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Pharmacology of Honey: A Review

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Abstract: Honey has been extensively used as healing agent throughout the human history in addition to its widespread usage as popular food. Honey is a sweet substance produced as a food source mainly from the nectar and secretions of plants by honey bees. Honey is used to feed bees during the winter. For centuries, honey has been used as food and as natural medicine, being prescribed by physicians of many ancient cultures for the treatment of a wide variety of ailments. In most ancient cultures honey has been used for both domestic and medical purposes. The belief that honey is a nutrient, a drug and an ointment has been carried into our days and thus, an alternative medicine branch, called apitherapy has been developed in recent years, offering treatments based on honey and other bee products against many diseases including bacterial and fungal infections. The present review focussed on the pharmacological properties of honey. The topics covered in this present review includes: History of honey as medicine, Composition of honey, Medicinal properties of honey, Antimicrobial activity of honey and Uses of honey.

Key words: Honey · Pharmacology · Antimicrobial activity and Medicinal properties

INTRODUCTION

Honey has been highly appreciated as an alimentary product and has been largely used since ancient times as well as in cosmetic manufacturing. Honey is a sugary substance obtained from the nectar of the flowers or from the secretions which come from or lie on the living parts of the plant and which honey bees crop, transform and combine with their own specific substances and store in the honeycomb of the beehive. Honey is a product extremely rich in sugars of which glucose and fructose are outstanding. It also possesses vitamins, mineral salts and microorganisms in honey have long been used to control the spoilage of honey. Microorganisms in honey may influence quality and safety. Due to the natural properties of honey and control measures in the honey industry, honey is a product with minimal types and levels of microbes. The microbes of concern in honey are primarily yeasts and spore-forming bacteria [1].

Honey forms part of the traditional medicine in many cultures. According to Gomez - Caravaca [2], antibiotic resistance emerged as major global problem hospitals [3], especially in the clinical treatment of ulcers, bed sores, burns, injuries and surgical wounds. The antibacterial properties of honey may be particularly useful against bacteria which have developed resistance to many antibiotics. For example, *Staphylococcus aureus*, which was the major cause of wound sepsis in hospitals. Honey is thus an ideal topical wound dressing agent in surgical, infections, burns and wound infections [4].

Honey has been extensively used as healing agent throughout the human history in addition to its widespread usage as popular food. Honey is a sweet substance produced as a food source mainly from the nectar and secretions of plants by honey bees. Honey is used to feed bees during the winter [5]. For centuries, honey has been used as food and as natural medicine, being prescribed by physicians of many ancient cultures

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for the treatment of a wide variety of ailments. The art of apiculture and the benefits of honey have been known. Since, the Egyptian first dynasty [6] and ancient Greeks used honey as a sweetener [7]. In classical Greece, laws concerning apiculture were suggested and Plato included honey in their concept of a healthy diet [8]. The use of honey in folk medicine is thought to be as old as civilization, but in recent times there has been a renaissance in interest in its use as a medicinal product. The colour of honey can vary from clear to dark amber according to its floral source and mineral content and it has a close relationship with its flavour and quality [9]. Honeys may be viscous liquids or even solid with differing honeys identifiable by their colour, flavour, crystallization and the presence of pollen grains in honey sediment [10].

Honey is mainly composed of water and sugar (about 96 %) with the remainder being substances such as amino acids, enzymes, minerals, flavonoids, phenolic acids, ascorbic acid, carotenoid-like substances, organic acids and several other compounds [11- 13]. D-fructose and D-glucose are the predominant sugars. Sucrose occasionally exceeds 1 % of the total sugar content while maltose may be found at levels three times higher than that of sucrose. The mineral fraction of honey is mainly composed of potassium and smaller amounts of magnesium, sodium, calcium, phosphorous, iron, manganese, cobalt and copper [10]. Enzymes such as invertase, amylase, catalase and glucose oxidase are also present and proline is the major amino acid constituent comprising about half the content of total free amino acids [11].

The beneficial role of honey is attributed to its antibacterial property with regards to its high osmolarity, acidity (low pH) and content of hydrogen peroxide (H_2O_2) and non-peroxide components, i.e., the presence of phytochemical components like methylglyoxal (MGO) [14, 15]. The antimicrobial agents in honey are predominantly hydrogen peroxide, of which the concentration is determined by relative levels of glucose oxidase, synthesized by the bee and catalase originating from flower pollen [14]. Most types of honey generate H_2O_2 when diluted, because of the activation of the enzyme glucose oxidase that oxidizes glucose to gluconic acid and H_2O_2, which thus attributes the antimicrobial activity [16]. But, in some cases, the peroxide activity in honey can be destroyed easily by heat or the presence of catalase.

Besides H_2O_2, which was produced in most conventional honeys by the endogenous enzyme glucose oxidase, several other non-peroxide factors have been found to be responsible for the unique antibacterial activity of honey [17]. Honey may retain its antimicrobial activity even in the presence of catalase (absence of glucose oxidase) and thus this type of honey is regarded as “non-peroxide honey” [18, 19]. Several components are known to contribute the non-peroxide activity, such as the presence of methyl syringate and methylglyoxal, which have been extensively studied in Manuka honey that is derived from the Manuka tree [20, 21]. Unlike Manuka honey, the activity of ulmo honey is largely due to H_2O_2 production: 25 % (v/v) solution of ulmo honey had no detectable antibacterial activity when tested in presence of catalase. At the same concentration, the Manuka honey retained its antibacterial activity in the presence of catalase (absence of H_2O_2) [22]. Neither type of activity was influenced by the sterilizing procedure of gamma-irradiation [23].

Citric and gluconic acids are also present in honey though malic, folic, lactic, succinic, butyric, acetic and formic acids have also been identified [24]. Honey, depending on variety, is a poor source of vitamins with only a few honeys showing evidence of vitamins A, B_2, C and B_6 and carotenoid - like substances [25]. Polyphenols, especially flavonoids and phenolic acids are known to play an important role as antioxidants and honey was regarded as an important source of different compounds [26, 27]. The presence and concentrations of these phytochemicals in honeys can vary depending upon the floral source, geographical and climatic conditions. Consequently, polyphenols have been suggested as floral markers for the botanical authentication of unifloral honeys [28, 29].

Molan and Cooper [30] reported that the difference in antimicrobial potency among the different honeys can be more than 100-fold, depending on its geographical, seasonal and botanical source as well as harvesting, processing and storage conditions. The antibacterial nature of honey was dependent on various factors working either singularly or synergistically, the most salient of which are H_2O_2, phenolic compounds, wound pH, pH of honey and osmotic pressure exerted by the honey. Hydrogen peroxide is the major contributor to the antimicrobial activity of honey and the different concentrations of this compound in different honeys result in their varying antimicrobial effects [31]. It has further been reported that physical property along with geographical distribution and different floral sources may play important role in the antimicrobial activity of honey [32].

Several authors reported that different honeys vary substantially in the potency of their antibacterial activity, which varies with the plant source [33-35]. Thus, it has been shown that the antimicrobial activity of honey may range from concentrations < 3 % to 50 % and higher [36- 38]. The bactericidal effect of honey was reported to be dependent on concentration of honey used and the nature of the bacteria [39, 40]. The concentration of honey has an impact on antibacterial activity and the higher the concentration of honey the greater its usefulness as an antibacterial agent [41]. Taormina *et al.* [42] reported that the concentration of honey needed for complete inhibition of *Salmonella typhimurium* growth as <25 %.

Antimicrobial agents are essentially important in reducing the global burden of infectious diseases. However, as resistant pathogens develop and spread, the effectiveness of the antibiotics is diminished. This type of bacterial resistance to the antimicrobial agents poses a very serious threat to public health and for all kinds of antibiotics including the major last-resort drugs, the frequencies of resistance are increasing worldwide [43, 44]. Therefore, alternative antimicrobial strategies are urgently needed and thus this situation has led to a re-evaluation of the therapeutic use of ancient remedies, such as plants and plant-based products, including honey [45, 46].

The use of traditional medicine to treat infection has been practiced since the origin of mankind and honey produced by *Apis mellifera* (*A. mellifera*) is one of the oldest traditional medicines considered to be important in the treatment of several human ailments. Currently, many researchers have reported the antibacterial activity of honey and found that natural unheated honey has some broad-spectrum antibacterial activity when tested against pathogenic bacteria, oral bacteria as well as food spoilage bacteria [47- 49].

Tan *et al.* [50] reported that the Tualang honey was variable but broad-spectrum activities against many different kinds of wound and enteric bacteria. Unlike glucose oxidase, the antibacterial properties from *Leptospermum* spp. honeys are light and heat-stable. Natural honey of other sources can vary as much as 100-fold in the potency of their antibacterial activities which is due to hydrogen peroxide [51, 52]. In addition, honey is hygroscopic which means that it can draw moisture out of the environment and dehydrate bacteria and its high sugar content and low level pH can also prevent the microbes from growth.

History of Honey as Medicine: Honey is a popular sweetener throughout the world. According to an Associated Marketing survey conducted for the National Honey Board in 1997, almost 77 per cent of U.S. households use honey along with other sweeteners and syrups and 45 per cent of them consider honey a good value because it is "natural/good for you/better for you than sugar". Overall, honey has a positive profile with nearly 62 per cent of users "especially liking" it for its taste and flavor, 24 per cent because it is natural and 16 percent because it is good for humans (Report on consumer uses and attitudes towards honey, 1997).

From ancient times, honey was not only used as a natural sweetener but also as a healing agent. Many health-promoting and curative properties attributed to it are the basis for some traditional folk medicine treatments throughout the world today. Of the consumers who use honey, 93 per cent consider honey a healthful product, recognizing it as a pure, natural product. Fifteen percent think of it as a good home remedy (Report on consumer uses and attitudes towards honey, 1997).

Stone age paintings in several locations dating to 6000 B.C or earlier depict honey hunting, documenting human use of honey for at least 8000 years. References to honey as a medicine are found in ancient scrolls, tablets and books Sumerian clay tablets estimated to be 6200 B.C, Egyptian papyri dated from 1900-1250 B.C, Veda (Hindu scripture) about 5000 years old [53], the Holy Koran [54], the Talmud, both the old and new testaments of the Bible, Sacred books of India, China, Persia and Egypt and Hippocrates 460-357 BC. Clearly, honey was ubiquitous and our ancestors use of it for medicinal purposes was universal.

Honey was prescribed for a variety of uses including baldness, contraception and as a wound treatment. Frequently, honey was mixed with herbs, grains and other botanicals from the geographic area. Uses that have continued into modern folk medicine include treatment for coughs and sore throats, lotus honey for eye diseases in India, infected leg ulcers in Ghana, earaches in Nigeria, topical treatment of measles in the eyes to prevent corneal scarring, gastric ulcers and constipation [55].

Composition of Honey

Nutrients: Honey is a supersaturated sugar solution with approximately 17.1 per cent water. Fructose is the predominant sugar at 38.5 per cent, followed by glucose at 31 per cent. Disaccharides, trisaccharides and

oligosaccharides were present in much smaller quantities. Besides carbohydrates, honey also contains small amounts of protein, (including enzymes), vitamins and minerals. Honey yields 64 calories per tablespoon, making it a more concentrated source of energy than other common sweeteners. While the amino acid content is minor, the broad spectrum of approximately 18 essential and non - essential amino acids present in honey is unique and varies by floral source. Proline is the primary amino acid with lysine being the second most prevalent. Other amino acids found in honey included phenylalanine, tyrosine, glutamic and aspartic acids. The glutamic acid is a product of the glucose oxidase reaction.13 Proline and other amino acids were contributed by pollens, nectar or by the bees themselves [56]. Bees use a variety of plants to create honey and consequently, the nutritional profile of honey varies accordingly. Some studies have been done on honeys from different botanical origins to evaluate the differences in sugar content [57], amino acid content [58] and other components. These compositional differences can influence the value of a specific honey for medicinal or health-promoting purposes.

Phytochemicals: In recent years, researchers have identified a number of phytochemicals in various foods, including honey. Phytochemicals are the chemical substances which are present in plants. It is now recognized that many phytochemicals can have health - promoting activities. Antioxidants, a major group of phytochemicals, reduce the risk of tissue oxidative damage.

Honey is known to be rich in both enzymatic and non-enzymatic antioxidants, including catalase, ascorbic acid, flavonoids and alkaloids [59- 61]. A unique flavonoid, pinocembrin is present in high quantities in propolis and honey. Other flavonoids found in honey are pinobanksin, chrysin, galangin, quercetin, luteolin and kaempferol. Different honeys have different flavonoid profiles, depending on the floral source for the nectar. Similarly, the ascorbic acid content of honey ranges from 0.5 - 6.5 mg/100 g with an average of 2.4 mg/100 g or 5 mg/ml. However, some specific varieties of honey have been reported to contain as much as 75 - 150 mg ascorbic acid per 100 g, while most honey contain less than 5 mg/100 g [62].

In vitro experiments on the inhibition of oxidation in a model system using various honeys demonstrated a wide variation in the antioxidant capacity among floral sources. Honey made by bees fed herbal extracts exhibited greater antioxidant activity than normal honey [63]. In general, higher antioxidant content was found in darker honeys and in honeys with higher water content [64]. Some honeys such as buckwheat honey are comparable to fruits and vegetables such as orange pulp, broccoli and sweet peppers in their antioxidant content on a weight basis.

Enzymes: Honey contains a number of enzymes including glucose oxidase, invertase, diastase (amylase), catalase and acid phosphatase [65]. The glucose oxidase reaction produces glutamic acid and hydrogen peroxide from glucose. It also produces glucolactone that equilibrates with gluconic acid. The hydrogen peroxide contributes to the antimicrobial properties of honey. The invertase enzyme converts sucrose to fructose and glucose. It was added to the nectar by the bees as either gluco-invertase or fructo-invertase [66]. Some invertase is found in honey and may continue its activity in extracted honey. However, high temperatures will inactivate the invertase.

Diastase (amylase) splits starch chains to randomly produce dextrins and maltose [65]. The diastase content varies according to floral source. Long storage periods and exposure to high temperatures for a prolonged period of time inactivate diastase. Researchers recommend 85 °C for 5 minutes to denature diastase in honey; also a pH outside the optimum range of 5.3 - 5.6 will decrease diastase activity [67]. Catalase, found in small amounts in honey, produces oxygen and water from hydrogen peroxide. The inverse relationship between catalase activity and hydrogen peroxide content has been used to determine the hydrogen peroxide level of honey, formerly called the “inhibine number” [68].

Organic Acids: Organic acids contribute a slight tartness to the flavor of honey and add to its antimicrobial properties. Gluconic acid, the major organic acid, is the product of the enzymatic glucose oxidase reaction. It has been shown to increase calcium absorption [69]. Honey contains many other organic acids - butyric, acetic, formic, lactic, succinic, malic, citric, oxalic and pyroglutamic. The organic acid content varies according to the floral source [70].

Medicinal Properties of Honey: Honey is an ancient remedy for the treatment of infected wounds which has recently been ‘rediscovered’ by the medical profession, particularly where conventional modern therapeutic agents fail. The first written reference to honey, a Sumerian tablet writing, dating back to 2100 - 2000 B.C,

mentions honey's use as a drug and an ointment. Aristotle (384 - 322 B.C), when discussing different honeys, referred to pale honey as being "good as a salve for sore eyes and wounds". Manuka honey has been reported to exhibit antimicrobial activity against pathogenic bacteria such as *Staphylococcus aureus* and *Helicobacter pylori* making this honey a promising functional food for the treatment of wounds or stomach ulcers [71].

The honey has been used from ancient times as a method of accelerating wound healing [72] and the potential of honey to assist with wound healing has been demonstrated repeatedly [73, 74]. Honey is gaining acceptance as an agent for the treatment of ulcers, bed sores and other skin infections resulting from burns and wounds [75]. The healing properties of honey can be ascribed to the fact that it offers antibacterial activity, maintains a moist wound environment that promotes healing and has a high viscosity which helps to provide a protective barrier to prevent infection [76]. There are many reports of honey being very effective as dressing of wounds, burns, skin ulcers and inflammations; the antibacterial properties of honey speed up the growth of new tissue to heal the wound [77]. The med honey and Manuka honey have been shown to have *in vivo* activity and are suitable for the treatment of ulcers, infected wounds and burns [78, 79].

The honey when applied topically, rapidly clears wound infection to facilitate healing of deep surgical wounds with infection [80]. The application of honey can promote the healing in infected wounds that do not respond to the conventional therapy, i.e., antibiotics and antiseptics [80], including wounds infected with Methicillin - resistant *Staphylococcus aureus* [81]. Moreover, it can be used on skin grafts and infected skin graft donor sites successfully [82].

The Manuka, jelly bush and pasture honeys are capable of stimulating the monocytes, the precursors of macrophages, to secrete TNF-α [83]. On the other hand, glycosylated proteins can induce TNF-α secretion by macrophages and this cytokine is known to induce the mechanism of wound repairing. Furthermore, the ability of honey to reduce 'reactive intermediates release [84] may well limit tissue damage by activated macrophages during wound healing. Thus, the immune modulatory property of honey is relevant to wound repair.

The support for using honey as a treatment regimen for peptic ulcers and gastritis comes from traditional folklore as well as from reports in modern times [85]. Honey may promote the repair of damaged intestinal mucosa, stimulate the growth of new tissues and work as an anti-inflammatory agent [85]. Raw honey contains copious amounts of compounds such as flavonoids and other polyphenols which may function as antioxidants [86]. Clinical observations have been reported of reduced symptoms of inflammation when honey is applied to wounds. The removal of exudates in wounds dressed with honey is of help in managing inflamed wounds [87].

Antimicrobial Activity of Honey

Mechanisms of Antimicrobial Activity: A number of characteristics of honey contribute to its antimicrobial activity. The enzymatic glucose oxidation reaction and some of its physical properties are considered to be the major factors. Other factors include high osmotic pressure/low water activity (A_w), low pH/acidic environment, low protein content, high carbon to nitrogen ratio, low redox potential due to the high content of reducing sugars; a viscosity that limits dissolved oxygen and other chemical agents/ phytochemicals [88]. The most familiar Honey researcher, Dr. Peter Molan has written an extensive review of the research on the antimicrobial factors in honey and has summarized the key aspects of his research on a website at the University of Waikato, Hamilton, New Zealand.

- Honey is a supersaturated sugar solution with a low water activity (A_w), which means that there is little water available to support the growth of bacteria and yeast. Many species of bacteria will grow if the A_w was between 0.94 - 0.99 and the A_w of ripened honey (0.56 - 0.62) does not support the growth of yeast. Diluted honey with a higher A_w will not be effective against those species of bacteria that grow most rapidly at an A_w of 0.99.
- The natural acidity of honey will inhibit many pathogens. The minimum pH value for some species that commonly infect wounds ranges from 4.0 - 4.5. Dilution of honey, especially with body fluids will raise the pH and lessen the antibacterial effectiveness that results from its acidity.
- Glucose oxidase is an enzyme secreted by the bees to form honey from nectar. It converts glucose in the presence of water and oxygen to gluconic acid and hydrogen peroxide. The resulting acidity and hydrogen peroxide preserve and sterilize the honey during the ripening process. Full-strength honey has negligible amounts of hydrogen peroxide and active

glucose oxidase. Transition ions and ascorbic acids rapidly decompose hydrogen peroxide to oxygen and water while the low pH inactivates the enzyme. However, dilution of honey results in a 2,500 - 50,000 increase in enzyme activity and a "slow-release" antiseptic that does not damage tissue.

- The peroxide-generating system does not account for all of the observed antibacterial activity. Several substances with antibacterial activity were found in honey in small quantities that are too low to contribute significantly to antibacterial activity: pinocembrin, terpenes, benzyl alcohol, 3,5-dimethoxy-4-hydroxybenzoic acid (syringic acid), methyl-3,5-dimethoxy-4-hydroxybenzoate (methyl syringate), 3,4,5-trimethoxybenzoic acid, 2- hydroxy-3-phenylpropionic acid, 2-hydroxybenzoic acid and 1,4-dihydroxybenzene. Support for the existence of non-peroxide antimicrobial factors comes from reports of continued activity after honey has been treated with heat, thereby inactivating the glucose oxidase and after honey has been treated with catalase to remove the peroxide activity.

Not all honeys are created equal in antimicrobial activity due to differences in levels of peroxide production and non-peroxide factors, which vary by floral source and processing. The presence of metal ions, ascorbic acid and catalase from the nectar can destroy the hydrogen peroxide. Heat and light can destroy the glucose oxidase enzyme. The original method for measuring antibacterial activity was to determine the "inhibine number" defined as the degree of dilution (done in a stepwise fashion) to which a honey will retain its antibacterial activity. Most studies now report antimicrobial activity as minimum inhibitory concentration (MIC), the minimum concentration necessary for complete inhibition of growth [89]. Various studies on large numbers of honey samples showed a wide range of activity and many with only a low level of activity [90].

While there are insufficient data to clearly identify the antibacterial activity of all honeys, there is some evidence of high levels in honeydew honey (a sweet liquid excreted by sucking insects which tap into leaves) from the conifer forests of the mountainous regions of central Europe and Manuka honey (honey from the *Leptospermum* species) from New Zealand. Honey had the highest levels of non-peroxide activity among 26 different types of honey from various floral sources. It strongly inhibited two strains of bacteria (*Escherichia coli* and *Staphylococcus aureus*) [91].

An *in vitro* study compared the antibacterial action of a pasture honey (a polyfloral honey in which the nectar comes from various clovers and pasture weeds such as thistle and dandelion) and Manuka honey on coagulase positive *Staphylococcus aureus* strains from infected wounds. The isolates showed little difference in their sensitivity to both honeys. The pasture honey with a higher peroxide generation and the Manuka honey with non - peroxidal antibacterial activity were both effective at low concentrations (3 - 4 percent v/v and 2 - 3 percent v/v, respectively) [92].

Antibacterial Activity: There are several studies investigating the antimicrobial activity of honey. The antibacterial activity of honey is usually associated with the release of hydrogen peroxide, from the oxidation of glucose to glucolactone and then to gluconic acid in presence of the enzyme glucose oxidase. This activity was called peroxide-activity and constitutes, at variable extent, the mode of action of some honeys [93]. The use of honey as a traditional remedy for microbial infections dates back to ancient times.

Research has been conducted on Manuka (*L. scoparium*) honey [94], which has been demonstrated to be effective against several human pathogens, including *Escherichia coli*, *Enterobacter aerogenes, Salmonella typhimurium, Staphylococcus aureus* [94, 95]. Many laboratory studies have revealed that the honey was effective against methicillin-resistant *Staphylococcus aureus* (MRSA), β- haemolytic *Streptococci* and vancomycin resistant *Enterococci* (VRE) [96, 97]. However, the newly identified honeys may have advantages over or similarities with manuka honey due to enhanced antimicrobial activity, local production (thus availability) and greater selectivity against medically important organisms [98]. The coagulase negative *Staphylococcus* are very similar to *Staphylococcus aureus* [99, 100] in their susceptibility to honey of similar antibacterial potency and more susceptible than *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Enterococcus* species [101].

Gram positive bacteria such as *Staphylococcus aureus,* the causal agent of a range of illnesses from skin infections to life-threatening diseases such as pneumonia and meningitis, did not grow in the presence of honeys produced by *A. mellifera* and *Tetragonisca angustula* bees in the Brazilian states of Paraná and Minas Gerais. In order to study this effect, honeys were analysed by high performance liquid chromatography (HPLC) and the antimicrobial activity was connected to phenolic

compounds, such as 4- hydroxybenzoic acid (HBEN). These compounds occur in higher concentrations in propolis than in honey and propolis was more effective against *Staphylococcus aureus* than honey [102]. This bacterium has proved to be variable in susceptibility to different honeys. Turkish honeys from Anatolia showed a moderate inhibition towards some strains of *Staphylococcus aureus* [103], while Turkish rhododendron honeys partially inhibited the growth of this bacterium [104].

Honey from stingless bees had powerful activity against *Staphylococcus aureus* when compared to that exhibited by Manuka honey produced by honeybees belonging to Apidae family (*A. mellifera* and *A. cerana*) [105]. Argentinean honeys from the province of Cordoba evidenced high activity against *Staphylococcus aureus,* which was considered to be of remarkable clinical importance, since an increase in difficult-to-treat skin infections had been reported in the last decade and resistance against several antibiotics had developed [106]. A study of the properties of several Cuban honeys demonstrated that Gram positive bacteria are more sensitive than Gram negative bacteria with *Staphylococcus aureus* the most sensitive bacterium [107].

Honeys from *A. mellifera* produced in Thailand also showed inhibitory effects against many infectious diseases [108]. Strains of *Staphylococcus aureus* were found to be very sensitive to Spanish honeydew honeys [109] whereas in other studies using honeys from Galicia (northwest of Spain) two strains of the bacterium, including a difficult-to-treat strain in humans such as the Methicillin-resistant *Staphylococcus aureus* (MRSA), exhibited different sensitivities [110]. South African honeys from indigenous *Leucospermum cordifolium* and *Erica* species showed poor antibacterial activity against this Gram positive bacterium [111].

Basualdo *et al*. [112] demonstrated that *Escherichia coli* can be inhibited by some Argentinean honeys while, Fangio *et al*. [113] demonstrated the effectiveness of honeys produced in the province of Buenos Aires (Argentina) against this *Enterobacterium*. The antimicrobial activity of these honeys was mainly non-peroxide and the presence of phytochemicals such as phenolic compounds was considered in the most active honeys. Nevertheless, rhododendron Turkish honeys showed no inhibitory effect [114].

Baltrusaityte *et al*. [115] observed that Lithuanian honeys exhibited antibacterial effects on *Staphylococcus aureus* and concluded that this was mainly due to the presence of hydrogen peroxide. Honeys produced in the Czech Republic are also antimicrobially effective with some honeydew honeys possessing the greatest effects [116]. In a study with unifloral and multifloral Portuguese honeys, Henriques *et al*. [117] analyzed their antibacterial activity against a strain of *Staphylococcus aureus* and observed that all of the samples tested possessed peroxide activity except some honeys derived from *Lavandula stoechas* which revealed non - peroxide antibacterial activity.

Basson and Grobler [118] found poor antibiotic activity of South African honeys from indigenous *L. cordifolium* and *Erica* species. Some Czech Republican honeys were also tested for their antibacterial activity against *Escherichia coli* and researchers concluded that honeydew honeys are the most effective [119]. Recently, Brudzynski and Miotto [120] investigation with twenty Canadian unheated honeys, quantified Maillard reaction- like products (MRLPs) and total phenol contents, apart from assessing the antioxidant activity using the ORAC method. One of their results indicated that both the recorded antioxidant activity and the content of MRLPs of these honeys mainly contributed to the antibacterial activity against *Escherichia coli*. This antibacterial activity confirms the work of Rufian Henares and De La Cueva [121] who suggested that the antibacterial activity of coffee melanoidins against *Escherichia coli* is due to their behavior as metalchelators.

Isla *et al*. [122] observed that algarrobo honey (*Prosopis nigra*) and a multifloral honey from the northwestern provinces of Argentina had activity against *Staphylococcus aureus.* They identified at least five antibacterial compounds in the algarrobo honey and four compounds in the multifloral honey and found that most of them corresponded to flavonoids. One of these flavonoids was identified as pinocembrin. The authors also pointed out that the antibacterial activity of the analysed honeys might be mainly due to their phenol content because of the significant correlation observed between the phenolic content and the antibacterial activity.

Among the Gram negative bacteria, *Escherichia coli* is of great concern from a health point of view. It may cause life threatening gastric infections and diarrhoea, following consumption of contaminated food, as well as other infections such as cystitis, meningitis, peritonitis and pneumonia. There are several studies on the antibiotic effect of honey towards *Escherichia coli.* The *Escherichia coli* exhibited sensitivity to stingless honeybee honey [123], Spanish honeys [124], Cuban honeys [125] and Thailand honeys [126].

Pseudomonas aeruginosa, an important pathogenic bacterium which can cause several health disorders in humans including lung, urinary, tissue, blood and wound infections was studied in many published reports. Silici *et al*. [127] showed that rhododendron honeys from Turkey have antimicrobial activity against *Pseudomonas aeruginosa* when diluted at 50 % and 75 % in water. *A. mellifera* honeys produced in Thailand also inhibited the growth of this bacterium [128]. Honey from stingless honeybees showed significant inhibitory effects on the growth of *Pseudomonas aeruginosa* [129]. The bactericidal potency of Saharan honey against this pathogen was studied by Boukraa and Niar [130] who reported that Saharan honey showed higher potency than Algerian honeys, probably due to antibacterial substances from the botanic flora occurring in the Sahara. This Gram negative and aerobic micro-organism was sensitive to some honeys produced in the province of Cordoba (Argentina) [131], but was the least sensitive in comparison with other bacteria [132], while not sensitive to honey samples evaluated by Gallardo - Chacon *et al*. [133].

Helicobacter pylori, can occur in the stomach and is linked to the development of ulcers and many types of gastritis. There is evidence that honey can have inhibitory effects against this bacterium. Kucuk *et al*. [134] reported a moderate inhibitory effect by honeys harvested in Anatolia (Turkey) and studies conducted with Manuka (*L. scoparium*) honey showed interesting antibacterial activity [135 - 137]. It has been suggested that this honey can also act by healing the gastric mucosa and stimulating epithelial cells growth.

Bacillus cereus, a Gram positive, aerobic and beta - hemolytic bacterium is a food-borne pathogen for humans whose growth results in the production of enterotoxins causing nausea, vomiting, abdominal cramps and diarrhoea. There are reports of the sensitivity of the bacterium towards some honeys. For example, some Thai honeys can inhibit growth of the *Bacillus* [138] and similar activity was observed in studies using different honeys which included honey from Galicia (Spain) [139]. In contrast, *Bacillus cereus* was found to be resistant when rhododendron Turkish honeys were tested for their antibacterial activity [140].

Honeys produced in Anatolia (Turkey) in Cuba and in the Turkish Black Sea Region showed inhibition effects on strains of *Bacillus subtilis* [141- 143], a Gram positive sporing bacterium occurring in soil which can contaminate food but rarely causes infections in humans. Some other honey sensitive - pathogens described in the literature are *Bacillus anthrasis* (anthrax), *Corynebacterium diptheriae* (diphtheria), *Klebsiella pneumoniae* (pneumonia), *Mycobacterium tuberculosis* (tuberculosis), *Salmonella typhi* (typhoid fever), *Vibrio cholerae* (cholera) and different *Streptococci,* among others. For example, *Klebsiella pneumoniae* was found to be sensitive to Argentinean [144] and Thai honeys [145]. The growth of *Enterococcus faecalis* was inhibited by stingless honeybee honey [146] and this bacterium also showed sensitivity to honey according to the research performed by Gallardo - Chacon *et al*. [147]. In addition, other bacteria sensitive to different types of honey are *Staphylococcus epidermidis* [148, 149], *Staphylococcus uberis* [148], *Pediococcus mirabilis* [150], *Aeromonas hydrophila* [151], *Micrococcus luteus* [152], *Streptococcus oralis* [153], *Streptococcus anginosus* [154], *Salmonella enterica* ser. *typhimurium* [155, 156], *Shigella sonnei* [156], *Listeria monocytogenes* [157, 158] and *Streptococcus mutans* [159]. Among yeasts, some *Candida* species were inhibited by Turkish honeys [160].

The initial event in the development of bacterial infections of the gastrointestinal gut is the attachment of bacteria to the mucosal epithelial cells [161] and the blocking of this event represents an interesting strategy for the prevention of diseases [162, 163]. Alnaqdy *et al*. [164] studied the antimicrobial activity of Omani honeys against *Salmonella interitidis* and the ability of these honeys to prevent the bacterium from adhering to intestinal epithelial cells *in vitro*. However, in spite of the antimicrobial activity, there are yeasts like *Candida albicans* and *Saccharomyces cerevisiae* which showed resistance towards some honeys [165, 166], while rhododendron honeys were not effective against strains of *Bacillus cereus, Escherichia coli* and *Yersinia enterocolítica* [167].

The bactericidal properties of honey led researchers to investigate its applications on cutaneous wound healing and the treatment of burns. Mohd Nasir *et al*. [168] and Kirnpal-Kaur *et al*. [169] found that tualang honey (*Koompassia excelsa*) had important bactericidal and bacteriostatic effects in the treatment of burns by using dressings soaked with this honey. Also, non - toxicity of honey against tissue cell cultures of human keratinocyte and fibroblasts has recently been found *in vitro.* This kind of evidence may positively influence the choice of wound dressings in clinical prescriptions [170].

Antiviral Activity of Honey: Antiviral properties of honeys are also of great concern from a therapeutic point of view. Chritchfield *et al*. [171] showed that some important flavonoids of honey such as chrysin, acacetin andapigenin can inhibit the human immunodeficiency

virus (HIV-1) activation *via* a probable mechanism involving the inhibition of viral transcription. Other researchers have demonstrated the inhibitory effects of chrysin against Herpes simplex virus type 1 (HSV-1) [172]. Hu *et al*. [173] observed that chrysin and apigenin have a significant antiviral activity against HIV-1 in acutely infected H9 lymphocytes. Apigenin also exhibited antiviral activity against influenza virus (H3N2) *in vitro* [174].

Molecular biological processes at DNA level are responsible for cell events that lead to the development of some phenomena such as carcinogenesis and, in this line, binding studies of different flavonoids were undertaken. Apigenin, a cancer chemopreventive agent, has the highest affinity of ligand-DNA binding when compared to those of morine and naringin [175]. Chiang *et al*. [176] observed that apigenin behaves as a potent antiviral substance against Herpes virus type - 2 (HSV-2), Adenovirus (ADV-3), Hepatitis B surface antigen (HDCA) and Hepatitis B e antigen (HBeA).

Al - Waili [177] studied the activity of honey on two types of herpes: labial and genital herpes. His results demonstrated that the topic application of honey on recurrent attacks of this viral disease was effective. Their study reported that in the labial herpes the mean time of healing was 43 % better than with the conventional treatment with acyclovir, while for genital herpes the mean healing time was improved around 59 %. The authors remarked that some cases remitted completely after treatment with honey, although none of the attack remitted when using acyclovir. Honey has also demonstrated anti-Rubella activity in experiments performed on monkey kidney cell cultures infected with the Rubella virus [178].

Uses of Honey: The use of honey as a traditional remedy for microbial infections dates back to ancient times. The ability of honey to kill microorganisms has been attributed to its high osmotic effect, high acidic nature, hydrogen peroxide concentration and its phytochemical nature [179].

Therapeutic Uses: In most cases, honey is used when conventional antibacterial treatment with antibiotics and antiseptics are ineffective. Numerous studies have shown that these difficult-to-heal wounds respond well to honey dressings. Inflammation, swelling and pain rapidly subside, unpleasant odours stop, debridement was enhanced as the honey dressings remove dead tissue painlessly and without causing damage to the regrowing cells. Honey promotes rapid healing with minimal scarring. Honey can also be used as first aid treatment for burns as it has potent anti-inflammatory activity.

Medicinal Properties: Recent tests carried out in collaboration with the Central Public Health Laboratory in London, UK, on many strains of multi-antibiotic resistant bacteria such as MRSA strains MRSA, VRE and *Acinetobacter baumarii* have shown that these bacteria have no resistance to honey (These "superbugs" are a serious clinical problem as infections with them often cannot be treated at all with antibiotics). All of the testing of sensitivity of wound infecting species of bacteria that we have carried out has been done with honeys selected to have mid-range levels of antibacterial activity. Another important factor for growth of new tissue is a supply of nutrients, usually limited because of damage to the underlying circulation resulting from injury or infection. Honey will supply the cells with a wide range of vitamins, amino acids and minerals. It will also supply white blood cells with the glucose necessary for their "respiratory burst" to destroy bacteria. Further, it will supply nutrients to the cells by drawing serum out through the tissue by osmosis induced by the high sugar content of honey.

Honey as Antibiotic: Manuka honey has potent antibacterial properties, making it especially beneficial for preventing and treating wound infections by drug-resistant bacteria, according to physician Robert Frykberg of the Veterans Affairs Medical Center in Phoenix, Ariz.

Diabetic Benefits: FDA-approved Manuka honey product, Medi honey, has proven beneficial for healing foot ulcers in diabetic patients. Diabetics with foot ulcers that do not heal sometimes require foot amputation.

Gastrointestinal Effects: Manuka honey shows promise for healing peptic ulcers caused by *Helicobacter pylori* bacteria, in research cited by the University of Waikato in New Zealand. It is also effective against various strains of bacteria that cause gastroenteritis.

Recent Medicinal Research on Honey: For centuries honey had been known as nature's medicine. Ongoing medical research is turning up a multitude of curative uses for honey. Honey is not only for eating, but has several different medicinal uses.

Arthritis: Take one part honey to two parts of luke warm water and add a small teaspoon of cinnamon powder, make a paste and massage it on the itching part of the body. It was noticed that the pain recedes within a minute. For arthritis, patients daily morning and night take one cup of hot water with two spoons of honey and one small teaspoon of cinnamon powder. If drunk regularly even chronic arthritis can be cured. In a recent research done at the Coppenhagen University, it was found that when the doctors treated their patients with a mixture of one tablespoon honey and half teaspoon cinnamon powder before breakfast, they found that within a week out of the 200 people so treated practically 73 patients were totally relieved of pain and within a month, mostly all the who could not walk or move around because of arthritis started walking without pain.

Bladder Infections: Take two tablespoons of cinnamon powder and one teaspoon of honey in a glass of luke warm water and drink it. It destroys the germs of the bladder.

Cholesterol: Two tablespoons of honey and three teaspoons of cinnamon powder mixed in 16 ounces of tea water if given to a cholesterol patient; it reduces the level of cholesterol in the body by 10% within 2 hours. As mentioned for arthritic patients, if taken 3 times a day any chronic cholesterol cured. As per the information received in the said journal, pure honey taken with food daily relieves complains of cholesterol.

Upset Stomach: Honey taken with cinnamon powder cures stomachache and also clears stomach ulcers from the root. Gas: according to the studies done in India & Japan. It was revealed that if honey is taken with cinnamon powder the stomach is relieved of gas.

Immune System: Daily use of honey and cinnamon powder strengthens the immune system and protects the body from bacterial and viral attacks. Scientists have found that honey has various vitamins and iron in large amounts. Constants use of honey strengthens the white blood corpuscles to fight bacterial and viral diseases.

Influenza: A scientist in Spain has proved that honey contains a natural ingredient, which kills the influenza germs and saves the patient from flu.

Skin Infections: Applying honey in combination with cinnamon powder in equal parts on the affected parts cures eczema, ringworm and all types of skin infections.

Cancer: Recent research in Japan and Australia has revealed that advanced cancer of the stomach and bones have been cured successfully. Patients suffering from these kinds of cancer should daily take one tablespoon of honey with one teaspoon of cinnamon powder for one month 3 times a day.

Wound Healing: Honey is one of the oldest known medicines that have continued to be used up to present times in folk - medicine. Its use has been "rediscovered" in later times by the medical profession, especially for dressing wounds. The numerous reports of the effectiveness of honey in wound management, including reports of several randomized controlled trials, have recently been reviewed, rapid clearance of infection from the treated wounds being a commonly recorded observation. In almost all of these reports, honey was referred to generically, there being no indication given of any awareness of the variability that generally is found in natural products.

Any honey can be expected to suppress infection in wounds because of its high sugar content, but dressings of sugar on a wound have to be changed more frequently than honey dressings do to maintain an osmolarity that is inhibitory to bacteria, as honey has additional antibacterial components. Since, microbiological studies have shown more than one hundred - fold differences in the potency of the antibacterial activity of various honey, best results would be expected if a honey with a high level of antibacterial activity were used in the management of infected wounds [180].

CONCLUSION

Honey has been highly appreciated as an alimentary product and has been largely used, since ancient times, as well as in cosmetic manufacturing. Honey is a product extremely rich in sugars of which glucose and fructose are outstanding; it also possesses vitamins, mineral salts and microorganisms in honey has long been used to control the spoilage of honey. Honey consists of various constituents such as water, carbohydrates, proteins, vitamins, amino acid, energy and minerals. Besides the major ones, there must also be several minor constituents in honey, which may be playing a key role in determining the antimicrobial behaviour of honey. Use of honey as a therapeutic substance has been rediscovered by the medicine profession in more recent times, it is gaining acceptance as an antibacterial agent for the treatment of various ailments like urinary treat infection, diarrheoa, necrotic breast ulcers, gastrointestinal problems and other

skin infections resulting from burns and wound. The use of honey as a wound dressing material was an ancient remedy that has been rediscovered.

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