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The multifaceted health benefits of honey: A natural antimicrobial, antioxidant, and complementary therapeutic agent

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Abstract

Honey is a natural product of ethnopharmacology widely used worldwide and in the fast-changing world of science and technology. Packed with the rich chemical compositions, this traditional nutrient has been indicated for a variety of new uses. In this paper, different varieties of honey with rich nutritional value and multidimensional use are comprehensively discussed for their antibacterial, antiviral, anticancer, anti-inflammatory, and antiparasitic effects. In addition, the effects of honey in promoting wound healing, regulating oxidative stress, regulating cardiovascular, nervous, respiratory, and gastrointestinal systems are discussed comprehensively. The underlying reasons for the numerous benefits of honey are analyzed in detail, such as its unique chemical environment, the special composition of its inclusions, and its nutritional treasure trove of polyphenols, flavonoids, bioenzymes, amino acids, and glucose. More importantly, the article explores in detail the value of honey's use as an alternative to antibiotics for a wide range of bacteria and fungi, as well as in addressing serious problems such as antibiotic resistance. In conclusion, honey is a widely used natural product with minimal side effects and boasts huge potential in a wide range of applications, especially as a new type of antibiotic with virtually no countermeasures, which deserves further exploration through clinical research.

Keywords: Honey; Virus; Bacteria; Glucose; Manuka honey

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1. Introduction

The discovery of antibiotics was an important milestone in the history of human chemistry, putting an end to human helplessness in the face of bacterial infections. Due to the increasing misuse of antibiotics,[1,2] the gradual decline in their clinical effectiveness and the shortage of innovative antibiotics have turned our attention to natural products and drug candidates that can be used therapeutically without side effects.[3,4]

Honey is a class of natural products commonly found in daily life and it is a concentrated sweetener that can be obtained directly in nature.[5] Honey has been used as a natural antibacterial agent for thousands of years all over the world. Examples of honey's use in the treatment of wounds, infections, and diseases are documented in

the history of ancient Egypt, Greece, and Rome.[6,7] The earliest use of honey as an antimicrobial date back to 2500 B.C., when the ancient Egyptians used honey to treat skin wounds and infections. In the Ebers Papyrus and Smith Papyrus medical texts, the ancient Egyptians often mixed honey with fats or essential oils of plants to make a salve that was applied externally to wounds to promote recovery and alleviation of pain. Records show that in 1901, German bacteriologists began to study the ability of honey to inhibit the vital activity of bacteria, which is seen as the starting point for modern antibacterial research on honey. In the 1980's, Molan and his team of researchers systematically investigated the unique activity of honey to establish the antibacterial activity, with a primary focus on the structure of methylglyoxal (MGO) in Manuka honey.[8] In ancient Chinese medicine, honey was also used to treat trauma and constipation. According to traditional Chinese medicine, it is believed that honey can tonify the center of the body, moisten the lungs, and relieve coughs.

Honey is produced by bees that collect plant nectar, secretions, or manna and then undergo cross-feeding (trophallaxis), which reduces the water content. Pure honey has a moisture content of 14 – 25%. The global honey market features a vast array of varieties, of which the production and quality are influenced by a multitude of factors. These include the season in which the bees collect the honey, regional variations in plant species, climatic conditions, soil nutrients, flora and enzyme types, honey ripeness, pollen content, and length of exposure to light.

Honey is composed of diverse compounds, including water, sugars (glucose and fructose), enzymes (glucose oxidase, amylase, invertase, phosphatase, catalase), amino acids (proline, lysine, arginine), and others. In addition, honey contains vitamins (vitamin C and vitamin B), proteins, minerals[9,10] (calcium, magnesium, iron, copper, manganese, phosphorus, potassium and zinc), organic acids (gluconic acid, acetic acid, citric acid, lactic acid) and natural colors (carotenoids, lutein). Manuka honey also contains MGO,[11,12] a compound that gives it a significant advantage in counteracting the increasingly antibiotics-resistant strains of bacteria. The moisture content of honey has a direct impact on its properties, storage stability, and antimicrobial activity. Furthermore, the ratio of glucose to fructose influences the crystallinity and sweetness of honey.

Honey has a wide range of biological and pharmacological properties, such as antibacterial, anti-inflammatory, and antioxidant activities. More importantly, it can promote wound healing; regulate cardiovascular, nervous, respiratory, and gastrointestinal systems; modulate anti-parasitic and antidiabetic activities, as well as anti-atherosclerotic, antihypertensive, neuroprotective, and immunomodulatory effects; and prevent acute alcoholic liver injury.[13-15] The unique antibacterial mechanism of honey is primarily grounded in low levels of bound water, high sugar environments, acidic conditions, and the presence of hydrogen peroxide.

Honey contains polyphenols, Vitamin C, and flavonoids, which reduce tissue inflammation and scavenge free radicals from the body for antioxidant purposes. Antioxidants help to reduce low-density lipoprotein oxidation and prevent cardiovascular disease.[16] In addition, flavonoids are not only able to clear free radicals in the body through antioxidant action to reduce the damage of oxidative stress on blood vessels but also through a variety of pathways to expand blood vessels, so as to achieve the effect of lowering blood pressure. Although honey itself contains sugar, studies have shown that moderate consumption of honey may help improve glycemic control in diabetics. Medical honey products currently approved for clinical use include Medihoney® range,[17] Revamil®,[18,19] Apinate® Honey Dressing, and HoneySoft®.

In the context of international standards,[20] the following definitions are provided: the current international standards that pertain to this subject matter are the Codex Alimentarius and the EU Honey Directive 2001/110. The EU Honey Directive stipulates that honey should not contain more than 20% of water, while the Codex Alimentarius standard is slightly more lenient, allowing for up to 23% of water in acacia honey. The maximum permitted level of free acid is 50 mg/1000 g, the minimum required level of glucose and fructose is 60 g/100 g, and the maximum permitted level of sucrose is 5 g/100 g. The EU Honey Directive explicitly prohibits the addition of any other substances (*e.g.*, food additives) or processing to honey, and mandates that it be kept intact and natural.

2. The characteristics of honey

2.1. Acidic environment

Honey is acidic, with a pH between 2 and 5, and the acidity is attributed mainly to the organic gluconic acid that glucose breaks down under the action of oxidative enzymes.[6] This acidic environment not only gives honey its unique flavor but also has a pH lower than that of a condition at which most microorganisms can survive, forming a natural antimicrobial barrier against *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa,* and yeasts.[21] Honey has been demonstrated to possess antimicrobial activity and antioxidant properties with a concentration dependency. When honey is diluted with water, the glucose oxidase system is activated; however, it is known that the antimicrobial effect of honey is diminished by dilution after it has reached its maximum.

2.2. High osmolality

Honey is a natural product comprising primarily of glucose and fructose, with the sugar component typically accounting for approximately 80% of its total composition. This makes it a popular choice as a sweetener. The low water content of honey, in conjunction with the high osmotic pressure environment it generates, can result in the dehydration of microbial cells, thereby disrupting the microenvironment within the cells. This impairs their normal physiological processes, preventing them from surviving and reproducing. The high osmotic pressure not only destroys the cellular structure of the microorganisms but also prevents the influx of water needed for bacterial reproduction, thus further enhancing the antibacterial effect of honey. The dual inhibitory mechanism, comprising low water content and high osmotic pressure, is responsible for the antibacterial properties of honey.[22]

2.3. Moisture content

It has been demonstrated that water activity (aw) within the range of 0.94 – 0.99 is capable of completely inhibiting bacterial growth.[23] The average water content of honey is 17% and the normal range of water activity is between 0.56 and 0.62, which does not provide favorable conditions for microbial growth thereby achieving bacterial inhibition.[24] Glucose and fructose have strong water absorption and can form hydrogen bonds with water molecules, and the water therefore exists in a bonded state within honey. The water content of honey is also affected by factors such as the harvesting season as well as the geographical environment.[25]

2.4. Protein content

The proteins in honey mainly include amino acids and enzymes. There are 20 types of amino acids, of which proline is the most abundant, accounting for 50% of the total free amino acids in honey. Proline can undergo a Maillard reaction with sugar, giving it a unique flavor. In addition to being involved in the Maillard reaction, proline has antioxidant properties of its own, which can neutralize free radicals and reduce cellular damage, thus achieving antioxidant effects. Some studies have shown that proline can also promote wound healing and tissue regeneration.[26] The main enzymes in honey are glucose oxidase, catalase, and acid phosphatase.[27] Glucose oxidase releases hydrogen peroxide when it acts on glucose, enhancing its antimicrobial and antioxidant properties.

2.5. Hydrogen peroxide

Hydrogen peroxide is a class of oxidizing agent that typically inhibits the growth of bacteria and microorganisms.[28] The environmental pH of honey ranges from 2 to 5. In an environment with a lower pH, enzymatic reactions proceed slowly. Glucose oxidase catalyzes the conversion of glucose to gluconic acid, during which hydrogen peroxide is produced (Figure 1). The glucose oxidase is responsible for the generation of hydrogen peroxide, which is a byproduct of the oxidation of glucose to gluconic acid. The amount produced in honey is related to the minimum inhibitory concentration of honey. However, due to the environmental effects, the hydrogen peroxide produced is not capable of exerting a strong antimicrobial effect. Therefore, the antimicrobial effect of honey is more reliant on its hypertonic environment and low water content. The amount of hydrogen peroxide is not controlled by a single factor. Honey is rich in polyphenolic compounds, and the auto-oxidation of polyphenols also produces hydrogen peroxide, which enhances the antibacterial activity of honey. It has been suggested that honey contains microorganisms such as *Penicillium* and yeast that also produce small amounts of hydrogen peroxide.[29]

2.6. Phenolic compounds

Phenolic compounds[30] are the main source of antioxidant activity in honey and contain one or more aromatic rings with multiple phenolic hydroxyl groups in their structure. Phenolic compounds reduce the level of reactive oxygen species in cells and minimize a wide range of damage at both the molecular and cellular levels. Phenolic compounds in honey mainly include phenolic acids (Figure 2) and flavonoids (Figure 3). It has been found that darker-colored honey has a higher phenolic acid content than lighter-colored honey and has better antioxidant capacity than lighter-colored honey.[31] Common phenolic compounds in honey include quercetin, kaempferol, apigenin, caffeic acid, and *p*-coumaric acid. The composition and concentration of these compounds vary, depending on the floral source of the honey, which influences its overall therapeutic and health benefits. These compounds also contribute to honey's flavor, color, and its ability to scavenge free radicals.

2.7. Carbohydrates

Honey is predominantly composed of carbohydrates, which account for approximately 80% of its total composition, making it a rich source of quick energy. The majority of these carbohydrates consist of simple sugars, namely glucose and fructose,[27,32-34] both of which are easily absorbed by the human body. These monosaccharides are rapidly metabolized, providing an immediate and readily accessible source of energy. Glucose typically makes up about 30% of the carbohydrate content in honey, while fructose constitutes around 40%. This unique ratio of glucose and fructose is responsible for the characteristic sweetness of

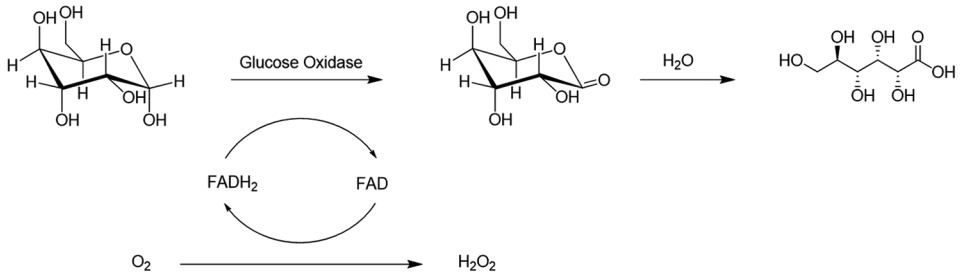

Figure 1. Processes for generating hydrogen peroxide: Glucose ($C_6H_{12}O_6$) is oxidized by glucose oxidase, with the cofactor FAD facilitating the reaction, resulting in the production of gluconic acid ($C_6H_{12}O_7$) and hydrogen peroxide (H_2O_2). Oxygen (O_2) is consumed during this process, and hydrogen peroxide is generated as a byproduct of glucose oxidation.

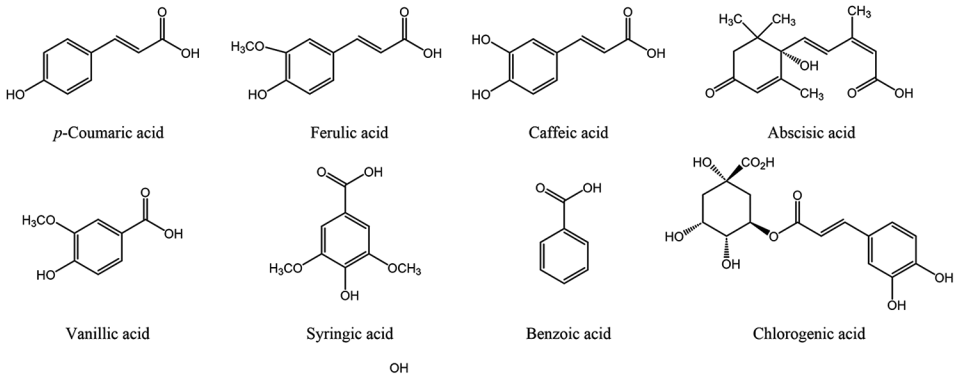

Figure 2. Some phenolic compounds in honey

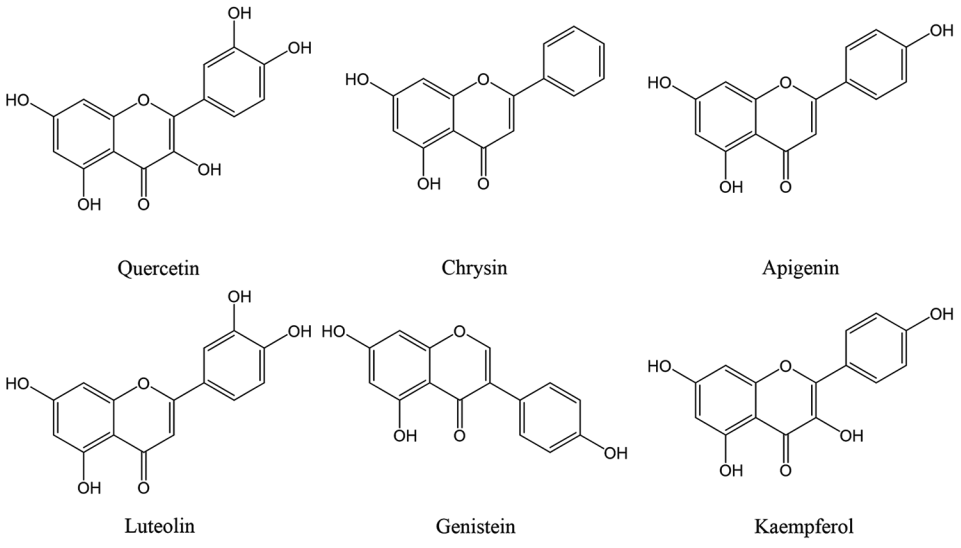

Figure 3. Some flavonoids compounds in honey

honey, as fructose is sweeter than glucose. In addition to glucose and fructose, honey contains small but significant amounts of sucrose, maltose, and trace amounts of various oligosaccharides (Figure 4). These minor sugars contribute to the overall flavor and texture of honey, as well as its potential health benefits. For example, maltose, a disaccharide, results from the breakdown of starches in the nectar and can influence the sweetness profile of different types of honey. The carbohydrate composition of honey can vary depending on the floral source from which the nectar is collected.[35]

Different nectar types (such as clover, acacia, or manuka) produce honeys with slightly different carbohydrate profiles, which in turn affect not only the sweetness but also the viscosity, color, and tendency to crystallize.[36] Crystallization, for instance, is often influenced by the ratio of glucose to fructose – honeys with higher glucose concentrations tend to crystallize more quickly.[37] Furthermore, some honeys may contain trace amounts of sugars such as maltotriose and levan, which contribute to the overall diversity of their carbohydrate content. This variation gives each honey its unique flavor, texture, and appearance, and is a key factor in determining the honey's sensory qualities and potential nutritional benefits.

3. Beneficial properties of honey

3.1. Antibacterial activity

Honey, as a valuable natural product, has been shown to have significant antibacterial activity,[38-40] which holds promise for addressing the growing problem of antibiotic resistance in conjunction with advancements in modern medicine.[41] Some of the honeys that have been studied include: Manuka honey, Tualang honey, Sidr honey, Revamil honey, Jarrah honey, Buckwheat honey, Gelam honey, and Kelulut honey, with their origins and mechanisms of action detailed in the table (Table 1).

Table 1. Comparison of the antibacterial activity of several types of honey

Honey	Source	Mechanisms	Applications	References
Manuka honey	New Zealand, Australia	Methyl glycol	*Staphylococcus aureus, Escherichia coli, Helicobacter pylori, Pseudomonas aeruginosa*	42-46
Tualang honey	Malaysia	• Inhibits cell wall synthesis • Interferes with cellular metabolism	*Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Staphylococcus aureus, Salmonella typhimurium*	47-53
Sidr honey	Yemeni	• Disrupts cell membranes • Affects protein synthesis	Oral bacteria, *Escherichia coli*	19,53,54
Gelam honey	Malaysia	• Inhibits cell wall synthesis • Interferes with cellular metabolism	*Staphylococcus aureus, Escherichia coli*	48
Revamil honey	Netherlands	H_2O_2	*Listeria monocytogenes, Salmonella enterica*, wound healing	55-57
Jarrah honey	Australia	H_2O_2	*Streptococcus pyogenes, Klebsiella pneumoniae*	58-61
Buckwheat honey	North America, Europe	Disrupts cell membranes	*Enterococcus faecalis, Proteus mirabilis*	62-64

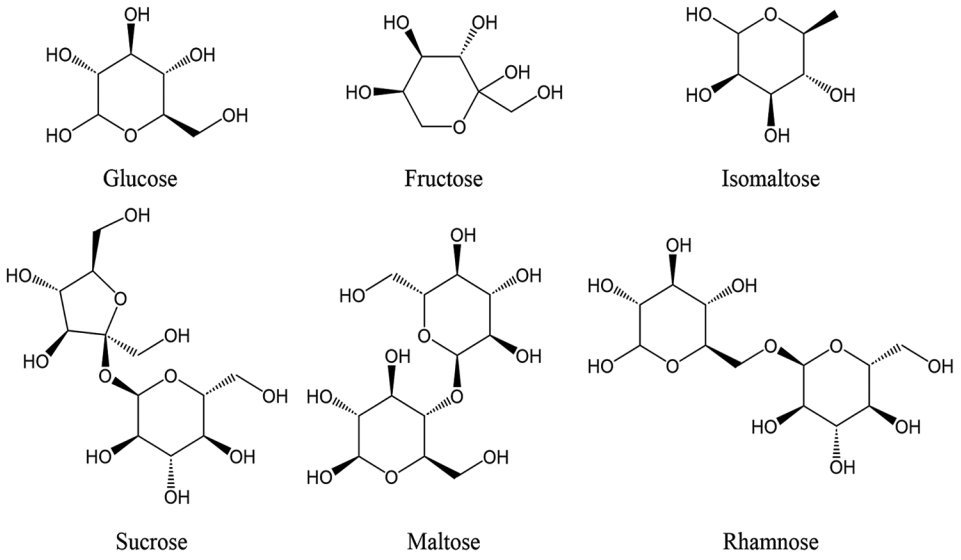

Figure 4. Some sugar compounds in honey

The principal methodologies employed to ascertain the antibacterial efficacy of honey[5,21,22] encompass the following: agar diffusion method, microdilution method, electron microscopy, turbidity measurement, flow cytometry, and bacterial growth curve assay. The agar diffusion method is a straightforward and widely employed technique. Typically, the bacteria to be tested are spread on nutrient agar to ensure uniform growth. Subsequently, holes are punched in the agar and honey samples are added. On incubation in a constant temperature box, the honey diffuses into the agar, forming a ring of bacterial inhibition around the samples. This visual representation demonstrates the inhibitory effect of honey on bacteria. Furthermore, the concentration of the sample can be varied to ascertain the impact of different concentrations on the bacteria. The microdilution method is a more precise and commonly employed assay for determining the minimum inhibitory concentration. The honey sample is diluted to varying concentrations and added to a 96-well plate, followed by the addition of an equal volume of the bacterial suspension to each well. Once the incubation period has elapsed, the optical density of each well is determined, and the rate of inhibition is calculated. The well exhibiting the lowest concentration of the honey sample and no bacterial growth is identified, representing the minimum concentration of bacterial inhibition.

In addition to its low water content, acidic nature, and high osmotic pressure, Manuka Honey also contains MGO, a non-peroxide which is the most important antibacterial ingredient in Manuka Honey,[12] and reacts with the amino and sulfhydryl groups of nucleic acids, proteins, and polysaccharides. When bacteria come into contact with this substance, the structure of their cell wall breaks down, preventing the formation of a barrier to protect the balance of the internal and external environments, and leading to an alteration of the ionic concentration and osmotic pressure, which interferes with the normal survival and proliferation of the bacteria; when bacteria synthesize nucleic acids, they need the synergy of many enzymes and ATP, and the MGO reacts with amino acids within the enzymes, so that the bacteria cannot replicate and transcribe normally. This multi-target inhibitory mechanism of MGO presents a challenge for bacteria to escape from the action through resistance to drugs.

Manuka honey has been shown to inhibit *Staphylococcus aureus* and methicillin-resistant *S. aureus*,[42-44] *E. coli*[43-46] *Helicobacter pylori*,[45] and *P. aeruginosa*.[45] The antibacterial activity of Tualang honey is comparable to that of Manuka honey and studies have shown that Tualang honey inhibits *E. coli*, *K. pneumoniae*, *S. aureus*, and *Salmonella typhimurium*.[47-51]

Al-Sayaghi *et al.*[45] found that Sidr honey and Manuka honey interfered with the permeability of *E. coli* cell membranes and induced DNA rupture, presumably due to a combination of polyphenolic compounds and hydrogen peroxide. Acevedo *et al.*[46] found that Ulmo honey is rich in benzene derivatives such as benzaldehyde and benzyl alcohol, which can treat intestinal infections caused by *E. coli*, *S. aureus*, *K. pneumoniae*, and *Salmonella intestinalis* among others. Gośliński *et al.*[65] compared Manuka honey with polish honey, which also had strong antibacterial activity, but was overall inferior to Manuka honey, which also inhibited Gram-positive bacteria at much lower concentrations, has potential for future clinical incorporation. Biluca *et al.*[66] investigated the bioactivity of stingless bee honey (SBH) and found that it had a potent inhibitory effect on a wide range of Gram-positive and Gram-negative bacteria, but, SBH usually has a high moisture content, which may affect its stability. Afrin *et al.*,[41] made an in-depth comparison of the inhibitory effect of honey on the activity of *S. aureus* and *E. coli* and found that the inhibitory effect was better on Gram-negative organisms, taking into account the fact that negative organisms are more susceptible to the effects of antimicrobial substances in honey due to their thinner cell walls.

3.2. Antifungal activity

Compared to antimicrobial research, research on honey's ability to fight fungi is commonly overlooked. Common fungi include yeasts, molds, and *Aspergillus*, which are widely used in food, agriculture, and pharmaceutical development, as well as pathogenic fungi such as *Candida albicans*, *Aspergillus*, *Coccidioides*, *Cryptococcus neoformans,* and others. *C. albicans* is a common fungus of the genus *Candida*, which usually parasitizes the skin and mucous membranes, and in severe cases can cause systemic infections by entering the bloodstream; *Aspergillus* can invade the lungs of immunocompromised people and grow rapidly, leading to necrotizing pneumonia. Hau-Yama *et al.*,[67] tested the inhibitory effect of *Melipona beecheii* honey against *C. albicans* and found that it showed inhibition at lower concentrations. Yuan *et al.*,[38] compared the antifungal activity of *Agastache* honey with other honeys, and found that *Agastache* honey inhibited fungi better than Manuka honey at lower concentrations, which is expected to be an adjunctive treatment for topical fungal infections. It has been demonstrated that unifloral honey showed strong antifungal activity,[68] which was mainly attributed to the high osmotic environment, low pH environment, hydrogen peroxide, and phenolic compounds of honey itself, which inhibited the fungus. Previous studies have demonstrated the isolation of *Bacillus velezensis* from honey, followed by the purification of a lipopeptide with antifungal properties. This compound was shown to effectively inhibit *C. albicans* and *Aspergillus*, suggesting its potential as a natural antifungal agent.[69]

3.3. Antiviral activity

Honey has some antiviral properties, especially in inhibiting viral replication. Honey contains flavonoids such as quercetin, which can block the spread of viruses, as well as polyphenols, which can reduce inflammatory responses and reduce tissue damage.

Computer simulations have been used to model the protective effects of honey in COVID-19, revealing that flavonoids and phenols in honey inhibit viral entry into host cells and suppress RNA polymerase activity, thereby preventing viral replication.[70] Rocha *et al.*[71] compared honey with acyclovir in the treatment of the herpes simplex virus (HSV) and found that honey can promote recovery rate from herpes, promote healing of damaged tissues, reduce HSV recurrence, and is suitable as a novel adjunct therapy for patients resistant to acyclovir.

3.4. Antiparasitic activity

Parasites constitute a significant part of the etiology of various infectious diseases. Honey is not only antibacterial and antiviral but also exhibits inhibitory effects on parasites.[72] Its anti-parasitic activity is attributed to its anti-inflammatory and antioxidant properties, as well as its ability to modulate the immune system to combat parasitic infections.

Manuka honey has been found to inhibit the growth of parasites such as tapeworms and hookworms.[73] The polysaccharides and phenolics in honey are able to affect the egg-laying and hatching process of the parasites, disrupting the normal reproductive process.[74] Activation of macrophages and T-cells enhances the host's resistance to parasites. It can also promote healing and inhibit infection in skin injuries caused by parasites.

Laksemi's team[75] investigated the inhibition of *Plasmodium* activity by honey, which significantly reduced parasitemia levels when combined with citrus extract (*Citrus aurantifolia*), suggesting a synergistic effect between the two. The antiparasitic activity of honey has been validated in animal models, but further studies are needed on the effects in humans.

3.5. Anticancer activity

Conventional use of chemotherapeutic drugs not only results in irreversible adverse effects but also weaken their therapeutic efficacy against cancer cells as a result of drug resistance; therefore, this necessitates a search for natural products to fight cancer. In this respect, honey stands out as a viable option as a growing line of evidence demonstrates that honey is the rich in antioxidant components that can reduce cell damage, thereby inhibiting the growth of cancer cells, and is packed with phenolic acids and flavonoids that can affect the cell cycle preventing cancer cell proliferation.[76-79]

Márquez-Garbán *et al.*[80] found that Manuka honey inhibited the proliferation and survival of mouse breast cancer MCF-7 cells by activating the AMPK signaling pathway and blocking signaling in the PI3K/AKT/mTOR pathway and STAT-3 pathway, as well as being able to reduce the size of the tumor and enhance the drug's anticancer effect when used in combination with tamoxifen. The study claims that natural phytoestrogens contained in honey may be the source of the anticancer activity, with a chemical structure similar to that of estrogen in mammals.[81,82]

Research has explored the anti-metastatic potential of Manuka honey on colon cancer stem-like cells, revealing its ability to regulate key transcription factors involved in epithelial-mesenchymal transition, such as Slug, Snail, and Twist, to reduce cancer cell metastasis.[83] In addition, Manuka honey was found to modulate the *c-Myc* gene, leading to telomere shortening in cancer stem cells and limiting their reproductive capacity.

When used in combination with the chemotherapeutic drug 5-fluorouracil, honey enhances the therapeutic effect of the drug, with potential synergistic effects, and helps to reduce the resistance to chemotherapeutic drugs. Bouali *et al.*[52] found that Sidr honey also showed inhibitory effects on breast and colon cancer, not only inhibiting the growth of cancer cells but also inducing apoptosis and inhibiting spread. It is considered because Sidr honey can interfere with signaling pathways related to proliferation, thus affecting cancer cell survival.

Interleukin 6 (IL-6) is a proinflammatory cytokine that regulates the activity of different types of cancer cells and, on binding to the receptor, initiates the JAK-STAT signaling pathway, a pathway that is an important therapeutic target in many cancers. Flavonoids in Manuka honey have been shown to competitively bind to the IL-6Rα protein, disrupting IL-6 signaling in cancer cells.[84] This interference inhibits STAT3 phosphorylation and reduces gp130 and JAK2 protein levels, thereby disrupting the signaling pathway and exerting anti-tumor effects.

Aliyu *et al.*[85] explored the application of Acacia honey in lung cancer and found that the use of a certain dose of Acacia honey could inhibit the growth of NCI-H460 cells, which could upregulate the expression of p21 and p27 proteins, prevent the cells from continuing to develop in the G0/G1 phase and interfere with the normal cellular process. In addition, Acacia honey could also regulate JNK and JAK2 protein levels, and interfere with normal cellular processes. Honey also regulates the JNK and p38 MAPK pathways, enhancing the apoptotic signaling.

Pichichero *et al.*[86] investigated the effect of Acacia honey in melanoma cells. After implementing the Acacia honey treatment, proteins responsible for the regulation of the cell cycle such as cyclin D1, CDK4, cyclin B1, and CDK1, which are key proteins for advancing the cell cycle properly, were reduced, and the downregulation resulted in cell cycle blockage and inability to enter S phase.

Tulang honey has demonstrated a positive inhibitory effect on human breast and cervical cancers by activating the caspase-3 and caspase-9 pathways to induce apoptosis.[87] It also alters mitochondrial membrane potential, leading to the release of cytochrome c, which further activates the caspase pathway. Similar to Acacia honey, Tualang honey can regulate the cell cycle, preventing cancer cells from progressing into the S phase. By investigating the effects of Tualang honey on oral squamous cell carcinoma and osteosarcoma, Ghashm *et al.*[88] found that the honey-treated cells experienced increased levels of oxidative stress, marked by an accumulation of reactive oxygen species that led to mitochondrial damage and membrane potential abnormalities, which accelerated apoptotic cell death.

3.6. Antioxidant activity

The body produces a number of active free radicals during normal oxidative processes, usually found in respiration and enzymatic reactions. The external environment can also contribute to the formation of free radicals, such as ultraviolet light exposure and exposure to heavy metal chemicals and air pollutants in the environment. The antioxidant activity in honey comes mainly from phenolic compounds,[64,89-91] including phenolic acids (*p*-coumaric acid, ferulic acid, caffeic acid, chlorogenic acid) and flavonoids (quercetin, kaempferol, and populin). These compounds neutralize free radicals, reducing cell and tissue damage, reducing the incidence of chronic diseases, and boosting immunity.[92] The structure of phenolic acids generally includes one or more phenolic hydroxyl groups and an aromatic ring. Phenolic hydroxyl groups can provide hydrogen atoms or electrons to neutralize free radicals, and chlorogenic acid can also chelate copper and iron ions, preventing these ions from continuing to catalyze the production of more free radicals. Oxidative stress generated by free radicals activates the nuclear factor kappa B (NF-κB) pathway, stimulating cytokine release and inducing inflammation. Phenolic acid can inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymatic activities and reduce prostaglandin and leukotriene synthesis, thus slowing down inflammatory responses.[93]

The content of phenolic acids in honey is affected by source, region, and season, which dictate the variations in antioxidant activity. Adgaba *et al.*[94] claimed that the type and content of phenolic acids tend to vary depending on the source of the plant and the geographic location. The analysis of Becerril-Sánchez *et al.*[90] pointed out that phenolic compound concentration is also related to the color of the honey, and that there were significant differences in the phenolic compound content and antioxidant capacity of honey originating in different regions. A comparison revealed that compared with Polish honey, Manuka honey possesses higher levels of phenolic acids and flavonoids, which contribute to its superior antioxidant properties.[60] These findings highlight that the antioxidant properties of different honeys are primarily influenced by their phenolic and flavonoid content, which can vary significantly between species. It was found that the phenolic acid content of honey was positively correlated with oxidative activity.[95-97]

Silva *et al.*[93] found that flavonoids in honey effectively inhibited COX and LOX, reducing the production of inflammatory mediators, modulating the NF-κB signaling pathway, and reducing the expression of anti-inflammatory genes. Their *in vitro* experiments demonstrated that different types of honey possess natural anti-inflammatory agents due to the presence of flavonoids, which excel in reducing oxidative stress and inhibiting cytokine release, but caution should be exercised with regard to their safety.

3.7. Anti-inflammatory activity

The anti-inflammatory activity of honey is achieved through a variety of mechanisms and active ingredients,[98,99] such as regulating cytokine release, inhibiting enzyme activity to reduce prostaglandin synthesis, scavenging free radicals to inhibit and reduce oxidative damage, enhancing cytoprotection, and regulating the immune system to enhance anti-inflammatory capacity. The anti-inflammatory activity of honey is also partly responsible for promoting wound healing. Phenolic acids and flavonoids in honey inhibit COX-1 and COX-2 activity and block the NF-κB pathway, thereby reducing inflammation. Topical application of honey reduces swelling and oozing, promotes new tissue growth, and accelerates healing. Some studies have found that honey can inhibit the release of tumor necrosis factor-alpha (TNF-α) and IL-6,[100] and that its wound-healing-promoting effects are also linked to antimicrobial activities. As a natural anti-inflammatory agent, honey shows potential in the treatment of chronic diseases, making it a class of natural medicines worth investigating.

3.8. Wound healing effects

Due to its antibacterial and anti-inflammatory properties and its hypertonic, low pH environment, honey forms a barrier on the surface of broken skin, promoting

new tissue production and accelerating healing,[101] and the high osmotic pressure environment allows for the suction of lymphatic fluids out of wounds for autolytic debridement and cleanup of damaged tissues. Honey stimulates the activity of B and T lymphocytes and activates neutrophils for immune phagocytosis. Honey further enhances the body's immune response by promoting cytokine secretion, enhancing antibody production, and modulating the endogenous nitric oxide signaling pathway. It was documented that Hippocrates used honey to treat wounds and ulcers; ancient Egyptians used honey as an antiseptic; and the original inhabitants of the Americas used honey to protect wounds and relieve pain. With the advancement of technology, these traditional empirical applications have been proven to be beneficial in all stages of wound healing (hemostasis, swelling, and healing).[102,103] In the management of burns, the use of honey dressings reduces healing time, promotes the growth of new blood vessels, and prevents scarring. In addition, the high osmotic pressure environment traps wound exudate while keeping it moist, providing a favorable environment for healing. Honey has now been incorporated into various biomaterials, such as hydrogels, nanofibers, collagen, and chitosan, as a dressing, and its therapeutic potential will be further explored.[65,102,104]

Abou Zekry's *et al.*,[104] produced a nanofiber wound dressing consisting of pomegranate peel extract and honey and tested the dressing's effectiveness in inhibiting *S. aureus* and *E. coli* through *in vitro* investigations. These ingredients inhibit cell wall formation, which effectively reduces bacteria around the wound, promoting recovery and preventing infection.

3.9. Others

As a natural health food, honey not only excels in improving metabolism and boosting immunity but also demonstrates remarkable results in the adjunct treatment for a wide range of diseases. It improves poor respiration, effectively prevents cardiovascular disease, and improves liver health as well as improves blood infections by lowering cholesterol levels, optimizing blood sugar metabolism, and boosting antioxidant capacity. Abuelgasim *et al.*[97] found that honey can reduce upper respiratory tract infections and reduce the frequency of coughing at night, by virtue of its high viscosity allowing for attachment to mucous membranes and amelioration of respiratory irritation, as well as antibacterial and anti-inflammatory properties. Ahmed *et al.*[105] found that honey has a positive effect on the improvement of metabolic aspects, such as glucose and blood lipid levels. Honey improves insulin sensitivity and promotes the entry of glucose into the cells, which has the effect of regulating blood glucose levels. Honey reduces low-density lipoprotein cholesterol and total cholesterol levels, regulating blood lipid levels, and reducing the risk of cardiovascular disease. Polyphenol extracts from honey have also been found to reduce serum alanine transaminase activity, enhance antioxidant capacity, and improve lipid metabolism in the liver.[106-108] Honey has shown potential in treating bloodstream infections such as sepsis and malaria by reducing inflammation, enhancing immune system, and complementing therapeutic medications. It not only boosts the effectiveness of treatments but also helps mitigate side effects and reduces the risk of drug resistance.[109] Henatsch *et al.*[110] explored the use of honey in otorhinolaryngology, where it can act as an antimicrobial and anti-inflammatory agent in the treatment of common sinusitis, otitis media, and pharyngitis to promote wound healing and alleviate pain. Kumar *et al.*[103] combined honey with herbs such as garlic, thyme, and ginger, which enhanced antimicrobial activity and antioxidant effects, providing a synergistic approach to treating diseases.

4. Conclusion

This paper presents a comprehensive review of honey as a widely studied and highly promising natural product. In recent centuries, honey has been the subject of extensive study as a significant component of ethnopharmacology. In addition to its use as a sweetener and a nutrient, it has been shown to possess a diverse range of *in vivo* or *in vitro* activities. For example, antimicrobial properties are conferred by the hypertonic and low-water environment, while anti-inflammatory and antioxidant properties are conferred by the abundance of active substances. In addition, honey exhibits notable *in vivo* free radical scavenging properties. Furthermore, honey possesses unique non-resistant characteristics that make it an invaluable antibiotic, a quality that is particularly promising in the context of the ongoing advancements in modern medicine. In addition, this article provides a comprehensive overview of the promising clinical applications of honey, including antimicrobial, anticancer, wound healing, and bloodstream infection treatments, as well as cardiovascular disease risk reduction. However, most of the claims about honey and its applications are grounded largely in data from animal and *in vitro* studies, and a dearth of human clinical trial data is limiting the further applications of honey. In the future, more clinical studies are necessary to establish a wider role of honey in medical treatments and to standardize the production of honey products.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Yuhan Xie
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