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Mini Review

Antibacterial Activity of Honey in Combination with Cinnamon

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Abstract

Emergence of antimicrobial resistance (AMR) is a major global concern today. High prevalence of multidrug resistant (MDR) bacteria cause the treatments to be less effective or ineffective and finally leads to higher rates of mortality. This situation urges the development of novel antimicrobial agents. Natural products have gained more attention as safe and cost-effective sources of candidate compounds. Honey possesses a potent antibacterial activity against a wide range of bacteria. High osmolarity, acidic pH, hydrogen peroxide production, and presence of non-peroxide compounds provide various mechanisms for honey to act against bacteria. Cinnamon also has the ability to act on a number of bacteria through destruction of cell membranes, anti-quorum sensing effect, ATPase inhibition and membrane porins inhibition. Thus, the combinations of honey and cinnamon have shown important interactions such as synergistic, additive and antagonistic effects due to the interactions among various constituents in them. Their combined action varies depending on the honey type, cinnamon plant species, cinnamon extract type, etc. Therefore, both honey and cinnamon can be considered as good candidates for developing new antimicrobial agents. Further studies are required to isolate and identify bioactive compounds and to clarify their exact mechanisms of action, antibacterial spectrum, and toxicities.

Keywords: Antimicrobial resistance (AMR); Antibacterial activity; Honey; Cinnamon; Synergism

Introduction

Over the last few decades, the whole world has been experiencing an antimicrobial resistance (AMR) crisis due to the persistent, irrational use and the slow discovery of novel antimicrobial agents. The evolution and high prevalence of multi-drug resistant (MDR) bacteria cause the antibiotic treatments to be less effective or ineffective against once treatable infections. To address these issues, researchers are making more efforts to develop new antibiotics. In this context, natural products from plants or animals have become major candidates for developing cost-effective, less toxic and efficacious antibiotics than synthetic compounds (1).

Honey is the natural sweetening agent produced by honey bees (genus *Apis*) using flower nectar, secretions from living parts of the plants or excretions from plant sap sucking insects, such as aphides (2). It is a complex mixture of sugars, mainly fructose and glucose, various amino acids, organic acids, lipids, vitamins, lactones, minerals, enzymes, phenolic compounds, flavonoids, etc. (3). Honey has a higher percentage (70-75%) of sugars. The chemical composition and physical properties of honey show considerable variations depending on botanical or floral sources, soil characteristics, seasonal factors, climatic conditions, bee species, honey maturity, extraction process and storage conditions (3). Honey has been proven to have important biological properties such as antimicrobial, antioxidant and anti-

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inflammatory activities (4). Because of that, honey is a popular natural compound used in traditional home remedies and Ayurvedic medicinal system, and it has a long history of being used in the treatment of various infections (5). In previous studies, honey has shown both bactericidal and bacteriostatic properties depending on the concentration of honey used and the type of the bacteria.

Cinnamon is a spice obtained from plants belonging to the genus *Cinnamomum*. Bark, leaves, fruits, flowers, and roots of the cinnamon plants are used to obtain essential oils that are useful in medicine, food and cosmetic industries. The chemical composition of essential oils varies significantly depending on the extraction method, cultivation conditions, geographical origin, growing seasons, plant maturity and the parts of the plant used to extract essential oils. Thus, their pharmacological effects may also vary accordingly (6). Cinnamon extracts contain alkaloids, flavonoids, saponins, tannins, terpenoids and glycosides in varying concentrations (7). *C. zeylanicum* bark essential oil contains 60-80% of cinnamaldehyde as the major constituent. It also contains 8-10% cinnamyl acetate and other compounds such as eugenol, linalool, benzyl benzoate and beta-caryophyllene. Eugenol is the major constituent (70-75%) in cinnamon leaves essential oil. Other than that, cymene, cinnamaldehyde, linalool, cinnamyl acetate, β- caryophyllene, and benzyl benzoate are also present in oil extracted from cinnamon leaves. Camphor is abundant in root essential oil. In addition to these volatile compounds, cinnamon also contains non-volatile compounds such as proanthocyanidins and catechins (6, 8, 9). Cinnamon has been used as a herbal remedy to treat indigestion, sore throat, diarrhea, gastric ulceration in *Helicobacter pylori* infections, toothaches, etc., and as a food spice or a natural preservative due to its antimicrobial properties (9).

Certain strategies have been suggested to overcome AMR, such as combinatory therapies and newer drug rotation (10). In order to use drug rotation, there should be higher availability of new antibiotics. Thus, combinatory therapies have received more attention as the synergistic or additive interactions of two or more combined antimicrobial agents may reduce the toxicity associated with higher doses of single agents because lower doses of antimicrobial agents may reduce dose-related adverse effects. Furthermore, they may reduce the emergence of resistance by acting on the bacteria through various mechanisms of action and thereby provide a broad spectrum of activity. This review is intended to provide an overview of the antibacterial effects of honey, cinnamon, and their combination.

Antibacterial activity of honey

Long ago, honey has been used to treat ulcers, wounds, burns, gastrointestinal infections, and infectious skin conditions. Also, it was an effective food preservative due to its profound antimicrobial activity (11). Recently, a number of studies have suggested several mechanisms for the antibacterial activity of honey. The high osmotic nature of honey contributes mainly to its antibacterial activity due to the presence of high sugar and low water content (5, 12). High osmotic pressure inhibits bacterial growth by drawing water out of bacterial cells. The acidic pH (range of 3.2 - 4.5) of honey contributes to its antibacterial activity because most bacteria require an optimum range of pH 6.5 - 7.5 to grow. The presence of various organic acids, especially gluconic acid, causes honey to be acidic (5).

Hydrogen peroxide (H_2O_2) is produced when the glucose oxidase enzyme in honey acts on glucose. Due to its low pH, the enzyme is inactive in undiluted honey and gets activated when it is diluted. H_2O_2 can oxidise various cellular components that are essential for bacterial growth such as cell membrane, proteins, and DNA (11). The presence of compounds such as phenolic acids, mainly the gallic acid, flavonoids such as pinocembrin and rutin, methylglyoxal (MGO), lysozyme, antibacterial peptides and other volatiles are also have a significant relationship with the antibacterial activity of honey (11, 12).

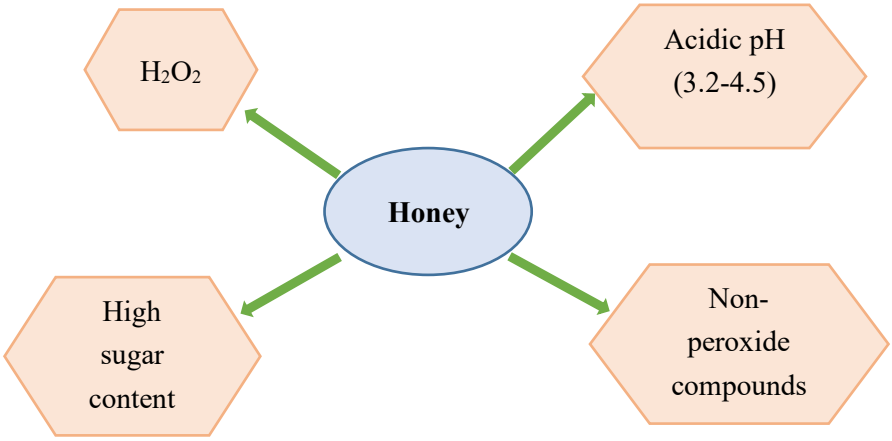

Figure 1. Characteristics of honey that support its antibacterial activity

A study conducted in 2018, has examined the antibacterial activity of 21 types of honey collected from Mount Olympus in Greece, which has high plant biodiversity, against methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Pseudomonas aeruginosa.* The activities have been compared with Manuka honey, a famous traditional medicine. According to their results, all the tested honey types have shown antibacterial activity against both organisms, and *P. aeruginosa* was less susceptible than *S. aureus.* The minimum inhibitory concentration (MIC) of all the tested honey samples was in the range of 3.125-12.5% (v/v) against MRSA while MIC of Manuka honey was 6.25% (v/v). MIC against *P. aeruginosa* has been in the range of 6.25-12.5% (v/v) while, for Manuka honey, it was 12.5% (v/v). Furthermore, researchers have proven the importance of H_2O_2 and proteinaceous compounds on the antibacterial activity of honey by treating it with catalase and proteinase-K (13).

In another study, four types of honey from Ethiopia demonstrated antibacterial effects against ten clinical isolates of MRSA. Methicillin resistance has been established based on its resistance to oxacillin and cefoxitin. The antibiotics, ciprofloxacin, gentamicin, tetracycline, co-trimoxazole, chlor- amphenicol, amikacin, clindamycin, erythromycin, and vancomycin have been used to determine the antimicrobial sensitivity of MRSA, and the study has found that 80% of MRSA were resistant to tetracycline while 40% were resistant to co-trimoxazole and 30% were resistant to erythromycin. However, MRSA has shown high sensitivity to vancomycin, amikacin, ciprofloxacin, and gentamicin. From the four tested honey samples, one potent honey type, which has a MIC ranging from 9.38-37.5% (v/v) against MRSA has been found (14).

Malaysian honeys, especially "*Tualang*" honey (a wild polyfloral honey produced by *Apis dosarta*), have exhibited a great antibacterial activity against *Escherichia coli, S. aureus, P. aeruginosa* and spore forming *Bacillus cereus.* Gram-positive bacteria have shown higher sensitivity than Gram-negative bacteria. The antibacterial effect of Malaysian honey is mainly due to the non-peroxide components (15). Manuka honey is derived from the nectar of *Leptospermum scoparium* bush, which is indigenous to New Zealand and Australia (16). It is available in the market as a therapeutic honey to treat ulcers, burns and wounds. A number of studies have confirmed its excellent antibacterial activity against a range of Gram-positive and Gram-negative bacteria. Non-peroxide compounds in Manuka honey have a large contribution to its antibacterial activity (17). MGO is the most abundant non-peroxide compound present in Manuka honey, and hence, the Manuka honey grading system, the Unique Manuka Factor (UMF) reflects the MGO concentration in Manuka honey (18). MGO has demonstrated bacterial cell lysis inhibits flagellation and disrupts bacterial cell division. Manuka honey has been identified to be effective against *Alcaligenes faecalis, Citrobacter freundii, E. coli, Enterobacter aerogenes, Klebsiella pneumoniae, Mycobacterium phlei, Salmonella california, Salmonella enteritidis, Salmonella typhimurium, Shigella sonnei, S. aureus, Staphylococcus epidermidis* and MRSA (16, 17).

A study performed to compare the antibacterial activities of four honeys from New Zealand, Cuba, and Kenya has shown that all the honey types were active against the tested 51 clinical isolates of bacteria (34 Gram-positive and 17 Gram-negative). In contrast, *Melipona beecheii* (a stingless bee) honey obtained from Cuba has shown the greatest inhibitory activity due to its high acidity. Moreover, all the honey types have had the ability to inhibit biofilm formation and reduce formed biomass. Cellular structural changes have also been observed in bacteria treated with *M. beecheii* honey (19).

Sri Lankan honey has also been reported to have antibacterial potential against S. *aureus* and *E. coli.* Fourteen honey samples of *Apis cerana* and *Apis dosarta* collected from different areas of the country have shown an increasing zone of inhibition, and hence, an increasing antibacterial activity with honey concentration (20). Another study performed in Sri Lanka has confirmed that those honey samples have a potent antibacterial effect against S. *aureus* and *E. coli* with MIC values ranging from 0.125-0.25 g/mL (21). Sri Lankan honey has been reported to have a higher antibacterial effect against S. *aureus* and a similar antibacterial effect against *E. coli*, compared to Manuka Honey (22). Furthermore, twelve Sri Lankan honey samples have exhibited significant antibacterial activity against Gram-positive and Gram-negative bacteria isolated from chronic wounds (23). Nevertheless, honey has shown a greater healing effect and a significant reduction of *P. aeruginosa* count, in comparison to silver sulfadiazine when used on burn wounds of rats (24).

Antibacterial activity of cinnamon

According to previous research, trans-cinnamaldehyde is the major constituent responsible for its antimicrobial activity (8, 25). The most predominant antibacterial mechanism of cinnamon is the alteration of the cell membrane and its lipid profile. Destruction of cell membrane leads to leakage of electrolytes, proteins and nucleic acids that are essential for cell growth (26, 27). Gram-positive bacteria are more susceptible to this mechanism than Gram- negative bacteria (28). Constituents of cinnamon such as trans-cinnamaldehyde have the ability to inhibit the enzyme ATPase and thereby suppress the cellular metabolic activities that require energy (29). The cinnamon essential oil has also proven its anti-quorum sensing effect. Quorum sensing is known as an intercellular communication system based on the secretion and detection of extracellular signal molecules. By suppressing this system, cinnamon can reduce the mobility and biofilm formation of bacteria (30, 31). Trans-cinnamaldehyde also inhibits the membrane porins through reducing the gene expression of porin proteins and amino acid transporters to inhibit active transport across the bacterial cell membrane and cell division (31, 32).

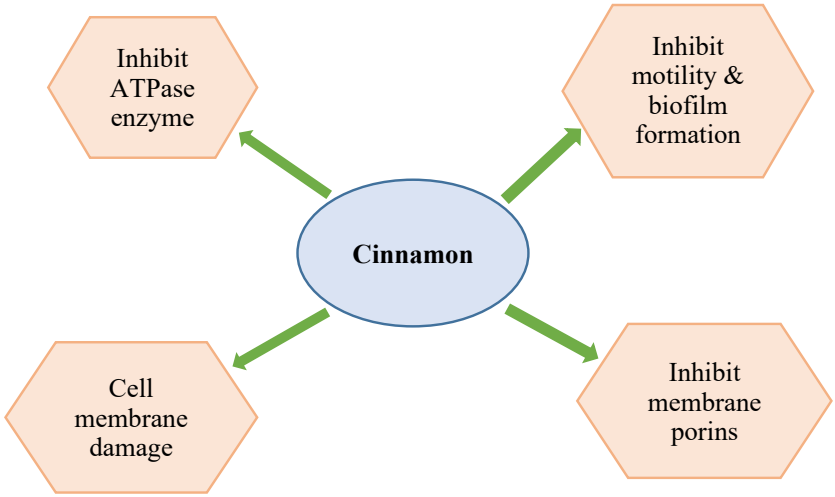

Figure 2. Mechanisms of action of cinnamon on bacterial cells

A study has revealed that cinnamon essential oil has a potent inhibitory activity on *E. coli* and *S. aureus* while, *S. aureus* was more susceptible. Researchers have confirmed a leakage of intracellular components of bacteria (33). Nine clinical samples of *Streptococcus mitis, S. sanguinis, S. salivarius, S. pluranimalium, S. pneumoniae, S. alactolyticus, Kocuria rosea, K. kristinae,* and *Spingomonas paucimolis* obtained from oral cavities have shown a significant sensitivity to *Cinnamomum brumannii* bark ethanol extract at all the concentrations tested (6.25%, 12.5% and 25%). A mouthwash prepared using the above extract has reduced the oral bacterial populations (CFU/ml) especially, *Streptococcus* growth in patients (34).

C. zeylanicum bark essential oil has also shown strong antibacterial activity against *S. aureus, Listeria innocua, Bacillus cereus, P. aeruginosa, E. coli* and *Salmonella typhi*. Gram-positive bacteria were reported as more susceptible to essential oil than Gram-negative bacteria (6). Moreover, *C. zeylanicum* bark essential oil has been reported to have an antibacterial effect against following extensively drug-resistant bacteria. This study performed using MRSA, vancomycin-resistant *Enterococcus faecium, Acinetobacter baumannii, P. aeruginosa,* and *E. coli* has shown that all the tested bacterial isolates were susceptible to essential oil. According to the study results, Gram-positive cocci were more sensitive than Gram-negative rods (35). Another study conducted in India has compared the antibacterial activity of commercially available cinnamon essential oil with methanol, chloroform and aqueous extracts of *Cinnamomum verum* bark and leaves against urinary tract infecting bacteria (*E.coli*, *S. aureus, Klebsiella pneumoniae, P. aeruginosa, Proteus mirabilis*) and *Aspergillus niger.* Results have shown that the bacteria were sensitive to cinnamon in the order of cinnamon oil > cinnamon chloroform extract > cinnamon methanol extract > cinnamon aqueous extract, when the inhibitory effects were assessed using a growth curve of bacteria. Moreover, cinnamon oil has shown a similar or larger inhibitory zone compared to streptomycin. Cinnamon has affected all the phases, while log phase prolongation is the most prominent effect. The growth of *A. niger* has been inhibited by cinnamon oil (7).

Ethanol extract from *C. zeylanicum* bark has shown a maximum antibacterial effect against *Listeria monocytogenes, S. aureus, E. coli, Enterococcus faecalis, Klebsiella pneumoniae, Enterobacter cloacae* and *Acinetobacter baumannii* over twelve other plant extracts such as lavender (*Lavandula officinalis*), clove (*Eugenia caryophylata*), thyme (*Thymus serpyllum*), rosemary (*Rosmarinus officinalis*) etc. Gram-positive bacteria have been identified as more susceptible (36). A study comparing *C. zeylanicum* and *C. cassia* bark oil against *Bacillus subtillis, Klebsiella pneumonia, P. aeruginosa, S. aureus,* and *E. coli* has shown that *C. cassia* oil has a more potent antibacterial activity (37). Studies have proven that *C. zeylanicum* essential oils have strong anti-*Helicobacter pylori* effects (38). Interestingly, cinnamon fruit extracts (benzene, ethyl acetate, methanol and water) have also shown significant antibacterial effects against *Bacillus cereus, B. coagulans, B. subtilis, E. coli, S. aureus* and *P. aeruginosa* (39).

Surprisingly, the cinnamon essential oil has shown a strong cytotoxic activity too (40, 41). Therefore, some studies suggest that the potent antibacterial activity of cinnamon is partly due to its toxic effects. A study conducted in 2007 has demonstrated that the essential oil obtained from *C. zeylanicum* is toxic to Vero cell line at concentrations above 0.00005 ml/ml (40). Thus, MIC should be lower than the minimum toxic concentration in order to use it in humans.

Antibacterial activity of honey and cinnamon combination

Both honey and cinnamon have been reported to have potent antibacterial effects. Thus, several studies have been performed to investigate the combined effect of honey and cinnamon on bacteria to check whether the combination of them would have greater effects than the individual products. Interactions between two antimicrobial agents can be classified as synergistic, additive or antagonistic (10, 42). Synergy can be explained as an interaction between two or more agents, that produces an effect greater than the sum of their individual effects. It is the most effective and most important interaction. Additivity occurs when the combined effect of the two agents is equal to the sum of the effects of each

agent. In antagonism, one agent suppresses or inhibits the action of the other. It reduces the effect of each agent (10).

A study conducted in 2017 has shown a synergistic antibacterial activity of sterilized and pasteurized Iranian honey with ethanol extract of cinnamon bark against *Streptococcus mutans* bacteria. The combination has been suggested for use in dental caries prevention and to simplify therapy against *S. mutans* (43). The synergistic activity of honey with both ethanol and aqueous extracts of *C. zeylanicum* bark has been proven against multi-drug resistant isolates of *Pseudomonas aeruginosa* obtained from burn wounds (44). Moreover, Indonesian raw honey and cinnamon bark ethanol extract have shown an additive effect against acne causing bacteria, *Propionibacterium acnes* and *Staphylococcus epidermidis* (1).

In another study, the antibacterial effect of the combination (honey with cinnamon bark ethanol and methanol extracts) has displayed an increased activity against *P. aeruginosa.* Conversely, the combinations have a reduced inhibitory effect against *S. epidermidis* and *S. aureus* (45). A similar study has reported that the addition of cinnamon to honey has reduced the antibacterial effect of honey against *S. aureus, S. epidermidis, P. aeruginosa,* and *E. coli* (46).

Conclusion

Both honey and cinnamon have displayed potent antibacterial activities against a wide range of bacteria. Combinations of honey and cinnamon have synergistic, additive, and antagonistic effects due to the interactions among their constituents. Some constituents may enhance the activity of others or provide several mechanisms for an antibacterial activity to show synergy. Meanwhile, some constituents may suppress or dilute the effects of another compound to show antagonism. However, they will be good candidates for developing new antimicrobial agents to overcome AMR. Therefore, further studies are required to isolate and identify bioactive compounds and clarify their exact mechanisms of action, antibacterial spectrum and toxicities when used alone and in combination.

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