



Medical-grade honey as an antimicrobial agent against *Helicobacter pylori*: A review of current evidence

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ABSTRACT

Article info:

Received: 19 May 2024
Accepted: 28 Jun 2024

Keywords:

Medical-grade honey
Helicobacter pylori
Antimicrobial properties

Honey, a natural product of apian biology, has been recognized for its medicinal properties for centuries. The bioactive compounds present in honey, particularly those found in mono-floral varieties, exhibit antimicrobial, anti-inflammatory, and antioxidant activities. These properties have been demonstrated to synergistically interact, allowing honey to effectively combat a range of microorganisms, including multidrug-resistant bacteria. This review focuses on the antimicrobial properties of medical-grade honey, with a specific emphasis on its potential to inhibit the growth and gene expression of *Helicobacter pylori*, a bacterium responsible for gastric ulcers and gastric cancer.

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1. Medicinal plant and mono-floral medical grade honey and its potential health benefits

Medicinal plants have been instrumental in safeguarding human health throughout history and continue to play a vital role in modern healthcare [1, 2]. Research suggests that approximately two-thirds of the world's plant species possess medicinal properties, making them a rich source of therapeutic compounds. The advantages of medicinal plants are multifaceted. These plants contain a diverse range of bioactive compounds, which can be used as medicines or formulated into treatments for various human diseases [3]. They are often more readily available and cost-effective than synthetic pharmaceuticals, and their non-toxic nature makes them a safer alternative for patients [4]. As a result, these natural products have become a valuable source of therapeutic agents, offering a promising approach to addressing the global healthcare needs.

The World Health Organization (WHO) has indicated that 80% of the global population relies on traditional medicine for their basic healthcare needs, with most treatments involving plant extracts and their active components [5]. In recent years, the significance of traditional herbal medicinal systems has become increasingly recognized in developed countries [6]. Medicinal plant species are characterized by their high content of phenols and flavonoids, as well as notable antioxidant activity [7, 8]. This antioxidant activity is significantly superior to that of artificial antioxidants, which have been linked to side effects and even carcinogenic properties [9]. Research shows that the presence of flavonoids, terpenoids, alkaloids, diterpenes, tannins, glycosides, and other phenolic compounds in medicinal plants contributes to their strong antioxidant activity, potentially protecting cells from oxidative damage caused by free radicals. These free radicals and reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical, and hydrogen peroxide play an important role in developing various diseases such as arthritis, asthma, dementia, cancer, and Parkinson's disease [7]. Furthermore, Herbal medicines, have been shown to selectively enhance the body's natural systems without side effects. As a result, medicinal plants with strong antioxidant potential are emerging as a promising supplement for treating diseases related to oxidative stress such as cancer [10]. The potential of plant compounds for cancer treatment and prevention lies in their safety, affordability, and suitability for oral consumption. In contrast, conventional cancer treatments such as chemotherapy and radiotherapy come with severe side effects, including cell suppression, neurotoxicity, and cardiac, pulmonary, and renal toxicity, which can significantly impair quality of life [11].

Honey is a natural product derived from the secretions of living plant parts or the excretions of plant-sucking insects, which are collected by *Apis mellifera* bees to produce honey [12]. Mono-floral types of honey which pre-

dominantly are from the nectar of a single plant species can be classified as medicinal-grade honeys (MGHs) due to their unique properties [13]. This unique composition has been recognized for centuries, with honey being used to treat various health issues, including liver, cardiovascular, and digestive system problems [2]. Ancient civilizations such as the Egyptians, Assyrians, Chinese, Greeks, and Romans utilized honey for its medicinal properties, including wound treatment and intestinal disease management [14]. In recent years, different honey types have undergone significant laboratory and clinical research. While there are no strict formulation guidelines, it has been shown that MGHs must adhere to stringent safety and efficacy standards. These include being certified organic, free from microbial contamination and chemical residues, and meeting specific physicochemical criteria such as low levels of hydroxymethylfurfural (HMF), suitable moisture content, and appropriate pH [15]. Additionally, MGHs possess unique antimicrobial, anti-inflammatory, and antioxidant properties, which can vary based on factors such as honey type and concentration, plant species, seasonal variations, and the geographical location of the plants [16]. Even honey samples from the same floral source but from different geographical locations can exhibit differences in biological activity [17]. In vitro studies showed that Honey's antimicrobial compounds work synergistically to kill or inhibit the growth of a wide range of microorganisms, including multidrug-resistant pathogens and gradually reduce microbial resistance to antimicrobial agents [18]. It has been demonstrated that honey consumption plays a role in enhancing the body's defense mechanisms against pathogens by strengthening the immune system. A Research conducted by Tonks et al. indicates that consumption of honey leads to an increased proliferation of T-lymphocytes and B-lymphocytes, along with the activation of neutrophils in cell cultures, reflecting its immunological benefits [19]. Additionally, it was found that Manuka honey elevates TNF-alpha levels by modulation of Toll-like receptors [20]. Honey is also capable of activating monocytes by promoting the release of cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6 [21]. Moreover, honey supports the glycolytic pathway, crucial for providing energy to macrophages, allowing them to function effectively in damaged and oxygen-deprived tissues. The acidic nature of honey also aids macrophage activity by establishing an acidic environment within the phagocytic vacuole [22].

The antibacterial properties of honey are attributed to its unique composition, including a range of bioactive compounds which mainly transfer to honey through foraging bees [23]. These compounds include enzymes, non-peroxide components such as methylglyoxal (MGO) and methyl syringate, as well as phenolic compounds like propolis, flavonoids, flavones, and tannins. Additionally, honey's low pH, high sugar content, and the presence of hydrogen peroxide also contribute to its antibacterial activity [24]. Recent studies have shed light on

the antimicrobial properties of honey, revealing that defensin-1 (a bee peptid) along with H_2O_2 and MGO, plays a crucial role in honey's antibacterial activity [25]. The composition of these compounds varies depending on the nectar source, type of bee, and storage conditions such as temperature and humidity [26]. Furthermore, honey derived from different floral sources and regions exhibits distinct differences in composition due to the influence of prevailing climatic conditions and soil characteristics on the thriving flowers and plants in those areas [27]. The unique composition of honey from various regions is therefore a reflection of the specific environmental conditions under which it is produced.

2. *Helicobacter pylori* and its impact on human health

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that inhabits the gastric mucosa of mammals, including humans. Historically, the human stomach was thought to be an inhospitable environment for microbes due to its acidic pH and digestive enzymes. The discovery of *H. pylori* by Warren and Marshall in 1982 marked a significant milestone in the understanding of this microorganism [28]. With over 100,000 years of coexistence with humans, *H. pylori* has become one of the most prevalent bacterial infections worldwide, affecting more than half of the global population and the estimated number of infected individuals exceeds 4 billion [29]. *H. pylori* has evolved a unique mechanism to colonize the stomach lining, navigating through the mucous layer using its spiral shape and drilling motion. The bacterium employs its mucinase enzyme to break down the mucous layer and reach the epithelial cells, where it establishes a neutral pH environment through the urease enzyme [30]. The urease enzyme is responsible for neutralizing the stomach's acidic environment by hydrolyzing urea and producing ammonia, which serves as a buffer protecting the bacterium from gastric acid [31]. Despite the activation of the human immune system and the recruitment of lymphocytes, *H. pylori* remains persistent, leading to chronic inflammation and infection [32]. The infection rate of *H. pylori* is significantly higher in developing countries (80%) compared to developed countries (25-50%), with a complex interplay between bacterial genetics, human host genetics, and environmental factors influencing digestive complications [33, 34]. *H. pylori* is well-established as the primary cause of various conditions, including gastritis, gastric and duodenal ulcers, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma [35]. This bacterium is considered a significant public health concern, ranking as the third most common cause of cancer globally. The International Agency for Research on Cancer (IARC) classified *H. pylori* as a type I carcinogen in 1994, emphasizing the importance of addressing this infection [36].

Treatment strategies for *H. pylori* infection have

evolved over time, often involving a combination of proton pump inhibitors and antibacterial agents. The most commonly used antibiotics include amoxicillin, metronidazole, clarithromycin, tetracycline, and levofloxacin, which may be supplemented with bismuth [37]. However, antibiotic resistance remains a major obstacle to successful eradication [38]. In recent years, researchers have focused on novel therapeutic approaches that target *H. pylori* or enhance treatment efficacy. These innovative strategies have shown promising results in both in vitro and in vivo studies (Figure 1). Notably, several studies have investigated the potential of natural remedies against *H. pylori* infection, with encouraging findings [39].

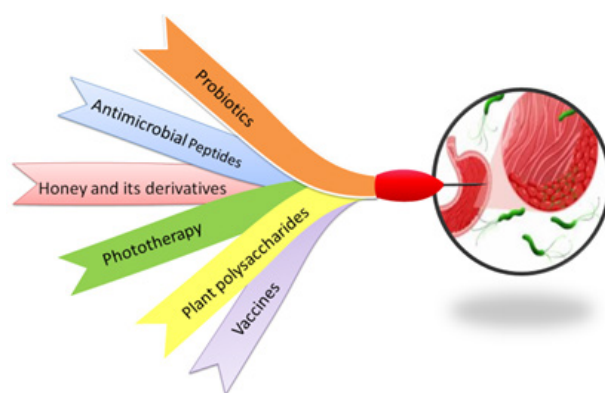


Figure 1: Emerging therapeutic approaches aim to combat *H. pylori* infection specifically target the infection or boost treatment effectiveness.

3. Exploring the antimicrobial properties and phyto-chemical composition of MGHs with potential anti-*H. pylori* activity.

In recent years, MGHs have been explored as a potential treatment for *H. pylori* infections [40]. One of the advantages of honey is its ineffectiveness on the bacterial antibiotic resistance and low risk of side effects. Combining honey with a triple therapy regimen could potentially reduce the time needed to eliminate *H. pylori* from the stomach [41]. Researchers have examined the in vitro activity of various mono-floral honeys, including Manuka [42], Capilano and Mountain honey [43], Goldcrest, and Acacia honey [44], as well as jujube and eucalyptus honey [45] against *H. pylori*. The studies used disk-diffusion and broth dilution methods showed varying degrees of anti-*H. pylori* activity, with some honeys exhibiting better activity than others. The disparity in results was attributed to the different floral sources and plant species used to produce the honey [46]. The efficacies of some MGHs are comparable to that of conventional antibiotics, such as metronidazole, which are effective against susceptible strains of *H. pylori* [47].

Researchers have been working to identify the bioactive compounds in honey and their specific molecular targets related to *H. pylori*, revealing antimicrobial and

anti-virulence mechanisms. Flavonoids, in particular, have been found to be effective against *H. pylori*, with minimum inhibitory concentration (MIC) values of ≤ 8 $\mu\text{g/ml}$ [48]. The acidic pH of honey may counteract urease enzyme in *H. pylori*, potentially aiding in the healing of ulcers caused by the pathogen [49]. A Research from south Africa has investigated the antibacterial properties of Goldcrest honey against *H. pylori*, revealing that the n-hexane extract may be effective due to the presence of volatile compounds, such as acetic acid [44]. Studies using AGS cell cultures have shown that natural honey can inhibit *H. pylori* growth in vitro and also reduce bacterial-induced NF- κ B and AP-1 activities in gastric epithelial cells, potentially alleviating *H. pylori* infections [39]. Additionally, a study examining the antibacterial effects of various mono-floral honeys on *H. pylori* found a positive correlation between antioxidant components, hydrogen peroxide content, and anti-*H. pylori* activity [50]. These findings suggest that honey may be a valuable therapeutic agent for *H. pylori* infections.

4. Impact of Honey on *H. pylori* gene expression

In pathogenic bacteria, the regulation of gene expression is crucial for pathogenicity [51]. This allows the bacterium to adapt to various environmental conditions and evade the host's immune response [52]. While numerous studies have investigated the anti-*H. pylori* properties of honey, few recent studies and clinical trials have explored the effects of honey on *H. pylori* gene expression and its role in reducing pathogenicity [39]. Notably, Guadalupe Ayala et al. found that honey significantly down-regulates the expression of urease genes in *H. pylori*, and may limit the bacterium's ability to establish and sustain an infection [53]. A study by S. Dinat et al. showed that honey can suppress the expression of key virulence genes in *H. pylori* [54]. Several flavonoids present in MGHs, such as chrysin, apigenin, kaempferol, and hesperetin, were found to inhibit the function of HsrA, a response regulator that plays a crucial role in coordinating metabolic processes and virulence with nutrient availability and cell division [55]. Molecular docking simulations revealed that these flavonoids bind preferentially to the C-terminal effector domain of HsrA, blocking its interaction with DNA. Additionally, apigenin, kaempferol, and hesperetin were found to affect other molecular targets in *H. pylori*, including enzymes, secretion systems, and cell membranes [55, 56]. In 2014, Matongo and colleagues examined the ability of Chloroform and diethyl ether-extracted fractions of manuka honey and one locally-produced natural honey to inhibit *H. pylori* urease. They measured urease activity spectrophotometrically by monitoring NADH reduction in a coupled urease-glutamate dehydrogenase system, and calculated inhibition by comparing NADH oxida-

tion before and after incubation with honey fractions. The study found that chloroform extracts of tested natural honey and diethyl ether extracts of manuka honey exhibited significant inhibitory activity against urease in different *H. pylori* strains, with 48 and 42% inhibition rates, respectively [57]. In 2021, Kim et al. investigated the effect of hesperetin on the expression of genes related to the growth and virulence of *H. pylori*. The study found that hesperetin significantly inhibits the growth of *H. pylori* reference strains and clinical isolates. The flavonoid also suppresses the expression of genes involved in DNA replication, transcription, and motility, as well as genes related to adhesion and urease production. Moreover, hesperetin down-regulates key virulence factors, including CagA and VacA, which are major pathogenic factors in *H. pylori* infections. The study suggests that hesperetin's antibacterial effects may be due to its ability to reduce the expression of type IV and type V secretion systems, which are involved in the transport of these virulence factors. Overall, the findings indicate that hesperetin may be a promising natural product for the eradication of *H. pylori* [58].

5. Conclusion

In conclusion, the cumulative results of in vitro studies have shown promising antimicrobial properties of honey, suggesting that MGHs hold considerable potential as an alternative treatment option for *H. pylori* infections. Although these findings are intriguing, further research is necessary to investigate the efficacy and safety of honey in treating *H. pylori* infections. Specifically, large-scale clinical trials are needed to determine the optimal dosing regimens and to establish the role of honey as a potential adjunctive therapy or treatment option for *H. pylori*. Furthermore, a comprehensive study on the compositions present in various types of honey, influenced by factors such as botanical origin, and its correlation with the anti-*H. pylori* properties of honey has yet to be conducted. Therefore, more extensive research is needed to fully characterize and understand the mode of action of effective honey to optimize its use in clinical practice.

Author contributions

SHA: Contributed to data collection and writing the original draft. PS: Contributed to supervision, writing the original draft, review, and editing. All authors read and approved the final version of article.

Conflict of interests

The authors have no conflict of interest to declare.

Ethical declarations

Not applicable.

Financial support

Self-funded.

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