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DERLEME /REVIEW

A MULTIFACETED BIOACTIVITY OF HONEY: INTERACTIONS BETWEEN BEES, PLANTS AND MICROORGANISMS

Balın Çok Yönlü Biyoaktivitesi: Arılar, Bitkiler ve Mikroorganizmalar Arasındaki Etkileşimler

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ABSTRACT

Honey has been recognized for its medicinal properties for centuries, with well-documented benefits such as antibacterial, anti-inflammatory, and antioxidant activities. However, despite the widespread use of honey for health-related purposes, many of the underlying mechanisms responsible for its bioactivity remain underexplored. This review delves into the complexity of honey's composition, particularly focusing on the active substances and the honey microbiota contribution to its properties. We aim to bridge the gap in understanding how honey's multifaceted bioactivity arises from interactions between bees, plants, and microorganisms. The review sheds light on the key compounds, including hydrogen peroxide, methylglyoxal, polyphenols, and antimicrobial peptides, which play vital roles in honey's health benefits. It also highlights the often-overlooked contributions of the honeybee's gut microbiota and the nectar's microbiota, which together influence the chemical transformation of nectar into honey and enhance its therapeutic efficacy. By examining the current literature, this article emphasizes the need for deeper investigation into how various factors-such as floral origin, bee subspecies, and environmental conditions-affect the medicinal quality of honey. Understanding these mechanisms could lead to optimized use of honey in medical applications and reveal new therapeutic potentials. This article provides a comprehensive review of the intricate processes and components that make honey not only a nutritional food source but also a potent natural medicine.

Keywords: Honey bioactivity, Prebiotic potential, Lactic acid bacteria, Antimicrobial properties, Honey microbiota

ÖZ

Bal, antibakteriyel, anti-enflamatuar ve antioksidan aktiviteler gibi iyi belgelenmiş faydaları ile yüzyıllardır tıbbi özellikleriyle tanınmaktadır. Bununla birlikte, balın sağlıkla ilgili amaçlarla yaygın

kullanımına rağmen, biyoaktivitesinden sorumlu olan altta yatan mekanizmaların çoğu yeterince araştırılmamıştır. Bu derleme, özellikle aktif maddelere ve bal mikrobiyomunun özelliklerine katkısına odaklanarak balın bileşiminin karmaşıklığını incelemektedir. Balın çok yönlü biyoaktivitesinin arılar, bitkiler ve mikroorganizmalar arasındaki etkileşimlerden nasıl kaynaklandığını anlamadaki boşluğu doldurmayı amaçlıyoruz. Bu derleme, balın sağlığa faydalarında hayati rol oynayan hidrojen peroksit, metilglioksal, polifenoller ve antimikrobiyal peptitler gibi temel bileşiklere ışık tutmaktadır. Ayrıca, nektarın bala kimyasal dönüşümünü birlikte etkileyen ve terapötik etkinliğini artıran bal arısının bağırsak mikrobiyomunun ve nektarın mikrobiyotasının genellikle göz ardı edilen katkılarını vurgulamaktadır. Bu makale, mevcut literatürü inceleyerek, çiçek kökeni, arı alt türleri ve çevresel koşullar gibi çeşitli faktörlerin balın tıbbi kalitesini nasıl etkilediğinin daha derinlemesine araştırılması gerektiğini vurgulamaktadır. Bu mekanizmaların anlaşılması, balın tıbbi uygulamalarda en uygun şekilde kullanılmasını sağlayabilir ve yeni terapötik potansiyelleri ortaya çıkarabilir. Bu makale, balı sadece besleyici bir gıda kaynağı değil aynı zamanda güçlü bir doğal ilaç yapan karmaşık süreçler ve bileşenler hakkında kapsamlı bir inceleme sunmaktadır.

Anahtar Kelimeler: Bal biyoaktivitesi, Prebiyotik potansiyel, Laktik asit bakterileri, Antimikrobiyal özellikler, Bal mikrobiyomu

GENİŞLETİLMİŞ ÖZET

Giriş: Bal tarih boyunca tedavi edici özellikleriyle değerlendirilmiş, yaraları iyileştirme, enfeksiyonları yönetme ve bağışıklık sistemini güçlendirme kabiliyetiyle tanınmıştır. Bununla birlikte, bu etkilerin ardındaki mekanizmalar halk veya bilim camiasının çoğu tarafından yaygın olarak anlaşılmamıştır. Arılar, çiçekler ve mikroorganizmalar arasındaki etkileşimler de dahil olmak üzere balın karmaşık bileşimi veya bal mikrobiyomunun rolü hakkında çok az şey bilinmektedir. Bu derleme, mikrobiyomuna özel bir vurgu yaparak balın biyoaktif özelliklerine katkıda bulunan kimyasal ve mikrobiyolojik faktörlere odaklanarak bu boşlukları ele almayı amaçlamaktadır.

Balın prebiyotik potansiyeli: Bal, şekerler, proteinler, lipitler ve mikrobiyal metabolitler dahil olmak üzere 200'den fazla bileşik içeren karmaşık bir üründür. Ayrıca, *Bifidobacterium* ve *Lactobacillus* gibi faydalı bağırsak bakterilerinin büyümesini destekleyen oligosakkaritleri nedeniyle önemli bir prebiyotik potansiyele sahiptir. Oligosakkaritler sindirilmeden alt gastrointestinal sisteme geçer ve burada bu mikroplar için besin görevi görür. Balın prebiyotik etkisi botanik kökenine göre değişir; manuka ve bal özü balları özellikle güçlü etkiler gösterir. Balın mikrobiyomu, prebiyotik yeteneklerini daha da geliştirerek bağırsak sağlığını ve bağışıklık fonksiyonunu artırır.

Bal arısı bağırsağı ve bal mikrobiyomu: Balın tıbbi özellikleri, arılar tarafından nektar toplama ve fermantasyon sırasında ortaya çıkan bakteri, maya ve mantarlardan oluşan mikrobiyomu tarafından şekillendirilir. Bal arısı bağırsak mikrobiyomu, nektar şekerlerinin biyoaktif bileşiklere dönüştürülmesinin ayrılmaz bir parçasıdır. *Lactobacillus*, *Gilliamella* ve *Bifidobacterium* gibi mikroplar balı koruyan ve biyoaktivitesini artıran organik asitler, bakteriyosinler ve enzimler üretir. Bu mikrobiyal süreçler, çiçek kökeni ve arı fizyolojisi ile birleştiğinde, bitki ve mikrobiyal faydaları birleştiren ve balın tedavi edici etkilerine katkıda bulunan benzersiz bir ürün ortaya çıkarır.

Laktik Asit Bakterileri ve Bifidobakteri türevi bileşikler nedeniyle balın prebiyotik potansiyeli

Lactobacillus ve *Bifidobacterium* dahil laktik asit bakterileri (LAB) bal arısı bağırsak mikrobiyomu için kritik öneme sahiptir. Bu bakteriler asidik bir ortam yaratarak patojen büyümesini engelleyen ve balın prebiyotik potansiyelini artıran organik asitler üretir. LAB ayrıca patojenleri hedef alan ve öldüren bakteriyosinler de üretir. Ek olarak, kısa zincirli yağ asitleri gibi LAB tarafından üretilen metabolitler, faydalı bağırsak bakterilerinin büyümesini teşvik eder. Balda ve insan bağırsağında doğal olarak bulunan LAB türlerinin varlığı, balı bağırsak sağlığını ve bağışıklık fonksiyonunu destekleyen etkili bir prebiyotik gıda haline getirmektedir.

Bacillales türevi bileşikler nedeniyle balın prebiyotik potansiyeli: Bal mikrobiyotasında öne çıkan *Bacillus* türleri prebiyotik olarak bilinen bakteriyosinler ve lipopeptitler gibi antimikrobiyal bileşikler üretir. Bu bileşikler, bakteriler öldükten sonra bile biyoaktif kalmaya devam ederek balın uzun vadeli antimikrobiyal etkilerini sağlar. *Bacillus* tarafından üretilen enzimler de karmaşık molekülleri

daha basit formlara dönüştürerek faydalı bağırsak bakterilerini destekler. Sürfaktin ve fengisin gibi lipopeptitler de dahil olmak üzere bu prebiyotik özellikler, balın patojen büyümesini önleme ve bağışıklık fonksiyonunu destekleme yeteneğine katkıda bulunarak onu etkili bir fonksiyonel gıda haline getirir.

Mantar türevi bileşikler nedeniyle balın prebiyotik potansiyeli: *Saccharomyces* ve *Zygosaccharomyces* gibi mayalar balın fermantasyonunda ve prebiyotik özelliklerinde rol oynar. Bu mantarlar balın pH'ını düşüren organik asitler üreterek zararlı patojenleri engellerken yararlı bakteriler için elverişli bir ortam yaratır. Mantar metabolitleri balın stabilitesine ve lezzetine de katkıda bulunur. Bazı mantarlar, balı bozulmaya karşı koruyan mikotoksinler gibi antimikrobiyal bileşikler üretir. Düşük konsantrasyonlarda bulunmasına rağmen, bu bileşikler balın uzun vadeli antimikrobiyal özelliklerini ve sağlık yararlarını artırarak güçlü bir prebiyotik gıda olarak kalmasını sağlar.

Bitki Metabolitlerinin Balın Prebiyotik Özellikleri Üzerindeki Etkisi: Polifenoller, flavonoidler ve fenolik asitler gibi bitki kaynaklı bileşikler balın prebiyotik, antioksidan ve anti-enflamatuar özelliklerine katkıda bulunur. Bu metabolitler serbest radikalleri nötralize ederek oksidatif stresi azaltır ve zararlı patojenleri inhibe ederken faydalı bağırsak bakterilerinin büyümesini teşvik eder. Bu bileşiklerin konsantrasyonu bal türüne göre değişir, daha koyu renkli ballar daha yüksek polifenol seviyeleri ve daha güçlü antioksidan özellikler içerir. Bitki metabolitlerinin bu varlığı balın bağırsak sağlığını, bağışıklık fonksiyonunu ve iltihaplanmayı azaltmayı destekleme kabiliyetini artırarak onu etkili bir fonksiyonel gıda haline getirir.

Sonuç: Bu derleme, balın terapötik özelliklerine katkıda bulunan karmaşık biyolojik mekanizmaları vurgulamaktadır. Balın biyoaktivitesi arılar, çiçekler ve mikroorganizmalar arasındaki etkileşimlerden kaynaklanır ve prebiyotik bileşikler açısından zengin bir ürün ortaya çıkar. Laktik asit bakterileri, Bacillales türleri ve mantarlar da dahil olmak üzere balın mikrobiyomunun rolü, bağırsak sağlığını geliştirme ve patojenlerle mücadele etme yeteneğini şekillendirmede çok önemlidir. Bu süreçleri anlayarak balın fonksiyonel bir gıda olarak potansiyelini daha iyi değerlendirebiliriz. Gelecekteki araştırmalar, balın tüm terapötik potansiyelini ortaya çıkarmak için bu etkileşimleri daha fazla keşfetmelidir.

INTRODUCTION

The honey bee (*Apis mellifera*) produces honey by fermenting flower nectar and enriching it with plant and bee metabolites. Honey comprises over 200 compounds, including sugars, proteins, lipids, vitamins, minerals, polyphenols, enzymes, and microbial metabolites (Kafantaris et al. 2020, Schell et al. 2022). Nectar influences honey’s taste, color, and therapeutic properties (Schell et al. 2022). The main carbohydrates are fructose and glucose, constituting up to 80% of total sugars, alongside water, proteins, acids, minerals, plant phytochemicals, and vitamins. Some honeys exhibit increased biological activity due to floral-derived metabolites like oligosaccharides, which are highly effective in vitro (Carter et al. 2016, Miguel et al. 2017, Schell et al. 2022).

Honey is a nutritious prebiotic food with antibacterial, anti-inflammatory, and antioxidant properties, offering therapeutic benefits such as immunomodulatory, antidiabetic, antimutagenic, and anticancer effects (Karabagias 2018, Kafantaris et al. 2020, Seraglio et al. 2019). Honey’s properties are influenced by bee subspecies, stomach microbiota fermentation, nectar’s botanical and geographical origin, and environmental factors (da Silva et al., 2016; Karabagias, 2018). Historically, honey has been a vital carbohydrate and energy source, reducing bacterial diarrhea in children and preventing organ failure in critically ill patients (Schell et al. 2022). It also protects against viral gastroenteritis and can have a mild laxative effect due to limited fructose absorption (Bogdanov et al. 2008, Schell et al. 2022).

Honey's antimicrobial activity is due to the presence of gluconic acid, which gives the honey an acidic pH of 3–5. This inhibits vegetative bacterial growth due to the low water activity, low pH, and antimicrobial elements like hydrogen peroxide and peptides (Bogdanov et al. 2008, Carter et al. 2016, Olaitan et al. 2007, Schell et al. 2022). Its broad-spectrum antibacterial properties remain effective against multidrug-resistant pathogens. Osmotolerant microorganisms, including spore-forming bacteria and yeasts, are introduced from nectar during pollination (Alvarez-Pérez et al. 2012). Importantly, honey does not induce microbial resistance, attributed to its diverse antimicrobial substances

(Nolan et al. 2019, Maddocks et al. 2013, x Schell et al. 2022).

Honey contains a variety of antimicrobial compounds that effectively inhibit or kill a wide range of microorganisms, including multidrug-resistant pathogens (Combarros-Fuertes et al. 2020, Nolan et al. 2019). It can prevent the growth of harmful bacteia like *Clostridium perfringens*, *Collinsella aerofaciens* in the intestines, and *Listeria monocytogenes* in milk (Shin & Ustunol 2005, Schell et al. 2022). Honey also inhibits various enteropathogenic microorganisms, including multidrug-resistant *Salmonella spp.*, *Shigella spp.*, enteropathogenic *Escherichia coli*, *Enterobacter spp.*, *Yersinia enterocolitica*, *Campylobacter spp.*, and *Clostridioides difficile* (Hammond & Donkor 2013, Schell et al. 2022). It prevents *Salmonella* species from adhering to mucosal epithelial cells, thereby preventing infection (Schell et al. 2022).

Identifying honey's active compounds is crucial for recognizing its antibacterial properties. Key antibacterial compounds in honey include hydrogen peroxide and methylglyoxal, which exhibit a nonspecific mechanism of action. The concentrations of these compounds are found to correlate with the antibacterial activity of honey; typical minimum inhibitory and bactericidal concentrations are observed to fall within the microgram per millilitre range (Brudzynski 2020, Mavric et al. 2008). Hydrogen peroxide causes oxidative damage to bacterial cell components and DNA (Brudzynski et al. 2012). Methylglyoxal, found in manuka honey, irreversibly glycates and cross-links macromolecules, resulting in loss of function (Mavric et al. 2008). Plant-derived secondary metabolites, such as polyphenols, flavonoids, and volatile compounds, also contribute to honey's antimicrobial activity. Although their antimicrobial effect is relatively weak, they add to honey's broad-spectrum activity (Figure 1) (Isah 2019).

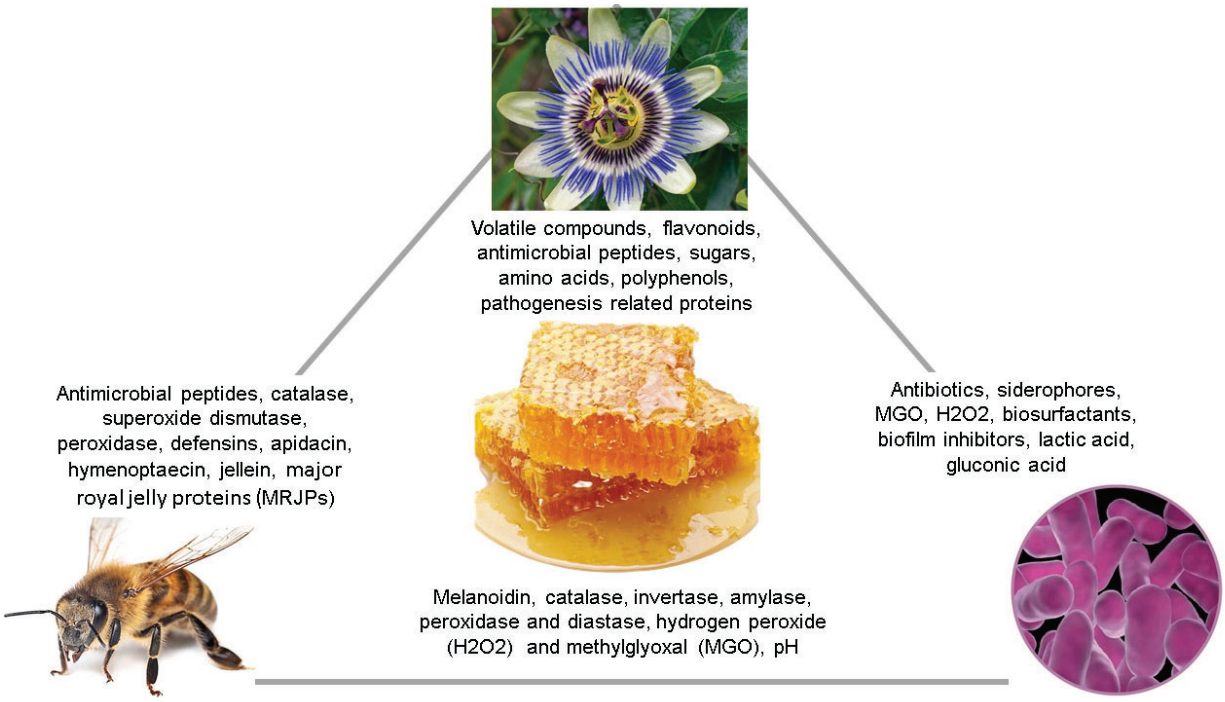

Figure 1. Active metabolites are produced and contribute to the antimicrobial activity of honey through three-way interactions involving microbes, plants, and honey bees.

The nectar-honey bee-honey microbiota axis plays a crucial role in producing various antimicrobial agents, including antimicrobial peptides, bacteriocins, surfactants, siderophores, proteolytic enzymes, and quorum sensing inhibitors (Brudzynski, 2021). Studies suggest honey's effects on bacterial cells include targeted mechanisms not solely explained by hydrogen peroxide or methylglyoxal, hinting at additional antimicrobial compounds (Henriques et al., 2011; Brudzynski & Sjaarda, 2014). These effects resemble those of β-lactams, antimicrobial peptides, or inhibitors of proton motive force and chemiosmosis. Thus, honey's wide-ranging antibacterial activity, including against multidrug-resistant strains, may involve multiple sources of antimicrobial compounds (Brudzynski 2021).

Phytohormones, or plant hormones, synthesized by plants and some yeasts, significantly impact various life processes in plants and animals even in minute concentrations. Notable phytohormones include auxins, abscisic acid, cytokinins, gibberellins, ethylene, polyamines, brassinolides, jasmonates, salicylic acid, and strigolactones. These hormones influence mammalian physiology and have potential therapeutic applications, such as combating cancer and diabetes and promoting cell growth. For instance, indole-3-acetic acid acts as an antitumor agent, gibberellins promote apoptosis, abscisic acid regulates glucose homeostasis and acts as an antidepressant, and cytokinins serve as anti-aging compounds (Mukherjee et al. 2022).

Pollen remaining after honey bees filter nectar during honey conversion is thought to be the primary source of phytohormones in honey (Herold & Leibold 2000). However, the microflora of the nectar and the bees' foregut might also secrete phytohormones into honey (Ilyasov et al. 2015, Mukherjee et al. 2022). The specific composition of substances released by honey bees during fermentation and ripening of honey remains largely unknown, although honey, nectar, pollen, and beebread have been confirmed to contain phytohormonal substances (Abdulgazina et al. 2015). Auxins and cytokinins primarily originate from nectar, while abscisic acid in honey may also be secreted by honey bees (Abdulgazina et al. 2015, Ilyasov et al. 2015).

Phytohormones impact human health in various ways. For instance, abscisic acid regulates human and animal cells growth and enhances immune responses (Scarfi et al., 2008). Cytokinins promote human and animal cells growth and act as anti-stress agents (Voller et al. 2017). Auxin is recognized as an antitumor agent in human and animal cells, and gibberellin has antioxidant properties (Hamayun et al. 2017, Mukherjee et al. 2022).

Honey contains phytoncides, biologically active substances that kill or inhibit microorganisms. These include benzoic acid, avenacin, juglone, phloridzin, pinosulfan, and tannins. Phytoncides in honey are potent medicines for treating infections and wounds. The botanical composition of honey plants influences the chemical properties and effectiveness of these phytoncides. Honeydew honey from spruce, pine, and fir has strong bactericidal properties, while darker flower honeys like chestnut and buckwheat have moderate bactericidal properties. Light flower honeys such as those from dandelion and white clover exhibit almost no bactericidal effect (Vakhonina 2002).

A comparative analysis of amino acids in pollen and honey of the same botanical origin suggests that additional amino acids in honey come from sources other than pollen, likely due to the bees' physiological activity and the gastric microflora during nectar processing (Vrabie et al. 2019).

The types of plants from which honey bees collect nectar also influence the diastase number, a measure of enzyme activity in honey. Different bee breeds and colony sizes affect the diastase number, with larger colonies producing honey with higher diastase content (Lebedev & Murashova 2004).

Honey's antioxidant effects are attributed to its phenolic components, which protect human blood cells when consumed. Darker honeys generally have higher antioxidant activity due to their higher phenolic content. These phenolics also contribute to honey's anti-inflammatory properties by blocking inflammatory mediators and reducing pro-inflammatory cytokines, making honey valuable in the treatment of wounds and burns (Schramm et al. 2003, Schell et al. 2022, Vallianou et al. 2014; Zhao et al. 2019).

Honey serves as a natural prebiotic, containing metabolites from microbial, plant, and animal sources. Prebiotics are foods containing certain compounds that promote the growth or activity of beneficial microorganisms such as bacteria and fungi. The most common environment affecting human health is the gastrointestinal tract, where prebiotics can alter the composition of microorganisms in the gut microbiota. Probiotics are food containing living microorganisms capable of supporting or improving beneficial bacteria (normal microflora) in gut. Honey, rich in sugars, preserves these biologically active substances, retaining their activity over time. Honey may regulate the immune system, enhance barrier functions, and support microbiota formation. They are considered safe and can be recommended for early childhood to support microbiota development and for preventing diseases influenced by the gut microbiota, such as inflammatory bowel disease, multiple sclerosis, and Alzheimer's disease. Prebiotic compounds in honey may also aid in preventing and treating SARS-CoV-2 infection (Brudzynski, 2021, Gou 2020).

Despite the widespread recognition of honey's medicinal benefits, the mechanisms responsible for its therapeutic effects remain largely unknown to the general public and even many researchers. Most people are familiar with honey's antibacterial, anti-inflammatory, and antioxidant properties, but few understand the biochemical pathways and interactions that drive these effects. The key active compounds, such as hydrogen peroxide, methylglyoxal, and polyphenols, are often overlooked, as is the significant role of honey's microbiota. The intricate relationship between honeybees, the flowers they pollinate, and the microorganisms involved in honey production is crucial to its bioactivity, yet remains underexplored. This review was written to fill these knowledge gaps and to provide a comprehensive analysis of the underlying mechanisms that contribute to honey's unique properties. Our goal is to offer readers a detailed understanding of how bees, plants, and microorganisms collaborate in shaping honey's composition and bioactivity. By focusing on the lesser-known aspects of honey's microbiota, lactic acid bacteria, and microbial metabolites, we aim to shed light on the factors that elevate honey from a simple natural product to a potent therapeutic agent. This review not only underscores honey's medicinal potential but also highlights the importance of understanding the interactions within the honey ecosystem to fully appreciate its therapeutic benefits.

Prebiotic potential of honey

Honey's primary composition is simple sugars, or monosaccharides, which are readily absorbed in the human intestine (Sanz et al. 2004, Schell et al. 2022). In smaller quantities, it contains di-, tri-, and oligosaccharides. Low-mass oligosaccharides and polysaccharides in honey resist digestion by host enzymes, reaching the lower intestine, where they exert prebiotic effects (Sanz et al. 2005, Schell et al. 2022). The prebiotic effects vary with the botanical origin of the honey, discernible through nuclear magnetic resonance (NMR) spectroscopy combined with chemometric analysis (Karabagias, 2018; Olawode et al., 2018; Kafantaris et al., 2020).

Nuclear magnetic resonance spectroscopy (NMR) spectroscopy and chemometric methods have successfully differentiated honeys by their botanical and geographical origins, including chestnut, acacia, linden, polyfloral types, and those from Greece, Brazil, South Africa, Zambia, and Slovakia (Karabagias 2018, Kafantaris et al. 2020, Olawode et al. 2018). This technology has also classified Vietnamese honey and identified unique compounds in honey samples (Kafantaris et al. 2020, Luong et al. 2019,). Additionally, NMR spectroscopy and ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry have identified chemical indicators in stingless bee honey, revealing unique compounds such as D-fructofuranose in Heterotrigona itama honey, and L-lactic acid in Tetrigona apicalis honey (Kafantaris et al. 2020).

Honey's protein composition includes major royal jelly proteins (MRJPs) and enzymes like glucosidase, amylase, and glucose oxidase, which are markers of authenticity and quality (Chua et al. 2014, Kafantaris et al. 2020; Machado De Melo et al. 2017). Bee-derived proteins such as MRJP 1-5, α-glucosidase, and defensin-1 are prevalent in honey from various floral sources (Di Girolamo et al. 2012, Kafantaris et al. 2020). The antibacterial activity of honey is primarily due to the antimicrobial peptide bee defensin-1 (Kafantaris et al. 2020, Kwakman et al. 2010). Proteomic profiling methods, including SDS-PAGE, native PAGE, MS methods, and 2D electrophoresis with MALDI MS, have identified proteins such as MRJP 1–9, α-glucosidase, and glucose oxidase in honey (Kafantaris et al. 2020, Zhang et al. 2019).

In vitro studies support honey's prebiotic potential, demonstrating its efficacy in promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* species (Jiang et al. 2020, de Melo et al. 2020, Schell et al. 2022). Honey's growth-promoting effects on these bacteria are comparable to oligosaccharide prebiotics such as fructooligosaccharides, galactooligosaccharides, and inulin (Chick et al. 2001; Shin & Ustunol 2005). Moreover, honey enhances bacterial metabolism in the human intestine (Figure 2) (Mohan et al. 2017, Schell et al. 2022).

Table 1. Prebiotic effects of various honeys.

Honey type and plant source	**Experimental approach**	**Prebiotic effects**	**References**
Sundarban, Litchi, Cumin, Eucalyptus and multifloral (India)	Study assessed antioxidant activities (ABTS, DPPH, FRAP, hydroxyl scavenging, lipid peroxidation) in Bifidobacteria from infant feces and Wistar rat intestines.	Enhances *Bifidobacterium* species, *Lactobacillus acidophilus*, and *Lactiplantibacillus plantarum*. Combats *Escherichia coli*, *Klebsiella aerogens*, *Staphylococcus aureus*, *Salmonella typhi*, and *Bacillus cereus*.	Nooh and Nour-Eldien, 2016; Schell et al., 2022
Multifloral (Jordan)	Study used optical density readings to determine colony counts.	Enhances the advantages of intestinal *Bifidobacterium infantis* and *Lactobacillus acidophilus*.	Schell et al., 2022
Multifloral (Indonesia)	Study analyzed intestinal microbiota diversity in honey-fed Pacific white shrimp using DNA sequencing.	Promotes beneficial gut bacteria and improves shrimp survival against *Vibrio parahaemolyticus*.	Weston and Brocklebank, 1999; Fuandila et al., 2019; Schell et al., 2022
Alfalfa and Eucalyptus (Australia)	Study measured bacterial growth using growth media and optical density readings.	Enhances the advantages of *Lactobacillus acidophilus*, *Lactobacillus delbrueckii subsp. bulgaricus*, and *Lactiplantibacillus plantarum*.	Conway et al., 2010
Acacia and Chestnut (Croatia)	Study used agar disk diffusion and colony counting on agar plates for bacterial analysis.	Enhances the efficacy of *Bifidobacterium lactis* Bb-12 and *Bifidobacterium longum* Bb-46 while suppressing *Listeria monocytogenes* FSL N1-017.	Slačanac et al., 2012
Linden honey (Poland)	Study using shake-flask screening method	Activates G-protein-coupled receptors, blocks NMDA and nicotinic receptors, and offers neuroprotective effects by kynurenic acid in honey, from yeasts *Yarrowia lipolytica* and *Candida magnolia*	Beretta et al., 2008; Turski et al., 2009
Honeydew (Spain)	Study employed fecal bacteria fermentation and utilized 16S rDNA sequencing of the V4 region.	Boosts lactobacilli and bifidobacteria, reduces enteric bacteria and *Bacteroides*.	Leeming et al., 2019; Schell et al., 2022
Buckwheat (China)	Study employed fecal bacteria fermentation and utilized 16S rDNA sequencing of the V4 region.	Enhances the favorable effects of *Bifidobacterium* species.	David et al., 2014; Schell et al., 2022
Juazeiro and Jurema-branca (Brazil)	Study used optical density readings to determine colony counts.	Enhances the beneficial effects of *Bifidobacterium lactis* and *Lactobacillus acidophilus*.	Tanes et al., 2021; Schell et al., 2022
Manuka (New Zealand)	Study analyzed microbiota changes with 20 g daily honey intake in a clinical trial using fecal sequencing.	Enhances *Limosilactobacillus reuteri*, *Lacticaseibacillus rhamnosus*, and B. *lactis*; inhibits *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi.*	Gibson and Roberfroid, 1995; Wang et al., 2019; Schell et al., 2022
Clover (New Zealand)	Study assessed the growth of probiotic pure cultures in skim milk with different sweeteners by counting colonies on agar plates for cultural enumeration.	Amplifies the advantageous effects of *Bifidobacterium bifidum* and *Lactobacillus acidophilus*.	Mohan et al., 2017; Schell et al., 2022
Sage, clover, alfalfa, sourwood (United States)	Study employed agar disk diffusion, colony counting on agar plates, and microbroth dilution to assess bacterial growth by measuring optical density.	Enhances *Lactobacillus* and *Bifidobacterium* activity, suppresses pathogenic bacteria, and boosts the effectiveness of prebiotics like fructooligosaccharide, galactooligosaccharide, and inulin.	Popa and Ustunol, 2011; Al-Sheraji et al., 2013; Schell et al., 2022
Acacia and chestnut (Saudi Arabia)	Study used agar disk diffusion and colony counting on agar plates for	Boosts growth *Bifidobacterium* and *Lactobacillus* species, slows their	Raschka and Daniel, 2005;

	bacterial analysis.	replication, and suppresses *Listeria monocytogenes*.	Schell et al., 2022
Acacia and chestnut (Croatia)	Study used agar disk diffusion and colony counting on agar plates for bacterial enumeration.	Enhances the advantages of *Bifidobacterium lactis*.	Nagpal and Kaur, 2011; Schell et al., 2022
Tualang and multifloral (Malaysia)	Study treated honey to remove simple sugars, used the remaining fraction to supplement skim milk, and counted bacterial colonies on agar plates.	Enhances *Bifidobacterium longum* effectiveness by removing simple sugars.	Chick et al., 2001; Schell et al., 2022
Cotton (Egypt)	Study with albino mice focused on collecting cecal contents and enumerating colonic bacteria through viable cell counts on agar plates.	Enhances *Bifidobacterium* and *Lactobacillus* species, increases beneficial bacteria, and suppresses harmful ones, restoring gut microbiota balance.	Roberfroid et al., 2010; Schell et al., 2022
Jarrah (Australia)	Study with 30 BALB/c mice included 16S rRNA sequencing of the V3–V4 region and measured fecal water content by weighing samples before and after drying.	Boosts beneficial bacterial groups and suppresses harmful ones, aiding in gut microbiota balance.	Chauhan and Chorawala, 2014; Schell et al., 2022
Prunella vulgaris (China)	Study involved 24 male Sprague Dawley rats with induced colitis, focusing on colon histology, intestinal mRNA analysis, and gut microbiota profiling via 16S rRNA sequencing of the V3–V4 region.	Boosts Firmicutes and *Lactobacillus*, reduces *Bacteroidetes* and Lachnospiraceae, aiding in ulcerative colitis symptom relief by impacting gut flora.	Haddadin et al., 2007; Schell et al., 2022

Honey also exhibits anti-inflammatory properties, mediated by an increase in anti-inflammatory cytokines (Ranneh et al. 2021, Vallianou et al. 2014). Phytohormones in honey, such as gibberellic acid and abscisic acid, contribute to these effects (Wang et al. 2017). The presence of these phytohormones enhances honey's potential as a functional food with prebiotic benefits (Chanclud & Lacombe 2017, Mohan et al. 2017, Schell et al. 2022).

In vitro studies demonstrate honey's ability to promote the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* species, comparable to other oligosaccharide prebiotics (Rosendale et al. 2008, Schell et al. 2022, Shin & Ustunol 2005). Honey's oligosaccharides selectively support beneficial bacteria while suppressing harmful ones (Sanz et al. 2005, Schell et al. 2022).

Honey's antibacterial properties are attributed to its high sugar content, low pH, hydrogen peroxide, and non-peroxide phytochemicals like methylglyoxal (da Silva et al. 2016, Johnston et al. 2018, Kafantaris et al. 2020). Honey influences bacterial processes, including cell division, motility, and biofilm formation, through gene expression modulation. Studies reveal honey's capability to reduce virulence and biofilm gene expression in pathogens like *E. coli* and *Staphylococcus aureus* (Lee et al., 2011; Kafantaris et al., 2020). RNA sequencing of *Pseudomonas aeruginosa* exposed to manuka honey showed increased expression of growth and adaptation genes, highlighting honey's multifactorial antibacterial effect (Bouzo et al. 2020, Kafantaris et al. 2020).

The anti-inflammatory properties of honey further contribute to its prebiotic potentia*l.* Studies show honey increases anti-inflammatory cytokines and decreases pro-inflammatory cytokines in various models, such as rats with induced gastric ulcers or ulcerative colitis (Ranneh et al. 2021, Schell et al. 2022, Vallianou et al. 2014). Honey's polyphenols are responsible for these effects, reducing inflammation and suppressing harmful organisms (Zhao et al. 2019).

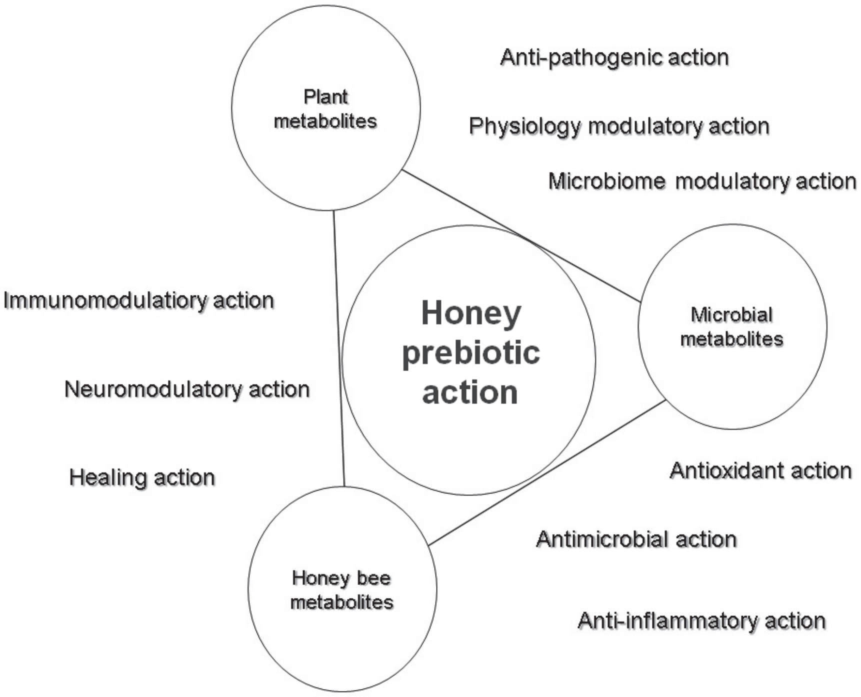

Figure 2. Honey is a complex prebiotic resulting from the interactions between microbiomes, honey bees, and plants.

Honey's oligosaccharide composition, influenced by plant sources, determines its prebiotic properties (Kolayli et al. 2012). New Zealand honey, for example, contains high levels of isomaltose and melezitose, whereas Italian honey is rich in raffinose, leading to variations in prebiotic potential (Kolayli et al. 2012, Schell et al. 2022). Honeydew oligosaccharides increase beneficial bifidobacteria and lactobacilli populations while reducing harmful *bacteroides* and clostridia (Sanz et al., 2005; Schell et al. 2022). These oligosaccharides have prebiotic effects comparable to commercial fructooligosaccharides (Brudzynski 2021).

Human clinical trials have shown that daily honey consumption, including manuka honey, does not significantly alter major gut bacteria families. However, the quality and storage conditions of honey can affect these results (Brudzynski 2021, Schell et al. 2022). In vivo studies on animal models support honey's role as a prebiotic, promoting probiotic bacteria growth and alleviating symptoms of constipation and ulcerative colitis (Li et al. 2020, Schell et al. 2022, Wang et al. 2019). In shrimp, honey stimulates probiotic growth and improves gut health, reducing pathogen load and increasing survival rates when infected with *Vibrio parahaemolyticus* (Table 1) (Fuandila et al. 2019, Hasyimi et al. 2020, Schell et al. 2022).

Honey bee gut and honey microbiota

A. mellifera, the honey bee, serves as an exemplary model organism due to its adaptable microbial community, which, while sharing similarities with mammalian microbiota, is notably simpler (Nowak et al. 2021). Newly emerged honey bees focus on hive maintenance, while worker honey bees undertake various tasks. Routes of infection for newly emerged honey bees include interactions with adult bees, contact with comb, and consumption of bee bread (Dong et al. 2020, Nowak et al. 2021). Gut colonization begins within a day of hatching, with bacteria such as *Gilliamella*, *Frischella*, and *Snodgrassella* establishing early residence. Over time, other bacterial species including *Lactobacillus*, *Bifidobacterium*, and *Commensalibacter* become established, exhibiting dynamic abundance changes (Dong et al. 2020, Nowak et al. 2021).

The honey bee microbiota occupies different gut sections, with *Parasaccharibacter sp.* prominently found in the hypopharyngeal glands of workers (Corby-Harris et al. 2014, Nowak et al. 2021). Adult worker bee intestines harbor specialized microorganisms organized into nine bacterial species clusters, characterized by high resistance to ambient oxygen and transferred through social contacts (Jones et al. 2017, Nowak et al. 2021). Studies using 16S rDNA and metagenomics have revealed that the honey bee worker's intestine is populated by nine clusters of bacterial species, including *Snodgrasella alvi* and *Gilliamella apicola*, both from the Proteobacteria phylum (Tola et al. 2020, Nowak et al.,2021, Zheng et al. 2017).

Lactobacillus Firm-4 and *Lactobacillus* Firm-5, both Gram-positive species from the Firmicutes phylum, are prevalent in the distal rectum (Jones et al. 2017, Nowak et al. 2021, Tola et al. 2020). Adult workers generally harbor *Bifidobacterium asteroides* in lower amounts (Bleau 2020, Jones et al. 2017, Nowak et al. 2021). A crucial group of microorganisms in bee intestines is the "core bacteria" clusters (Kešnerová et al. 2020, Nowak et al. 2021).

Other bacterial genera commonly found in honey bee digestive systems include *Apibacter*, *Asaia*, and *Acetobacter*. Certain rare bacteria associated with diseases and honey bee mortality, such as *Enterobacter*, *Klebsiella*, *Citrobacter*, and *Serratia*, are also present in the honey bee gut (Raymann et al., 2018). Less common Proteobacteria include *Frischella perrara* (Orbaceae), *Parasaccharibacter apium*, *Bombella favorum*, *Bombella mellum*, *Bombella apis* (Acetobacteraceae), *Commensalibacter sp.* (Alpha 2.1), and *Bartonella apis* (Rhizobiaceae) (Bleau, 2020, Dong et al. 2020, Jones et al. 2017, Kešnerová et al. 2016, Hilgarth et al. 2021, Nowak et al. 2021, Tola et al. 2020). *Apibacter adventoris*, *Apibacter mensalis*, a *Bacteroidetes* members, has also been identified (Nowak et al. 2021).

The honey bee gut comprises 10 known taxa, including four *Lactobacillus sp.*, two *Gilliamella* species, one *Bifidobacterium* species, and one *Snodgrassella* species, considered part of the core gut microbiota. *Frischella* and *Bartonella* taxa may vary by habitat (Nowak et al., 2021). Dominant phyla in the honey bee gut include Proteobacteria (63.2%), Firmicutes (17.6%) with 15.9% *Lactobacillus sp.*, Actinobacteria (4.1%) with 3.34% *Bifidobacterium sp.*, and *Bacteroidetes* (1.7%) with 0.23% *Bacteroides sp.* (Wang et al., 2021; Nowak et al., 2021). The core member *Lactobacillus* firm-4 is detected in 98.4% of examined honey bees (Brudzynski, 2021, Kešnerová et al. 2020, Nowak et al., 2021).

Lactic acid bacteria isolated from honey bee workers, including *Enterococcus faecalis* (HBE1, HBE3, HBE4), *Lactobacillus brevis* (HBE2), and *Lacticaseibacillus* casei (HBE5), show potential as pharmacobiotics for functional dietary foods that promote human health (Elzeini et al. 2021). These bacteria exhibit enhanced antimicrobial, antioxidant, and anti-inflammatory effects and can survive in human and animal gastrointestinal tracts under stressful conditions (Elzeini et al. 2021, Nowak et al. 2021).

Research in Sub-Saharan Africa, particularly in Kenya, highlights significant members of the honey bee gut microbiota, including *Gilliamella*, *Snodgrassella*, *Lactobacillus* (Firm-4 and Firm-5), *Bifidobacterium*, *Frischella*, *Commensalibacter*, *Bombella*, *Apibacter*, and *Bartonella* (Nowak et al. 2021, Tola et al. 2020). Fungal taxa such as *Saccharomyces*, *Zygosaccharomyces*, and *Candida* are also present in honey bee digestive systems (Nowak et al. 2021).

Paenibacillus species, commonly found in honey bee hives and wild solitary bee nests, include pathogenic strains such as *P. alvei, P. apiarius*, and *P. larvae*, which coexist with *Melissococcus plutonius*, the agent of European foulbrood (Grady et al. 2016). *P. larvae* causes American foulbrood disease (Genersch 2010). *Paenibacillus* strains produce antimicrobial compounds like lantibiotics, bacteriocins, lipopeptides, and putative sactipeptides, exhibiting broad-spectrum activity against foodborne pathogens (Grady et al. 2016, Pomastowski et al. 2019). Polymyxins, produced by *P. polymyxa*, are particularly effective against Gram-negative bacteria, including multidrug-resistant strains, targeting the outer membrane to cause cell lysis (Poirel et al. 2017). *P. polymyxa* TH13 isolates from honey produce polymyxin E, showing broad antibacterial activity, including against *P. larvae* (Lee et al. 2009). *P. alvei* MP1 from buckwheat honey demonstrates activity against *L. monocytogenes*, *S. aureus*, and *E. coli* O157 (Pajor et al. 2020).

Microbial contaminants in honey, while a safety concern, can also produce beneficial antimicrobial compounds. These include *Lactobacillus*, *Bifidobacterium*, *Bacillus*, and yeast (*Saccharomyces cerevisiae*), which prevent food spoilage (Xiong et al. 2022; Brudzynski 2021). Studies show that raw honey can inhibit various food spoilage microorganisms and human pathogens, including *Aspergillus* niger, *Penicillium expansum*, *Lactobacillus acidophilus*, *Pseudomonas fluorescens*, *Bacillus cereus*, *E. coli* O157, *Listeria monocytogenes*, *Salmonella enterica* Ser. *Typhimurium*, and *S. aureus* (Xiong et al., 2022; Carter et al. 2016, Brudzynski 2021). Over 90% of bacterial strains found in honey show in vitro antimicrobial activity, highlighting the significant role of microbial strains in honey's antibacterial properties (Chanclud & Lacombe 2017, Xiong et al. 2022).

The honey microbiota is influenced by the microbial colonization of nectar, honey, and honey bees, shaping the metabolites produced through competition (Brudzynski 2021). This microbiota includes dominant bacterial orders Lactobacillales and Bacillales (genera *Bacillus* and *Paenibacillus*), along with fungi and yeasts, forming the core microbiota of honey and contributing to its antimicrobial activity (Brudzynski 2021).

Microbial contamination in honey originates from various environmental sources such as air, water, and pollination environments, with bees acting as primary vectors through their foraging activities (Alvarez-Pérez et al. 2012). During the transformation of nectar into honey, the diversity and composition of the microbiota decrease due to ripening processes (Wen et al. 2017). Metagenomic analyses reveal an overlap between the core microbiota of honey and those of nectar, pollen, bee stomachs, and crops, with Actinobacteria, Firmicutes, and Proteobacteria being dominant, and *Bacillus* and *Lactobacillus* the most abundant families (Anderson et al. 2013, Corby-Harris et al. 2014, Bovo et al. 2018).

While the composition of the honey microbiota can vary based on botanical and geographical origins, *Bacillus* and *Lactobacillus* consistently play significant roles and contribute to honey's antimicrobial properties (Alvarez-Pérez et al. 2012, Lee et al. 2008). The Lactobacillaceae and Bacillaceae families are key producers of antibacterial chemicals such as bacteriocins, surfactants, and siderophores (Caulier et al.,2019, De Vuyst & Leroy 2007, Zacharof & Lovitt 2012). These families significantly influence honey's antibacterial efficacy (Khan et al. 2016). The dynamic interactions within the honey microbiota are crucial for maintaining honey's quality and antimicrobial activity (Figure 3) (Brudzynski 2021).

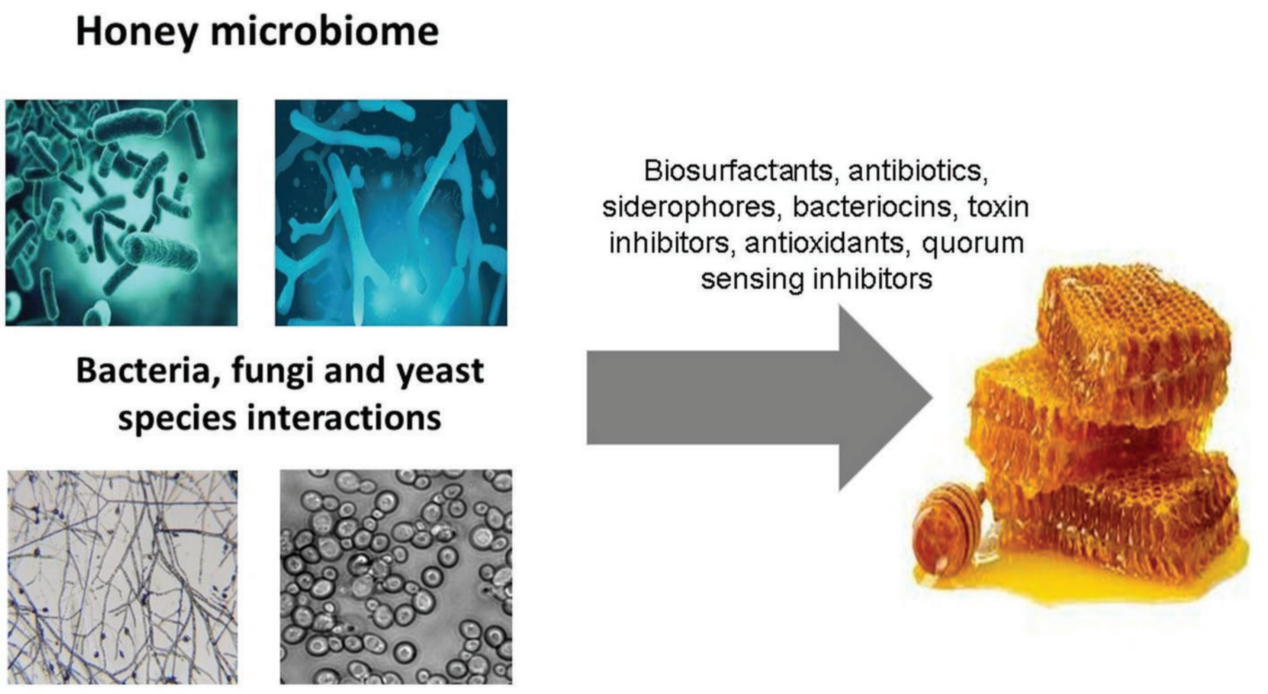

Figure 3. Contribution of the honey microbiota in the formation of prebiotic properties of honey.

Compared to other fermented foods, honey contains fewer microorganisms. Its microbiota mainly originates from pollen, flowers, soil, air, dust, and the digestive tract of honey bees (Snowdon & Cliver, 1996; Kafantaris et al., 2020). This microbiota includes bacteria, yeasts, and molds, with environmental factors influencing its composition (Kafantaris et al. 2020, Wen et al. 2017). Human processing can introduce secondary contaminants (Snowdon & Cliver 1996, Olaitan et al. 2007). Plant-associated microorganisms are transferred to hives during pollination, with the honey bee gut being a significant source of microbial transmission into honey. Lactobacilli and Bifidobacteria, conserved components of the honey bee gut microbiota, are also found in honey and bee nectar (Anderson et al. 2013, Raymann et al. 2018, Olofsson & Vásquez 2008).

Although most gut bacteria thrive only in the gut, *Lactobacillus kunkeei* and Acetobacteraceae (*Asaia spp.*) are exceptions, found in extreme conditions such as honey and royal jelly (Anderson et al. 2013, Xiong et al. 2022). Honey's physicochemical properties—high sugar content, low water activity, and low pH—mean most bacteria found in honey are osmotolerant, xerotolerant, and acidotolerant. Consequently, many bacteria in honey remain metabolically dormant (Brudzynski 2021, Xiong et al. 2022). The honey microbiota is influenced by factors like titratable acidity, water activity, and color (Balzan et al. 2020, Kňazovická et al. 2019, Xiong et al. 2022).

The honey microbiota serves as a bioindicator, reflecting agricultural and urban landscapes, microbial environments to which honey bees are exposed, and chemical contaminants along foraging routes. It also indicates hive immune status and overall hive health (Xiong et al. 2022). Next-generation sequencing (NGS) metagenomics provides taxonomic classification of the honey microbiota and serves as an indicator of honey origin and hive health (Bovo et al. 2020, Xiong et al. 2022).

Prebiotic potential of honey due to Lactic Acid Bacteria and Bifidobacteria derived compounds

Honey bees deploy both cellular and humoral immune defenses in response to infections caused by various pathogens, including bacteria, fungi, viruses (Evans et al. 2006). Honey bees have own individual and social immunity, but their humoral immune responses are relatively limited, primarily involving the production of a few antimicrobial peptides. These include proline-rich apidaecins, abaecins, cysteine-rich defensins 1 and 2, and glycine-rich hymenoptaecin (Casteels-Josson et al. 1994). In honey, antimicrobial peptides such as defensin-1, hymenoptaecin, and jelleins, derived from honey bees, contribute to its antimicrobial properties (Brudzynski & Sjaarda, 2015, Di Girolamo et al. 2012, Klaudiny et al. 2005, Kwakman et al. 2010;). Defensin-1 and royalisin (defensin 2), found in honey and royal jelly respectively, exhibit distinct antimicrobial activities against Gram-positive bacteria and fungi (Fujiwara et al. 1990, Brudzynski 2021). Royalisin additionally shows activity against *Paenibacillus larvae larvae* (Bachanova et al. 2002). Hymenoptaecins, inducible antimicrobial peptides synthesized in response to bacterial infections, require proteolytic processing for activation and are introduced into honey through bee hypopharyngeal gland secretions (Xu et al. 2009). Jelleins, located within the major royal jelly protein 1 (MRJP 1), exert antimicrobial effects primarily against Gram-positive bacteria, following proteolytic release from MRJP 1 (Brudzynski & Sjaarda 2015).

Honey bees possess additional defenses against pathogens through their microbiota, particularly lactic acid bacteria. Lactic acid bacteria play a crucial role in the honey bee gut microbiota, contributing to the bees' overall health and immune function (Ilyasov et al. 2024). These bacteria produce lactic acid as a metabolic product, creating an acidic environment in the bee gut that inhibits the growth of harmful pathogens (Vásquez & Olofsson 2009).

Several species of lactic acid bacteria have been identified in the honey bee gut, including *Lactobacillus*, *Bifidobacterium*, and others (Anderson et al. 2013). Lactic acid bacteria and fructophilic lactic acid bacteria are particularly prevalent in carbohydrate-rich environments, such as honey and other bee products (Forsgren et al., 2009; Endo & Salminen, 2013). The honey bee's foregut serves as a food storage area and the starting point for lactic acid bacteria to break down carbohydrates, deriving from both the pollination environment and the bee's digestive system (Anderson et al. 2013, Corby-Harris et al. 2014, Olofsson et al. 2014).

The lactic acid bacteria not only compete for nutrients and space with potential pathogens but also produce antimicrobial compounds such as bacteriocins and organic acids that directly inhibit pathogen growth (Olofsson & Vásquez 2008). Moreover, lactic acid bacteria have been shown to stimulate the honey bee immune system, enhancing the expression of antimicrobial peptides and other immune-related genes (Forsgren et al. 2009, Raymann et al. 2017). This immune stimulation further strengthens the bees' ability to fend off infections caused by various pathogens, including bacteria, fungi, and viruses.

The antibacterial activity of bee-derived products is significantly influenced by lactic acid bacteria. The antibacterial activity of bee-derived products is significantly influenced by lactic acid bacteria (Ilyasov et al. 2024). Various lactic acid bacteria isolated from pollen, honey, bee bread, and crops demonstrate antimicrobial activity against foodborne and multidrug-resistant pathogens, as well as bee pathogens (Ramos et al. 2020). For instance, *Lactobacillus johnsonii*, *Lactobacillus plantarum*, *Lactobacillus brevis*, and *Lactobacillus apis* inhibit *Melissococcus plutonius* and *Paenibacillus larvae*, causative agents of European and American foulbrood infections (Forsgren et al. 2009). Lactic acid bacteria strains from Malaysian honey, like *Lactobacillus acidophilus*, show inhibition of antibiotic-resistant *S. aureus, Staphylococcus epidermis*, and *Bacillus subtilis*, and *L. kunkeei* prevents *P. aeruginosa* biofilm development (Berríos et al. 2018).

Lactic acid bacteria also produce potent antifungal compounds against various fungi and yeasts. Lactobacilli isolated from beebread, such as *Fructobacillus fructosus*, *Fructobacillus tropaeoli*, and *L. kunkeei*, show strong antagonism against *Zygosaccharomyces rouxii*, a common spoilage yeast (Ramos et al. 2020). When honey’s moisture content exceeds 18%, spoilage yeasts like *Zygosaccharomyces rouxii* and *Zygosaccharomyces bailii* can develop and ferment honey, but lactic acid bacteria’s antifungal activity can prevent this (Chaven, 2014; Muhialdin et al., 2018). Lactic acid bacteria also deactivate mycotoxins produced by fungi such as *Penicillium*, *Fusarium*, and *Aspergillus*, either through binding and adhering to cell walls or by metabolizing mycotoxins into non-toxic derivatives (Brudzynski 2021, Muhialdin et al., 2018, Sadiq et al., 2019).

Honey can contain up to 10^8 colony-forming units per gram of viable lactic acid bacteria (Vásquez et al. 2012). Honey bees transfer bacteria from their gut microbiota into nectar, influencing honey's bacterial composition, which includes species from Enterobacteriaceae and Firmicutes such as *Lactobacillus*, *Bacillus*, and *Weissella* (Kafantaris et al. 2020, Naseer et al. 2015; Olofsson et al. 2016). Commonly identified bacteria in honey also include *Achromobacter*, *Citrobacter*, *Enterobacter*, *Flavobacterium*, *Proteus*, and *Pseudomonas* species (Kafantaris et al., 2020).

Studies on stingless bee honey reveal *Lactobacillus malefermentans* as the most abundant species (Li et al. 2020, Xiong et al. 2022). However, lactobacilli may be absent in honey with less than 18% moisture during ripening (Wen et al. 2017, Xiong et al. 2022). The presence of *L. kunkeei* varies depending on bloom source and season (Vásquez et al. 2012, Wen et al. 2017, Xiong et al. 2022). *Enterobacteri*aceae in honey likely originate from the pollination environment and are often isolated from foraging honey bees (Corby-Harris et al. 2014; Xiong et al. 2022).

Honey's bacterial composition remains relatively conserved during ripening, with *Bacillus* and *Lactococcus* being the most common phylotypes, while fungal communities show more diversity (Xiong et al. 2022). Flowers such as Chasteberry harbor *Metschnikowia*, *Cladosporium*, and *Alternaria*, while Chasteberry honey contains *Metschnikowia*, *Phoma*, and *Candida*, highlighting a divergence in fungal communities (Kafantaris et al. 2020, Wen et al. 2017).

Beneficial plant microorganisms, such as actinobacteria, also contribute to bee health by producing secondary chemicals that inhibit fungal growth and spoilage (Anderson et al. 2013, Kurek-Gorecka et al. 2020). Secondary metabolites produced by lactic acid bacteria, like *L. kunkei*, support hive health by combating spoilage microbes and pathogens (Arredondo et al. 2018, Xiong et al. 2022).

A recent study using Illumina MiSeq NGS analyzed bacterial diversity in honeys from various countries, identifying 52 bacterial genera. *L. kunkei* and *L. apinorum* were most abundant in some samples, while pathogens like *Melissococcus plutonius* and *Enterococcus faecalis* were also present, likely due to sample contamination (Kafantaris et al. 2020, Kňazovická et al. 2019).

Lactobacillus kunkei, commonly found in flowers, fruits, soil, hive environments, and fermented bee products (Anderson et al. 2013), has been identified in honey bee bread and influences honey composition under various conditions (Xiong et al. 2022). Another prevalent bacterium in honey, *Lactococcus lactis*, universally present in all sequenced honeys (Xiong et al. 2022), participates in the fermentation of honey carbohydrates, producing lactic acid (Sinacori et al. 2014, Xiong et al. 2022).

Lactic acid bacteria, including *Lactococcus*, are introduced into bee species through horizontal transfer between hives and their environment. These bacteria, during their logarithmic growth phase, synthesize bacteriocins, small cationic antimicrobial peptides (Rutherford & Bassler 2012). Reviews have extensively covered the structure, classification, and mechanism of action of these bacteriocins (Alvarez-Sieiro et al., 2016, De Vuyst & Leroy 2007, Zacharof & Lovitt 2012). Despite the abundance of lactic acid bacteria in honeycomb products, only one bacteriocin, kunkecin A, has been identified in honey bee *L. kunkeei* to date (Zendo et al. 2020). However, other lactobacilli like *L. johnsonii*, *L. plantarum*, *L. brevis*, and *L. apis* show potential for producing bacteriocins with activity against honey bee pathogens (Endo & Salminen 2013, Forsgren et al. 2009).

Nisin A, also known as kunkecin A, derived from *Lactococcus lactis subsp. lactis*, is a class I lantibiotic bacteriocin that targets lipid II in Gram-positive bacterial cell walls (Zendo et al. 2020). It exhibits broad-spectrum antibacterial activity against bacteria such as staphylococci, streptococci, bacilli, clostridia, and mycobacteria. In contrast, kunkecin A specifically targets *Melissococcus plutonius*, the causative agent of European foulbrood (Zendo et al. 2020). Lantibiotics like nisin can disrupt Gram-negative bacteria when their outer membrane integrity is compromised by chelating agents such as EDTA (Parada et al. 2007).

Apart from bacteriocins, lactic acid bacteria produce biosurfactants, which alter cell envelope properties and inhibit biofilm formation by interacting with membrane components. These biosurfactants influence biofilm development by interfering with quorum sensing systems, crucial for bacterial survival and pathogenicity regulation (Rutherford & Bassler 2012). *Lactobacillus* species-derived biosurfactants demonstrate potent anti-biofilm activity against clinical isolates of Gram-positive and Gram-negative bacteria, as well as against fungi (Table 2) (Sharma & Saharan 2016).

Table 2. Prebiotic potential of honey due to Lactic Acid Bacteria and Bifidobacteria.

Species	**Antimicrobial compounds**	**Target species**	**References**
Lactobacillus acidophilus	acidocin, lactacins	*Lactobacillus sp., Listeria monocytogenes, Enterococcus faecalis, Limosilactobacillus fermentum, Enterococcus faecalis, Lactobacillus delbrueckii, Lactobacillus helveticus, Lactococcus lactis.*	Oscáriz and Pisabarro, 2001; Parada, et al., 2007; Brudzynski, 2021
Lactobacillus helveticus	helveticin J, lactocin 27	*Lactobacillus sp., Lactobacillus bulgaricus, Lactococcus lactis*	Upreti and Hinsdill, 1975; McAuliffe et al., 2001
Lactobacillus johnsonii	lactacin F	*Lactobacillus sp., Enterococcus faecalis, Lactobacillus delbrueckii, Lactobacillus helveticus*	Abee et al., 1994; Allison et al., 1995; McAuliffe et al., 2001
Lactobacillus kunkeei	kunkicin	*Listeria monocytogenes, Staphylococcus aureus*	McAuliffe et al., 2001; Brudzynski, 2021
Lactobacillus plantarum	plantaricin A	*Listeria monocytogenes, Staphylococcus aureus, Salmonella typhimurium, Escherichia coli, Bacillus cereus, Bacillus pumilus, Bacillus megaterium, Pediococcus, Carnobacteria, Clostiridia, Propionobacteria*	Gong et al., 2010; Meng et al., 2022
Lactobacillus lactis	nisin, lacticin 3147	*Staphylococcus aureus, Listeria innocua, Lactobacillus sakei, Lactiplantibacillus plantarum, Enterococcus faecalis, Propionibacterium acne, Streptococcus mutans, Bacillus sp., Micrococcus sp., Clostridium sp.*	Parada, et al., 2007; Alegría et al., 2010; Brudzynski, 2021
Pedicoccus pentosaceus	pediocin	*Listeria monocytogenes, Lactobacillus sp., Lactococcus sp., Leuconostoc spp, Pediococcus sp., Staphylococcus sp., Enterococcus sp., Clostridium sp.*	Jack et al., 1995; Parada, et al., 2007; Brudzynski, 2021

Prebiotic potential of honey due to Bacillales derived compounds

Bacillales, a dominant order within Firmicutes, thrives in nectar and honey environments, constituting a substantial portion of honey microbiota, ranging from 60% to 90% of all bacteria present. The genera *Bacillus* and *Paenibacillus* are particularly prominent within this order (Pajor et al. 2018; Pomastowski et al. 2019). Through advanced molecular techniques like 16S rRNA gene sequencing and MALDI-TOF analysis, *Bacillus* isolates have been categorized into three main phylogenetic clusters: the *B. subtilis* group (including *B. subtilis*, *B. methylotrophicus*, *B. atrophaeus*, *B. licheniformis*, and *B. amyloliquefaciens*), the *B. cereus* group (comprising *B. cereus*, *B. thuringiensis*, *B. mycoides*, *B. pseudomycoides*, and *B. weihenstephanensis*), and the *B. pumilis* group (represented by *B. pumilis*, *B. safensis*, and *B. altitudinis*) (Brudzynski, 2021, Chaven 2014, Zacharof & Lovitt 2012).

The family Bacillaceae dominates honey microbiota due to its robust production of antimicrobial compounds aimed at outcompeting other microorganisms (Caulier et al. 2019). *Bacillus* and *Paenibacillus* genera are prolific producers of antimicrobial substances such as bacteriocins, lipopeptides (surfactants), and siderophores, which confer a competitive advantage by inhibiting the growth of neighboring species (Jack et al. 1995).

Specific *Bacillus* groups present in honey, including *B. subtilis*, *B. amyloliquefaciens*, *B. licheniformis*, *B. thuringiensis*, and *B. cereus*, produce strain-specific bacteriocins like subtilin, subtilosin, lichenicidin, thuricins, and cereins (Caulier et al. 2019). These bacteriocins exert their antimicrobial effects through mechanisms such as pore formation and membrane permeabilization, leading to cell death (Brudzynski 2021).

One notable example is subtilin, structurally similar to nisin from *Lactococcus lactis*, which disrupts bacterial cell walls by binding to lipid II, thereby inhibiting peptidoglycan synthesis and inducing cell lysis (Caulier et al. 2019). Despite their production by *Bacillus* strains in honey, many of these bacteriocins have not been directly detected in the honey itself (Brudzynski 2021).

Bacillus species also produce lantibiotic bacteriocins like thuricins, which exhibit potent activity against various pathogens including *Clostridioides difficile* and other Gram-positive bacteria (Lee et al. 2009, Rea et al. 2010). These bacteriocins induce cell death through mechanisms involving membrane disruption and interference with peptidoglycan synthesis, similar to the action of β-lactam antibiotics (Cho et al. 2014).

In addition to bacteriocins, *Bacillus* strains are capable of synthesizing diverse non-ribosomal peptides and polyketides, which contribute to their competitive survival in microbial communities (Straight & Fischbach 2016, Zhao & Kuipers 2016). These compounds target various cellular components in competing species, providing *Bacillus* with a substantial survival advantage in diverse environments (Caulier et al. 2019).

Moreover, *Bacillus* and *Paenibacillus* genera are known for producing lipopeptides such as surfactin, fengycin, and iturin, which exhibit broad-spectrum antibacterial and antifungal activities by disrupting membrane integrity (Vlamakis et al. 2013, Janek et al. 2020). These lipopeptides function as biosurfactants, reducing membrane surface tension and inhibiting biofilm formation, thereby further enhancing *Bacillus*' competitive edge (Table 3) (Vlamakis et al. 2013; Deleu et al. 2013; Janek et al. 2020).

Furthermore, siderophores produced by *Bacillus* and *Paenibacillus* species sequester iron from the environment, depriving competing microorganisms of this essential nutrient and inhibiting their growth (Miethke et al., 2006). Bacillibactin, a catecholate siderophore produced by various *Bacillus* species, including *B. subtilis* and *B. cereus*, enhances iron uptake under low-iron conditions, contributing to their competitive success (Khan et al. 2016).

Table 3. Prebiotic potential of honey due to Bacillales.

Species	Antimicrobial compounds	Target species	References
Bacillus subtilis	subtilin, subtilosin A, sublancin, surfactin, fengycin, bacillomycin, bacillibactin, bacitracin, bacilysin, bacillaene	Gram+, *Listeria monocytogenes*, *Gardnerella vaginalis*, *Streptococcus agalactiae*, *Bacillus cereus*, *Streptococcus pyogenes*, *Staphylococcus aureus*	Abriouel et al., 2011; Zhao & Kuipers, 2016; Caulier et al., 2019
Bacillus licheniformis	lichenin, bacitracin, lichenicidin, lychenisin	Gram+, *Listeria monocytogenes*. *Streptococcus bovis*, *Staphylococcus aureus*	Abriouel et al., 2011; Zhao & Kuipers, 2016; Brudzynski, 2021
Bacillus amyloliquefaciens	amylolysin, iturin, bacillaene, bacilysin, subtiliosin, fengycin, surfactin	Gram+, *Listeria monocytogenes*, *Staphylococcus aureus*	Zhao & Kuipers, 2016; Brudzynski, 2021
Bacillus cereus	cereins, bacillibactin, thuricin	Gram+, *Bacillus cereus*, *Bacillus coagulans*, *Bacillus subtilis*, *Bacillus pumilus*	Abriouel et al., 2011; Zhao & Kuipers, 2016; Brudzynski, 2021
Bacillus thuringiensis	thuricin 17, thurincin H, thuricin CD	Gram+, *Bacillus thuringiensis*, *Bacillus cereus*, *Bacillus subtilis*, *Bacillus megaterium*, *Listeria monocytogenes*, *Listeria innocua*, *Listeria ivanovii*, *Staphylococcus aureus*, *Carnobacterim psicola*, *Geobacillus stearothermophillus*, *Clostridium difficile*, *Escherichia coli* MM294	Rea et al., 2010; Abriouel et al., 2011; Zhao & Kuipers, 2016
Bacillus pumilis	pumilicin, surfactin, bacilysin, pumilacidin, bacitracin	Gram+, *Staphylococcus aureus*, *Enterococcus faecalis*	Abriouel et al., 2011; Sumi et al., 2015; Brudzynski, 2021
Bacillus megaterium	megacin, surfactin, fengycin, bacillomycins	Gram+, *Staphylococcus aureus*	Sumi et al., 2015
Paenibacillus larvae	paenibacterin, iturin, tridecaptin, fusaricidin	Gram+, Gram-, *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*	Sood et al., 2014; Keller et al., 2018
Paenibacillus polymyxa	paenibacillin, bacillibactin, bacillaene, polymyxin, paenimacrolidin	Gram+, Gram-, *Escherichia coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*	Zhao & Kuipers, 2016; Keller et al., 2018; Brudzynski, 2021
Brevibacillus brevis	gramicidin	Gram+, Gram-, *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*	Sumi et al., 2015; Brudzynski, 2021

Prebiotic potential of honey due to fungi derived compounds

Yeasts and fungi are prevalent contaminants in nectar and honey, thriving under conditions such as low pH, high sugar concentration, and antagonistic interactions among microbes (Alvarez-Pérez et al. 2012, Snowdon & Cliver 1996). These resilient microorganisms, categorized as osmotolerant, xerotolerant, and acidotolerant, include predominant genera like *Candida*, *Eremascus*, *Metschnikowia*, *Bettsia*, *Monascus*, *Oidiodendron*, *Pichia*, *Saccharomyces*, *Skoua*, *Torulopsis*, and *Zygosaccharomyces* (Sinacori et al. 2014).

Ascomycetes, including filamentous fungi such as *Aspergillus*, *Penicillium*, *Cladosporium*, and *Fusarium*, also flourish, with less frequent occurrences of *Arthrinium*, *Chaetonium*, *Daldinia*, and *Emericella* (Sinacori et al. 2014). Notably, xerotolerant genera like *Bettsia*, *Ascosphaera*, *Metschnikowia*, and *Eremascus* survive at very low water activity levels (up to 0.82), while acidophilic or acidotolerant genera like *Pichia*, *Saccharomyces*, and *Zygosaccharomyces* thrive even in acidic environments below pH 2 (Brudzynski, 2021, Snowdon & Cliver 1996, Rodríguez-Andrade et al. 2019).

Serratia symbiotica constitutes about 4.8% of bacteria in polyfloral honey from Italy (Bovo et al. 2020), commonly found in Hymenoptera species (Xiong et al., 2022). Originating as a secondary endosymbiont of aphids, some *Serratia* species have evolved through aphid honeydew consumption by bees, influencing honey production (Bovo et al. 2020, Xiong et al. 2022). Certain *Serratia* strains can act as opportunistic pathogens for honey bees, impacting hive health (Raymann et al. 2018, Xiong et al. 2022).

Honey often contains yeast and mold (Kačániová et al. 2009, Kafantaris et al. 2020), with common fungal taxa including *Bettsia*, *Yarrowia*, *Skoua*, *Zygosaccharomyces*, and *Metschnikowia*. Chasteberry honey displays a diverse fungal profile, featuring prevalent genera like *Waitea*, *Phoma*, *Metschnikowia*, and *Cryptococcus*, reflecting their prevalence in chasteberry flowers (Xiong et al. 2022). Genera such as *Waitea* and *Cryptococcus* may be absent from certain honeys due to their floral specificity, commonly found in Vitex flowers (Wen et al. 2017, Xiong et al. 2022). Culture-dependent methods highlight *Zygosaccharomyces* and Debaryomyces as the most abundant yeast taxa in honey (Sinacori et al. 2014, Xiong et al. 2022), consistently identified via culture-independent ITS2 metabarcoding (Balzan et al. 2020, Xiong et al. 2022).

Fungal and yeast genera found in honey encompass *Aspergillus*, *Penicillium*, *Monascus*, *Bettsia*, *Skoua*, *Oidiodendron*, *Eremascus*, *Ascosphaera*, Schizo*saccharomyces*, *Zygosaccharomyces*, *Candida*, *Saccharomyces*, Cyberlindnera, *Starmerella*, *Cladosporium*, *Alternaria*, *Stemphylium*, *Fusarium*, and *Mucor* (Brudzynski, 2021, Sinacori et al. 2014, Rodríguez-Andrade et al. 2019). Notably, *Cladosporium*, a filamentous fungus widely distributed in the environment, is commonly found in honey and may coexist with bees, possibly transmitted from plants or through bee interactions, and persists in bee products (Martinson et al. 2012). Similarly, filamentous fungi like Botrytis, *Penicillium*, and *Mucor*, prevalent in plant pollen, are transferred to honey bees and are frequently found in beebread (Disayathanoowat et al. 2020). Common yeast genera isolated from pollen and beebread include *Candida*, *Cryptococcus*, Kloeckera, *Metschnikowia*, and Rhodotorula (Brudzynski 2021).

Certain fungi, such as *Aspergillus* and *Penicillium* species, are considered environmental contaminants in honey (Kačániová et al. 2009), with *Aspergillus flavus* identified as a significant fungus in polyfloral Italian honey, known for causing stonebrood disease in honey bees (Xiong et al. 2022). *Ascosphaera apis*, responsible for chalkbrood disease, predominates in various wildflower honeys (Xiong et al. 2022). Despite their presence, the mere detection of these potentially harmful fungi does not necessarily indicate hive infection, as evidenced by their asymptomatic presence in colonies over extended periods (Xiong et al. 2022).

Fungi and yeasts employ various survival strategies within the honey microbial ecosystem, including spore formation to endure adverse conditions and the production of secondary metabolites such as mycotoxins, antibiotics, siderophores, and surfactants (Deshmukh et al. 2015). Mycotoxins, known as killer toxins, are produced by yeasts like *Metschnikowia*, *Zygosaccharomyces*, *Saccharomyces*, and *Candida*, as well as by filamentous fungi including *Aspergillus*, *Fusarium*, and *Penicillium* species (Liu et al. 2015). These toxins exert lethal effects by disrupting essential cellular functions like DNA and cell wall synthesis

(Liu et al. 2015). For example, zygocin from *Zygosaccharomyces bailii* selectively targets *Candida* species, facilitating its own growth. Lactic acid bacteria and *Bacillus spp.* in honey possess enzymatic systems capable of degrading and transforming mycotoxins into non-toxic derivatives (Kačániová et al. 2009).

Some yeast genera, like *Aspergillus* and *Penicillium*, are known producers of β-lactam antibiotics such as penicillin and cephalosporin, which inhibit cell wall synthesis by targeting penicillin-binding proteins (Venkatesh & Keller 2019). *Candida* species produce sophorolipids with anti-biofilm properties, inhibiting adhesion and biofilm formation of various species including *Candida* and *Pichia*, as well as Gram-positive bacteria (Paraszkiewicz et al. 2019). Yeasts also secrete siderophores during iron starvation to chelate essential metals like iron Fe (III), manganese, and zinc from the environment, thereby restricting the growth of competing microorganisms (Brudzynski 2021).

Prebiotic potential of honey due to plant plant derived compounds

Plant metabolites in honey play a crucial role in shaping the prebiotic properties of honey, influencing its nutritional and therapeutic benefits. Honey, a complex mixture produced by honey bees from floral nectar and enriched with plant-derived compounds, exhibits diverse prebiotic effects due to these metabolites.

Plant-derived essential oils and terpenoids in honey provide potent antimicrobial effects, inhibiting pathogens and enhancing its shelf-life and therapeutic uses (Brudzynski & Sjaarda 2015). Plants use R genes to produce pathogenesis-related (PR) proteins like defensins (PR-12), thionins (PR-13), thaumatin-like proteins (PR-5), and lipid transfer proteins (PR-14), known for broad-spectrum antibacterial and antifungal properties (Sudisha et al., 2011). Enzymes such as chitinases (PR-2, PR-4, PR-8, PR-11) and glucanases degrade fungal cell wall components, while PR-8 chitinases also include lysozymes targeting bacterial peptidoglycan. PR-10 proteins with ribonuclease activity may combat RNA viruses, and the nectar redox cycle produces hydrogen peroxide, bolstering plant antimicrobial defenses (Carter & Thornburg 2004). These mechanisms collectively enhance the antimicrobial properties of honey infused with plant-derived compounds.

Additionally, defense compounds like polyphenols, phenolic acids, flavonoids, terpenes, and alkaloids further bolster plant defenses. Proteomic analyses of honey have identified proteolytic enzymes, including serine-proteases like trypsin and chymotrypsin, which likely contribute to honey's anti-fungal activity through plant-derived defense molecules (Brudzynski 2021).

Plant polyphenols, such as flavonoids and phenolic acids, are abundant in honey due to their presence in floral nectars. These compounds contribute significantly to honey's antioxidant capacity, protecting against oxidative stress and reducing the risk of chronic diseases (Samaranayaka & Li-Chan 2011). Polyphenols scavenge free radicals and enhance the stability of honey's bioactive components during storage (Aumeeruddy et al. 2018).

Oligosaccharides derived from plant nectars act as prebiotics in honey, promoting the growth and activity of beneficial gut bacteria such as Bifidobacteria and Lactobacilli (Tiihonen et al. 2010). These compounds ferment in the colon, producing short-chain fatty acids that support gut health and immune function (Hiel et al. 2019).

Plant-derived compounds in honey, including organic acids and enzymes, contribute to its digestive benefits. These components aid in nutrient absorption, alleviate digestive discomfort, and promote overall gastrointestinal well-being. Flavonoids and phenolic acids in honey exhibit anti-inflammatory properties by inhibiting pro-inflammatory cytokines and enzymes. This modulation of inflammatory pathways contributes to honey's therapeutic potential in treating inflammatory conditions such as gastritis and arthritis (Erban et al. 2019, Khalil et al., 2011).

Conclusions: This review has sought to unravel the intricate biological processes that contribute to honey’s renowned therapeutic properties. Although honey’s medicinal benefits are widely recognized, there is a lack of understanding about the specific mechanisms through which these effects are achieved. Our review reveals that honey’s bioactivity is a result of the complex interplay between its chemical composition and its microbiota, including contributions from both the honeybee’s gut and the nectar’s microbiota. The role of key compounds such as hydrogen peroxide, methylglyoxal, and plant-derived polyphenols is well-established, with these agents providing honey with its potent antibacterial, antioxidant, and anti-inflammatory properties. However, beyond these chemical constituents, the honey microbiota plays a critical role in enhancing honey's bioactivity. The bacteria, yeasts, and fungi present in honey contribute antimicrobial peptides, enzymes, and organic acids that further potentiate its therapeutic effects. Moreover, the honey microbiota's prebiotic effects are an emerging area of interest, with honey's oligosaccharides promoting the growth of beneficial gut bacteria and supporting overall gastrointestinal health. This review article underscores the importance of understanding the dynamic interactions between plants, bees, and microorganisms in shaping honey's medicinal properties. The nectar-honeybee-honey microbiota axis is a critical determinant of honey's composition, and the environmental factors that influence these interactions must be taken into account when evaluating honey's therapeutic potential. As climate change and other ecological factors continue to impact global honey production, it is vital that we deepen our understanding of these relationships to ensure the continued availability of high-quality, bioactive honey.

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