentration inhibiting 90% of isolates; MBC, minimum bactericidal concentration. Population-based metrics such as MIC_{50} and MIC_{90} provide a more clinically relevant assessment of antimicrobial efficacy across heterogeneous clinical isolates than single-strain MIC values.

5.4. MH and Antifungal Activity against Candida and Filamentous Fungi

MH has also demonstrated promising antifungal activity against *Candida* species, which are increasingly implicated in chronic wounds and biofilm-associated infections. It can inhibit the growth of *C. albicans* and interfere with fungal cell integrity and metabolic activity. MH exhibits significant antifungal effects against *C. albicans*, suggesting its potential as an alternative or adjunct antifungal agent [51]. Medical-grade MH has shown efficacy against drug-resistant fungal pathogens, including *C. auris*, a major emerging global health threat [52]. Given the increasing recognition of fungal–bacterial synergy in chronic wounds, MH's dual antibacterial and antifungal activity is of significant clinical importance.

MH impairs biofilm formation, a key virulence factor contributing to antifungal resistance. Supporting evidence summarized by Du et al. [53] further indicates that disruption of fungal biofilms and enhancement of antifungal susceptibility are critical strategies in combating resistant *Candida* infections. These findings suggest that MH may serve as a valuable adjunct in antifungal therapy, particularly in polymicrobial and chronic wound environments where bacterial–fungal interactions complicate treatment outcomes.

Both MH and Western Australian honey inhibited multiple clinically important yeasts, including *C. albicans*, *C. glabrata*, and *C. tropicalis*, with activity varying by honey type and concentration [54]. MH significantly reduced viable *C. tropicalis* within mixed biofilms containing *P. aeruginosa*, a clinically relevant model for diabetic foot ulcers and other chronic wounds [55]. These findings are notable because mixed bacterial–fungal biofilms are more resistant to conventional antimicrobials, and honey's ability to disrupt both components suggests a potential adjunctive role in complex wound infections. Additional studies confirm antifungal effects in mucosal and cutaneous contexts. Medical-grade MH inhibited vaginal isolates of *C. albicans*, reducing fungal burden and impairing growth kinetics [56]. Beyond yeasts, MH also demonstrates activity against filamentous fungi. MH and polyhexamethylene biguanide were evaluated against clinically relevant molds, showing that MH inhibited several filamentous fungal species while maintaining acceptable cytotoxicity profiles in human cell lines [57]. This expands the antifungal spectrum of MH and supports its potential utility in wounds colonized by both yeasts and molds.

These studies indicate that MH and other medical-grade honeys possess antifungal activity against *Candida* spp. and filamentous fungi, including within mixed-species biofilms. Although the number of studies remains limited compared with antibacterial research, current evidence supports MH as a biologically active adjunctive therapy in chronic wounds where fungal colonization may impede healing.

5.5. Synergy between MH and Antibiotics

The combination of MH with conventional antibiotics has emerged as a promising strategy to overcome antimicrobial resistance, particularly in multidrug-resistant pathogens associated with chronic wound infections. Unlike single-agent therapies, MH–antibiotic combinations exploit complementary mechanisms of action, whereby MH enhances antibiotic efficacy through membrane disruption, increased permeability, oxidative stress induction, and modulation of bacterial gene expression. These effects facilitate improved intracellular penetration of antibiotics and can restore susceptibility in otherwise resistant strains.

The most compelling evidence demonstrated that MH significantly sensitizes methicillin-resistant *S. aureus* (MRSA) to β-lactam antibiotics such as oxacillin, effectively reversing resistance phenotypes and improving bactericidal activity [33,58]. This resensitization effect has been linked to alterations in cell wall structure and

interference with resistance-associated pathways. Further studies have shown that MH enhances antibiotic activity against biofilm-associated infections, which are typically highly resistant to treatment. The combination of MH with rifampicin was significantly more effective than other antibiotic combinations in eradicating *S. aureus* biofilms, highlighting the importance of MH in disrupting biofilm architecture and improving antibiotic penetration [31]. Similarly, enhanced antibiofilm activity was observed when MH was combined with antibiotics, supporting its role in managing persistent infections [59].

Beyond Gram-positive pathogens, synergistic interactions have also been observed in Gram-negative bacteria. MH combined with penicillin-class antibiotics exhibited enhanced antibacterial activity against *E. coli*, indicating that MH can potentiate antibiotic effects even in organisms with intrinsic resistance mechanisms [60]. Improved activity of azithromycin when combined with MH against *Mycobacterium abscessus*, suggesting that this synergistic approach may extend beyond classical ESKAPE pathogens [61]. Clinical evidence further supports the translational potential of MH-based combination strategies. A randomized controlled trial demonstrated that medical-grade honey was effective in preventing catheter-associated infections, with comparable or improved outcomes relative to standard antibiotic prophylaxis [62].

Evidently, MH enhances antibiotic efficacy and reduces the likelihood of resistance development by targeting multiple bacterial pathways simultaneously. By restoring antibiotic susceptibility, enhancing biofilm eradication, and improving treatment outcomes across diverse pathogens, MH–antibiotic combinations offer a multifaceted approach that addresses key limitations of conventional antimicrobial therapy. These properties position MH as a valuable adjunct in the management of chronic and drug-resistant infections. Together, these findings support MH as a resistance-breaking adjuvant capable of restoring antibiotic efficacy against otherwise recalcitrant pathogens.

6. Manuka Honey in Wound Care and Ulcer Management

MH has been resurged as a clinically significant topical intervention for chronic wounds due to its broad-spectrum antimicrobial activity, antibiofilm properties, debridement efficacy, and capacity to facilitate tissue regeneration. Evidence derived from *in vitro* studies, animal models, randomized clinical trials (RCTs), and case series consistently indicates that MH reduces microbial bioburden, disrupts recalcitrant biofilms, accelerates granulation tissue formation, and supports healing in complex ulcers, including diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), burns, and infected surgical wounds.

6.1. Antibacterial and Antibiofilm Activity

MH demonstrates potent efficacy against both planktonic and biofilm-associated bacteria frequently isolated from chronic wounds. Merckoll et al. [63] reported that MH effectively inhibited *S. aureus* and *P. aeruginosa* isolates, achieving significant reductions in biofilm biomass. Shah and Williamson documented robust antibacterial activity against ESBL-producing *K. pneumoniae* recovered from burn wounds [46]. These antibiofilm effects are corroborated by a systematic review by Krishnakumar et al. [64], which emphasizes the ability of MH to disrupt established biofilms and impede their formation across various preclinical models. The hydrogen peroxide-mediated and non-peroxide activities of MH offer superior antibiofilm outcomes compared to multifloral varieties [65].

6.2. Clinical Evidence in Chronic Ulcers

The clinical utility of MH has been validated across diverse contexts, including MRSA-colonized ulcers, VLUs, and DFUs. Natarajan et al. [66] described the complete resolution of a hydroxyurea-induced, MRSA-colonized leg ulcer following MH application. Medical-grade MH eradicates antibiotic-resistant bacteria and prevents lower-limb amputations in diabetic patients with infected ulcers [67]. Successful VLU healing using MH dressings was also documented [68], while Kapoor and Yadav [69] reported favorable outcomes in a retrospective series of chronic non-healing wounds. The integration of MH into surgical and nursing protocols has been shown to enhance wound bed quality and mitigate infection burden [70]. In a randomized controlled trial, MH significantly reduced bacterial load and slough in VLUs relative to hydrogel dressings, underscoring its efficacy in wound bed preparation [71].

6.3. Preclinical Models and Novel Delivery Systems

Preclinical models further elucidate the wound-healing potential of MH. In both diabetic and non-diabetic rat models, MH significantly accelerated wound closure and improved histological parameters compared to acacia

honey [72]. Emerging delivery systems, such as MH-loaded microneedles, enhanced healing and prevented MRSA-associated surgical site infections in murine models, highlighting potential translational applications [73].

In summary, MH facilitates wound resolution through several integrated mechanisms supported across foundational and contemporary literature. Its antimicrobial activity is driven by MGO, hydrogen peroxide, and osmotic stress, as highlighted in clinical and mechanistic reviews [74]. MH also disrupts biofilms by inhibiting quorum sensing and destabilizing the extracellular matrix, an effect that was demonstrated *in vitro* by Merckoll et al. [63] and further reinforced by broader antibiofilm evaluations [65,75]. Its strong osmotic action promotes autolytic debridement by enhancing exudate flow and facilitating the removal of necrotic slough. In addition, MH exerts anti-inflammatory effects by reducing oxidative stress and modulating pro-inflammatory mediators. Finally, it supports granulation and re-epithelialization through its nutrient profile and by maintaining a moist wound environment conducive to tissue repair. These mechanisms align with broader regenerative pathways, including the modulation of apoptosis and mitigation of glycation-mediated tissue damage [76]. However, variability in honey composition and differences in study design highlight the need for standardized clinical protocols to ensure reproducible therapeutic outcomes.

7. Revisited Antimicrobial Effects of MH

7.1. Pure Methylglyoxal versus Whole MH

As discussed earlier [6], MGO is attributed to its capacity for protein modification and bacterial inactivation. Early work by Mavric et al. [77] identified MGO as the dominant antibacterial constituent in MH, demonstrating a strong correlation between MGO concentration and antibacterial potency. This finding established MGO as a key marker of MH bioactivity and led to its widespread use in grading systems such as the Unique Manuka Factor (UMF). However, subsequent mechanistic studies have revealed that the antimicrobial efficacy of MH extends beyond the activity of MGO alone. Whole MH exerts antibacterial effects through multiple complementary mechanisms, including hydrogen peroxide–mediated oxidative stress, osmotic effects, low pH, and the presence of antimicrobial peptides, such as bee defensin-1 [78]. Thus, MH operates as a multicomponent antimicrobial system, in which different factors act synergistically to disrupt bacterial physiology at multiple levels. Further evidence supporting this concept was provided by Carter et al. [79] to illustrate the combined action of its diverse constituents: phenolic compounds, flavonoids, organic acids, and reactive carbonyl species. Of note, whole MH induces broad cellular stress responses, disrupts metabolic pathways, and impairs biofilm formation more effectively than isolated components. This multi-target mode of action reduces the likelihood of resistance development and enhances efficacy against several pathogens, including multidrug-resistant organisms. Although MGO is a critical contributor to the antibacterial activity of MH, it functions within a complex and synergistic matrix that amplifies its effects.

7.2. The Antimicrobial Role of Polyphenols in Honey

While MGO is widely recognized as a major antimicrobial contributor, increasing evidence highlights a critical complementary role for polyphenolic compounds in mediating and enhancing antimicrobial effects. Honey-derived polyphenols, including flavonoids, phenolic acids, and related aromatic compounds, contribute not only to antioxidant capacity but also to direct and indirect antimicrobial mechanisms. These bioactive molecules exhibit a broad range of biological activities, including antimicrobial, anti-inflammatory, and cytoprotective effects, underscoring their importance in the therapeutic profile of honey [80].

Polyphenols participate in oxidative and non-oxidative antibacterial pathways. Honey polyphenols interact with hydrogen peroxide to generate ROS, leading to oxidative damage of bacterial cell components, including membrane lipids and DNA [81]. This polyphenol–H_2O_2 synergy represents a central mechanism by which honey exerts bactericidal effects beyond osmotic stress or acidity alone. This dynamic oxidative system can be amplified under physiological conditions, contributing to sustained antimicrobial activity. Polyphenols can also interfere with bacterial communication systems and virulence regulation. Some specific honey phenolics inhibit quorum sensing in bacteria, thereby reducing the expression of virulence factors and impairing biofilm formation [82]. This anti-QS activity is particularly relevant in chronic wound environments, where biofilm-associated infections are difficult to eradicate and contribute to delayed healing.

Polyphenols also contribute to direct antibacterial activity and compositional variability among honeys. The antibacterial efficacy of different monofloral honeys strongly correlates with their polyphenolic profiles, indicating that these compounds play a significant role in determining antimicrobial potency [83]. Similarly, phenolic composition varies with floral origin can serve as a biochemical signature, further supporting the functional

importance of polyphenols in honey bioactivity [84]. Polyphenols, including 3-phenyllactic acid, act synergistically with other key components of MH, particularly MGO, to enhance the antibacterial activity of MGO [16].

Through mechanisms involving oxidative stress generation, quorum sensing inhibition, direct antibacterial effects, and synergistic enhancement of MGO activity, polyphenols significantly contribute to the broad-spectrum and resistance-resilient properties of MH. Their inclusion in mechanistic models of honey activity is therefore essential for a comprehensive understanding of its therapeutic potential. Together, these findings reinforce that MH's antimicrobial activity emerges from a synergistic biochemical network rather than any single dominant molecule.

7.3. Revisited Role of Hydrogen Peroxide

H_2O_2 is also a major contributor to the antimicrobial activity of many honeys and represents a key component of the multifactorial defense system underlying their bacteriostatic and bactericidal effects. Unlike MGO, which is particularly prominent in MH, H_2O_2 is produced enzymatically through the activity of glucose oxidase when honey is diluted, generating a sustained and low-level release of ROS. This enzymatic reaction controls the production of H_2O_2, which allows honey to exert antimicrobial activity without causing rapid degradation or toxicity, distinguishing it from conventional antiseptics that rely on high concentrations of oxidants [85].

H_2O_2 plays a central role in oxidative damage to bacterial cells, including lipid peroxidation, protein oxidation, and DNA degradation. H_2O_2 contributes significantly to both bacteriostatic and bactericidal activity in honey [86], while its antimicrobial effect is strongly associated with the generation of highly reactive hydroxyl radicals (•OH) derived from H_2O_2 [27]. These radicals induce extensive damage to cellular components, ultimately leading to bacterial death. The H_2O_2-dependent activity results in complete DNA degradation in susceptible bacteria, highlighting its potent antimicrobial potential [87].

The antibacterial efficacy of H_2O_2 is not solely dependent on its concentration but also on its interaction with other honey components. Polyphenols amplify oxidative activity through redox cycling, thereby enhancing ROS generation and antimicrobial effects. The antibiofilm activity of honey is driven by a synergistic combination of osmotic stress, H_2O_2 production, and bee-derived antimicrobial peptides, such as defensin-1 [88]. The role of H_2O_2 has also been demonstrated in Gram-negative pathogens and biofilm-associated infections. H_2O_2 plays a key role in DNA damage and antimicrobial activity against *P. aeruginosa* [89]. Notably, variations in H_2O_2 production among different honeys correlate with differences in their antibiofilm efficacy [65]. These findings indicate that H_2O_2 contributes not only to planktonic bacterial killing but also to the disruption of biofilms, which are critical in chronic and resistant infections.

These studies demonstrate that H_2O_2 is a central mediator of honey's antimicrobial activity, acting through sustained oxidative stress and synergistic interactions with polyphenols, peptides, and osmotic factors. The contribution of H_2O_2, directly or through interaction with other components, remains an essential part of its overall antimicrobial profile. Understanding the balance between peroxide and non-peroxide mechanisms is therefore critical for fully elucidating the therapeutic potential of honey in combating multidrug-resistant pathogens.

8. MH versus other Types of Honey

Although MH has received considerable attention, a growing body of evidence indicates that antimicrobial activity is not unique to MH but is a widespread property of honeys derived from diverse floral and geographical origins. Multiple non-MHs have significant antibacterial activity against antibiotic-resistant pathogens.

Compositional analyses across different honeys reveal that antimicrobial activity is closely linked to polyphenolic content, enzymatic peroxide production, and other bioactive constituents, which vary depending on floral origin. Novel antimicrobial components in Scottish honeys are active against antibiotic-resistant bacteria [90], while diverse blossom honeys also exhibit substantial antibacterial activity, often comparable to MH [91]. Similarly, floral sources significantly influence antioxidant and antimicrobial properties, reinforcing the importance of phytochemical diversity in determining bioactivity [83,92].

Advanced chemometric and compositional studies further support the variability and functional relevance of honey composition. Honeys from different geographical regions can be distinguished based on physicochemical and phenolic profiles, which correlate with biological activity [93]. Therefore, antimicrobial potency is not exclusive to MH but reflects a broader structure–function relationship between composition and bioactivity. Mechanistic investigations provide additional evidence that non-MHs share similar antimicrobial modes of action. Canadian honeys induce bacterial cell wall damage resembling β-lactam antibiotic activity [94], whereas Egyptian honeys alter bacterial ultrastructure and gene expression in *E. coli* [95]. These findings indicate that multiple honeys can target essential cellular processes, including membrane integrity, cell wall synthesis, and gene regulation.

Comparative studies between MH and other honeys further reinforce this perspective. Agastache honey exhibits antimicrobial activity comparable to commercial honeys [96]), while Gobin et al. [97] demonstrated strong antibacterial effects of Croatian honey against resistant pathogens. Sidr and Tualang honeys display antimicrobial and antivirulence activities like MH against *S. aureus* [98]. Likewise, various European and Australian honeys possess antioxidant and antibacterial activities comparable to or, in some cases, exceeding those of MH [99–101].

While MH remains a well-characterized and clinically validated product, particularly due to its standardized MGO content, other honeys offer comparable antimicrobial potential through different combinations of bioactive components, including hydrogen peroxide, polyphenols, organic acids, and antimicrobial peptides. This broader perspective is important for both scientific understanding and clinical translation, as it highlights the potential of locally sourced or alternative honeys to serve as effective antimicrobial agents, particularly in resource-limited settings. Honey's antimicrobial activity is a generalizable and multifactorial property rather than a feature exclusive to MH. This broader perspective is particularly important in global health contexts where MH may be scarce or cost-prohibitive, and alternative honeys could offer practical antimicrobial value. This suggests that antimicrobial honey-based therapies could be adapted regionally using locally sourced products

9. Future Perspectives and the Role of Artificial Intelligence

MH is transitioning from a natural antimicrobial agent into a versatile platform for advanced wound-care technologies. Future research is coalescing around the three following primary domains that define the next frontier of MH innovation.

- MH-based composites that synergize with metals, nanoparticles, and biosurfactants
- Targeted therapeutic strategies for chronic wounds harboring polymicrobial, fungal, and spore-forming pathogens
- The integration of artificial intelligence (AI) to optimize MH authentication, composite architecture, and therapeutic prediction.

9.1. MH Composites and Next-Generation Antimicrobial Platforms

The intricate chemical profile of MH facilitates synergistic interactions with diverse materials, making it a viable component for advanced antimicrobial composites. MH chelates iron and disrupts iron-regulated metabolic pathways in key bacterial pathogens, suggesting a mechanism for impairing microbial nutrient acquisition [102]. This iron-sequestering property may be leveraged to enhance the performance of metallic nanoparticles or metal-dependent antimicrobials. Biosurfactant-based systems represent another promising direction, as they can be integrated with MH to improve biofilm penetration and surface activity [103]. Recently, rare-earth oxide nanoparticles, such as cerium and lanthanide oxides, have demonstrated potent activity against multidrug-resistant pathogens and may serve as synergistic partners in MH-based wound-healing composites [104]. Another critical frontier is the inhibition of efflux pumps, which contribute significantly to antibiotic resistance and biofilm persistence, particularly in *Pseudomonas* species. MALDI-TOF MS-based methodologies can quantify efflux pump efficiency, providing a platform for evaluating whether MH or MH-nanocomposites can attenuate efflux-mediated resistance [105]. These findings support the development of MH composites designed to target multiple resistance mechanisms simultaneously.

9.2. Chronic Wounds with Polymicrobial, Fungal, and Spore-Forming Pathogens

Chronic wounds are increasingly recognized as complex ecological systems comprising bacteria, fungi, and spore-forming organisms. Chronic wound biofilms are characteristically polymicrobial, structurally resilient, and metabolically cooperative, necessitating multifaceted therapeutic interventions [106]. The broad-spectrum antimicrobial and antibiofilm properties of MH position it as a candidate for disrupting heterogeneous communities. Fungal colonization is an underrecognized contributor to delayed healing, e.g., *Candida* and *Cladosporium* are integral components of the wound microbiome and interact with bacterial species to enhance biofilm tolerance [107]. The proven antifungal activity of MH against *Candida* spp. and filamentous fungi suggests its potential utility in managing these mixed infections. Furthermore, spore-forming pathogens present a unique challenge; MH exhibits bactericidal and spore-inhibition effects against *Clostridioides difficile*, a pathogen capable of persisting in harsh wound environments and contributing to recurrence [108]. These insights highlight the potential role of MH in managing wounds colonized by resilient, spore-forming organisms. Future research should explore MH-based strategies tailored to the comprehensive microbial spectrum of chronic wounds, specifically addressing bacterial–fungal interactions and spore persistence.

9.3. Artificial Intelligence for MH Research and Composite Design

Artificial intelligence (AI) is emerging as a transformative modality for advancing MH research, facilitating predictive modeling, compositional analysis, and the rational design of wound therapeutics. A significant advancement in this field is SCRATCH-AI, an interpretable machine-learning platform that classifies honey samples, including Manuka, into functional wound-healing categories based on antioxidant activity, botanical origin, and chemo-biological signatures. This model provides causal insights into the specific honey features that drive regenerative performance, establishing a data-driven foundation for the clinical selection and standardization of MH. Machine learning accelerates the design of mechanical and functional materials, a framework applicable to MH–nanoparticle hybrids, MH–biosurfactant systems, and MH–rare-earth oxide composites [109]. Similarly, AI's role in pharmacology for predicting drug interactions, toxicity, and release kinetics is applicable to the development of MH-based wound dressings [110]. AI also enhances MH authentication and compositional profiling through chemometric and pattern-recognition methods for analyzing bioactive ingredients, detecting adulteration, and predicting functional properties [111,112]. These approaches can be adapted to MH to ensure batch consistency, identify high-bioactivity lots, and correlate chemical fingerprints with antimicrobial or wound-healing outcomes.

Ongoing progress in MH research will rely on the integration of advanced composite engineering, an ecological understanding of chronic wound microbiomes, and AI-enabled predictive modeling. The unique chemical profile of MH, combined with emerging materials and computational tools, provides a pathway toward next-generation wound therapeutics that can address multidrug resistance, polymicrobial biofilms, fungal colonization, and spore persistence. The convergence of these three domains, composites, wound ecology, and AI, will define the next era of MH innovation. AI-driven models may eventually guide clinicians in selecting the optimal honey type or composite formulation for specific wound microbiomes, enabling personalized antimicrobial therapy.

10. Conclusions

MH represents a unique, multifunctional antimicrobial system with demonstrated activity against a broad range of clinically relevant pathogens, including multidrug-resistant ESKAPE pathogens. Its efficacy arises from the synergistic action of multiple components, primarily MGO, hydrogen peroxide, and polyphenols, which collectively target bacterial membranes, redox balance, gene expression, and biofilm formation. This multi-targeted mechanism likely explains the low propensity for resistance development compared with conventional antibiotics. MH shows strong activity against biofilms and enhances antibiotic efficacy, with several studies demonstrating restored susceptibility in resistant strains. These synergistic interactions highlight its potential as an adjunct therapy to extend the effectiveness of existing antimicrobials.

While other honeys also exhibit antimicrobial properties, MH provides more consistent and potent effects due to its well-defined composition. Nevertheless, the broader diversity of bioactive honeys remains an important area for future investigation. It is of importance to standardize formulations, optimize dosing, and validate clinical outcomes through controlled trials. Future research should integrate mechanistic, clinical, and computational approaches to fully harness the therapeutic potential of MH in modern antimicrobial practice. Overall, MH offers a promising, biologically complex approach to addressing antimicrobial resistance, particularly in chronic and biofilm-associated infections.

Conflicts of Interest

The author declares no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this manuscript, the author used CoPilot (version available as of April 2026) and Chat GPT (OpenAI, accessed in 2026; version based on GPT-5 series) for the purpose of collecting information and the re-arrangement of the cited references. AI software was used for English verification and correction. The author has reviewed and edited the output and takes full responsibility for the content of this publication.

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