Honey- The natural sweetener become a promising alternative therapeutic: a review

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Abstract
To date, researchers pay more attention to medicines with natural origin and believe that natural products may be efficient therapeutics in comparison with the synthetic drugs. One of the most important natural products is honey. Honey has a very complex chemical composition that varies depending on the botanical source. It has been used both as food and medicine since ancient times. It has been reported to have an antimicrobial effect on many pathogenic microorganisms. Antioxidant capacity of honey is important in many disease conditions and is due to a wide range of compounds including phenolics, peptides, organic acids, enzymes. Honey also been reported as an alternative medicine for gastrointestinal, cardiovascular, inflammatory states. It is also useful as anticancer, antidiabetic and weight management agent. Beside the medicinal values, it also acts as prebiotic compound and so it stimulates the growth of probiotics. This review covers the history, composition and some important medical uses of honey.

1. Introduction
Natural medicinal products have been used for ages for the treatment of several ailments. Though many have been masked by conventional pharmaceutical approaches, there is currently resurgence in awareness in the use of natural products, which forms the basis of a world-wide, multi-million dollar major commercial industry. The pharmaceutical industry continues to scan their potentiality as sources of novel medicinal compounds to detect novel growth factor, immunomodulatory and also potential anti-microbial activity. In contrast with most standard therapeutic, these products are often promoted and used by individuals in order to prevent, rather than to treat, diseases. Antimicrobial agents are essentially important in dropping the global burden of infectious diseases and as resistant pathogens develop and spread, the efficiency of the antibiotics is weakened. This type of bacterial resistance to the antimicrobial agents poses a very serious threat to public health and the frequencies of resistance are increasing worldwide (Levy and Marshall, 2004; Mandal et al., 2009). Besides this fact, these synthetic drugs are causes side effects. These circumstances have led to a re-evaluation of the therapeutic use of ancient medications, such as plants and plant-based products, including honey (Basualdo et al., 2007; Mandal et al., 2010). Honey is produced by honey bees (Apis mellifera) from the nectar of plants or from secretions of living parts of plants or excretions of plant sucking insects on the living parts of plants, which the bees collect and convert by combining with specific substances of their own, deposit, dehydrate, store and leave in the honey comb to ripen and mature (FAO 2001). The composition of honey depends the plant species (Bertoncelj et al., 2007; Guler et al., 2007).

Humans began using honey nearly 10,000 years ago and the evident for it is a cave painting revealed in the early 1900’s in Valencia, Spain in the Cave of the Spider (Cueva de la Arana) situated on the river Cazunta. Archaeologists have discovered honey comb in Egypt that were been buried in tombs at the pharaohs, the honey was still eatable. Honey is frequently used as a talisman and also as a symbol of sweetness (White and Doner 1980). In Ancient times, people of Egypt use honey for making of sweeten cakes and biscuits, and were used in many other dishes. Ancient people of Egypt and Middle-Eastern also applied honey for mummification. According to Aristotle “eating honey prolongs life” and Hippocrates stated “I eat honey and use it in the treatment of many diseases because honey offers good food and good health”. Pedanius
Dioscorides who was a Roman surgeon in army has mentioned in his book that “Honey could be used as treatment for stomach disease, wound with pus, hemorrhoids, and treatment to stop coughing.” Honey was utilized as a sweetening agent in Roman recipes which is cited by several Roman authors including Bassus, Cato and Athenaeus. Some of these are composed in the book Roman cookery (Martos et al., 2000). In the book Naturalis Historia, Pliny the Elder has depicted about bee and honey and its applications. Nevertheless, the Chinese went ahead the rest of the world in terms of preservation, consumption and collection of honey, as they were first to begin beekeeping. Based upon the extensive searches in several biomedical science journals and web-based reports, the updated facts and phenomena related to the history, chemical properties and medicinal property of honeys are discussed in this review.

2. Religious significance of honey
The use of honey is embraced by all religious and cultural beliefs. Its beneficial effects has been mentioned in all holy books, and without any obstruction, widely accepted by all generations, traditions and civilizations (Ajibola et al., 2012).

2.1. Significance of honey in Buddhism
When the Buddha observed rites in the Parilyeyok forest, a monkey brought him a beehive rich with nourishing honey. When the Buddha accepted his gift, the monkey was so overcome by elation that he fell from a tree, to his death. His joy was remembered in the naming of the month that he died Madhu-Purnima, which means “honey full moon” and it is celebrated in India and Bangladesh. On this particular day, Buddhists remember this act by offering honey to monks. Honey gave nourishment to the Buddha in several times of need, including the two meals he took immediately preceding and following his enlightenment. Buddha utters “as a bee gathers honey from the flower without injuring its color or fragrance, even so the sage goes on his alms-round in the village”.

2.2. Significance of honey in Christianity
There are references made to the significance of bees and honey in the Bible, and these include the Books of Exodus, Judges, Mathew and Proverbs. In Old Testament law, offerings were made in the temple to God. The Book of Leviticus states that “Every grain offering you bring to the Lord must be made without yeast, for you are not to burn any yeast or honey in a food offering presented to the Lord.” The Book of Exodus famously defines the Promised Land as a “land flowing with milk and honey. In fact, it was reported in the Bible that John, the Baptist actually thrived on a diet including wild honey for a long time when he was in the desert area or while travelling in the wilderness.

2.3. Significance of honey in Hinduism
In Hinduism, the honey is utilized for many ritual purposes. In this religion, some drops of honey is poured in a new born child to welcome the baby (Doner 1977). The importance of honey is mentioned in Rigveda in many ways. Some of it are: “This herb, born of honey, dripped in honey, sweetened by honey, is the remedy for all injuries”; “Let every wind that blows drop honey; let the rivers and streams recreate honey; let all our medicines turn into honey; let the dawn and the evening be full of honey; our nourisher, this sky above, be full of honey; let our trees be honey; let the sun be honey, let our cows secrete honey (Siddiqui 1970).

2.4. Significance of honey in Islam
In Islam, there is an entire chapter in the holy Quran named al-Nahl (the Honey Bee). According to hadith, Prophet Muhammad (PBUH) suggested honey for healing purposes (White 1975). The holy Quran promotes honey as a nutritious and healthy food. Abu Huraira reported that Prophet Muhammad (PBUH) said, "Whosoever eats honey (at least) three times per month will meet with no great affliction (Conti 2000).

2.5. Significance of honey in Judaism
In Judaism, honey is used as the symbol of a new year called Rosh Hashanah. On this ritual, Jews dip the apple slices in honey and eat it to bring a sweet new year. In some congregations, small straws of honey are givenout to usher in the new year.

3. Chemical properties of honey
The carbohydrates are the main elements, comprising about 95% of the honey dry weight. Beside carbohydrates, honey contains numerous compounds such as organic acids, proteins, amino acids, minerals, polyphenols, vitamins and aroma compounds. The composition of honey depends greatly on the botanical origin, a fact that has been seldom considered in the nutritional and physiological studies. The average composition of honey is summarized in Table 1 (Terrab et al., 2004).

<table>
<thead>
<tr>
<th>Component</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>82.4g</td>
</tr>
<tr>
<td>Fructose</td>
<td>38.5g</td>
</tr>
<tr>
<td>Glucose</td>
<td>31g</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1g</td>
</tr>
<tr>
<td>Other Sugars</td>
<td>11.7g</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>0.2g</td>
</tr>
<tr>
<td>Fat</td>
<td>0g</td>
</tr>
<tr>
<td>Protein</td>
<td>0.3g</td>
</tr>
<tr>
<td>Water</td>
<td>17.1g</td>
</tr>
<tr>
<td>Riboflavin (Vit. B2)</td>
<td>0.038mg</td>
</tr>
<tr>
<td>Niacin (Vit. B3)</td>
<td>0.121mg</td>
</tr>
<tr>
<td>Pantothenic acid (Vit. B5)</td>
<td>0.068mg</td>
</tr>
<tr>
<td>Pyridoxine (Vit. B6)</td>
<td>0.024mg</td>
</tr>
<tr>
<td>Ingredients</td>
<td>Amount in 100 g</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Carbohydrates (kcal)</td>
<td>300 1000-1100 1400-2700 2400-3100</td>
</tr>
<tr>
<td>Proteins (g)</td>
<td>0.5 13-14 17-46 44-59</td>
</tr>
<tr>
<td>Fats (g)</td>
<td>0 -- -- --</td>
</tr>
<tr>
<td>Minerals (mg)</td>
<td>1.6-17 300 410-550 550</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>3-31 600 700-1200 1000-1200</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>40-3500 1000 1400-1900 2000</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>0.7-13 80 120-310 300-400</td>
</tr>
<tr>
<td>Phosphorus (P)</td>
<td>2-15 500 600-1250 700-1250</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>0.05-2 3 5-9.5 7-10</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>0.02-0.6 0.5-1 0.5-1 0.5-1</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>0.03-4 8 8-15 10-15</td>
</tr>
<tr>
<td>Manganese (Mn)</td>
<td>0.02-2 1-1.5 1.5-5 2-5</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>0.01-0.3 0.02-0.06 0.02-0.1 0.03-1.5</td>
</tr>
<tr>
<td>Selenium (Se)</td>
<td>0.002-0.01 0.002-0.01 0.001-0.006 0.003-0.007</td>
</tr>
<tr>
<td>Vitamins (mg)</td>
<td>Phyllochinon ca. 0.025 15 20-50 60-70</td>
</tr>
<tr>
<td>Thiamin (B1)</td>
<td>0.00-0.01 0.6 0.8-1.4 1-1.3</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>0.01-0.02 0.7 0.9-1.6 1.2-1.5</td>
</tr>
<tr>
<td>Pyridoxin (B6)</td>
<td>0.01-0.32 0.4 0.5-1.4 1.2-1.6</td>
</tr>
<tr>
<td>Niacin2</td>
<td>0.10-0.20 7 10.0-18 13-17</td>
</tr>
<tr>
<td>Panthohenic acid</td>
<td>0.02-0.11 4 4.0-6 6</td>
</tr>
<tr>
<td>Ascorbic acid (C)</td>
<td>2.2-2.5 60 70-100 100</td>
</tr>
</tbody>
</table>

The information is obtained from (Bogdanov 2006).

### 3.3. Vitamins, minerals and trace compounds

The amount of vitamins and minerals is small and the contribution of honey to the recommended daily intake (RDI) of the different trace substances is marginal (Table 2). From the nutritional point of view chromium, manganese and selenium are vital, especially for 1 to 15 years old children. The elements sulphur, boron, cobalt, fluoride, iodide, molybdenum and silicon can be significant in human nutrition too, although there are no RDI values anticipated for these elements (Table 3). Honey comprises 0.3-25 mg/kg choline and 0.06 to 5 mg/kg acetylcholine. Choline is necessary for cardiovascular and brain function as well as for cellular membrane composition and repair, while acetylcholine responsible for neurotransmitter.

Table 3. Trace elements in honey

<table>
<thead>
<tr>
<th>Element</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alumimum (Al)</td>
<td>0.01-2.4</td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>0.014-0.026</td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>0.01-0.08</td>
</tr>
<tr>
<td>Boron (B)</td>
<td>0.05-0.3</td>
</tr>
<tr>
<td>Bromine (Br)</td>
<td>0.4-1.3</td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>0-0.001</td>
</tr>
<tr>
<td>Chlorine (Cl)</td>
<td>0.04-56</td>
</tr>
<tr>
<td>Cobalt (Co)</td>
<td>0.1-0.35</td>
</tr>
<tr>
<td>Fluoride (F)</td>
<td>0.4-1.34</td>
</tr>
<tr>
<td>Iodide</td>
<td>10-100</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>0.001-0.03</td>
</tr>
<tr>
<td>Lithium (Li)</td>
<td>0.225-1.56</td>
</tr>
<tr>
<td>Molybdenum (Mo)</td>
<td>0-0.004</td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>0-0.051</td>
</tr>
<tr>
<td>Rubidium (Rb)</td>
<td>0.040-3.5</td>
</tr>
<tr>
<td>Silicon (Si)</td>
<td>0.05-24</td>
</tr>
<tr>
<td>Strontium (Sr)</td>
<td>0.04-0.35</td>
</tr>
<tr>
<td>Sulfur (S)</td>
<td>0.7-26</td>
</tr>
<tr>
<td>Vanadium (V)</td>
<td>0-0.013</td>
</tr>
<tr>
<td>Zirconium</td>
<td>0.05-0.08</td>
</tr>
</tbody>
</table>
3.4. Aroma compounds, taste-building compounds and polyphenols

The sugars are the key taste-building compounds. Usually, honey with a high fructose concentration (e.g. acacia) are sweeter compared to those with high glucose concentration (e.g. rape). The honey aroma is influenced by the quantity and type of acids and amino acids present. In the past decades extensive research on aroma compounds has been carried out and these findings led to identify more than 500 different volatile compounds in different types of honey. This variation in these aroma building compounds depend on its botanical origin. Honey flavour is an important quality for its application in food industry and also a selection criterion for the consumer’s choice. Polyphenols are another important group of compounds with respect to the appearance and the functional properties of honey. 56 to 500 mg/kg total polyphenols were found in different honey types (Al-Mamary et al., 2002; Gheldof and Engeseth, 2002). Polyphenols in honey are mainly flavonoids (e.g. quercetin, luteolin, kaempferol, apigenin, chrysin, galangin), phenolic acids and phenolic acid derivatives (Tomás-Barberán et al., 2001). These are compounds known to have antioxidant properties. The main polyphenols are the flavonoids, their content can vary between 60 and 460 μg/100 g of honey and was higher in samples produced during a dry season with high temperatures (Kenjeric et al., 2007).

3.5. Contaminants and toxic compounds

Like other natural food, honey also can be contaminated and the causative contaminants can be heavy metals, pesticides and antibiotics etc. (Bogdanov 2006). At present the problem due to antibiotic contamination seems to be under control. A few plants used by bees are identified to produce nectar having toxic substances. Pyrrolizidine and diterpenoids alkaloids are two core groups of toxin relevant in nectar. The plants belonging to the sub-family Rhododendron (family Ericaceae), e.g. Rhododendron ponticum contain toxic polyhydroxylated diterpenoids or cyclic hydrocarbons. Researchers have found that the pyrrolizidine alkaloids also present in different honey types and the intoxication by these substances is studied (Edgar et al., 2002). Reports on honey poisoning have been reported not often in the literature and the affected individuals were from the following regions: South Africa, Caucasus, New Zealand, Nepal, Australia, Turkey, Japan and some countries in North and South America. So far the observed indications of honey poisoning are unconsciousness, vomiting, stomach ache, delirium, headache, sight weakness and nausea. Generally the contaminant honey is not marketed.

3.6. Glycemic index and fructose

The dietary significance of carbohydrates is termed as glycemic index (GI). Carbohydrates with high and low GI induce a high and low blood glucose level respectively. There is a noteworthy negative correlation between GI and fructose content that may be due to the different fructose/glucose ratios of the honey varieties tested. Unifloral honeys have varying fructose content and fructose/glucose ratios (PersanoOddo and Piro 2004). Honeys with relatively high concentration of fructose have a lower GI than other honey types. There was not any significant correlation between GI and the other honey sugars. In one study, It was found that the GI values of four honeys found varied between 69 and 74 (Ischayek and Kern 2006), whereas in another one the value of a honey was found to be 35 but the botanical origin was unidentified (Kreider et al., 2000). The low GI honeys might be a valuable substitute to high GI sweeteners (Jenkins et al., 2002). A new term which is the glycemic load, is introduced to take into consideration the quantity of ingested food. It is calculated by the following formula: the (GI value X the carbohydrate content in a given portion)/100 and interpretation of the data are as follows: lower than 10 are characterized as low, between 10 and 20 are intermediate and above 20 are categorized as high. The food with a low GI should provide benefits with respect to diabetes and to the reduction of coronary heart disease. The consumption of low GI honey (e.g. acacia honey) might have beneficial physiological effects on not only healthy people but also diabetes patients. A consumption of 50 g honey of unspecified type by healthy people and diabetes patients led to slighter increases of blood insulin and glucose compared to the ingesting of the same amounts of glucose or of a sugar mixture similar to honey (Al-Khalidi et al., 1980). It was shown that ingesting of honey has a promising effect on diabetes patients, triggering a significant decline in plasma glucose (Al-Waili 2004). Honey was well tolerated by diabetes type-2 patients (Katsilambros et al., 1988). According to studies, long term intake of food with a high GI is a major risk factor for type-2 diabetes patients (Liu et al., 2001) but the GI concept for the general population is still an object of debates (Pi-Sunyer 2002). Fructose is the chief sugar in most honey varieties (Table 1). Honey also help in faster recovery of humans from ethanol intoxication (Onyesom 2005).

4. Sensitivity of honey

4.1. Sensitivity to heat

The loss of antibacterial activity of honey on exposure to heat was of complete loss of inhibition by 17% honey after exposure of 50% honey to 56°C, 80°C and 100°C for 30, 10 and 5 min respectively.

4.2. Sensitivity to light

Honey lost its bacterial inhibiting ability (tested in a 17% solution) after exposing a thin film to sunlight. It is established that exposure of honey in a layer of 1-2 mm thick to sunlight for 15 min was led to complete loss of non-osmotic activity.

4.3. Storage effect

Enzymatic activity, microbial quality, antimicrobial
The zone diameter of inhibition (ZDI) of different honey samples (5%-20%) has been determined against *E. coli* O157: H7 (12 mm -24 mm) and *S. typhimurium* (0 mm -20 mm). The ZDIs of Nilgiris honey was found to be (20-21) mm, (15-16) mm and (13-14) mm for *S. aureus*, *P. aeruginosa* and *E. coli*, respectively (Rajeswari et al., 2010). Agbagwa and Frank-Peterside (2010), examined different honey samples: Western Nigerian honey, Southern Nigerian honey, Eastern Nigerian honey and Northern Nigerian honey, and compared their abilities to inhibit the growth of *S. aureus*, *P. aeruginosa*, *E. coli* and *Proteus mirabilis* with an average of ZDIs (5.3-11.6) mm, (1.4-15.4) mm, (4.4-13.5) mm and (9.1-17) mm, respectively, and with honey concentrations of 80%-100%. The extracts of raw and processed honey showed ZDI (6.94-37.94) mm, against gram-positive bacteria viz., *S. aureus*, *Bacillus subtilis*, *Bacillus cereus*, as well as Gram negative bacteria like *E. coli*, *P. aeruginosa* and *S. entericaserovar*, *Typhi* (Chauhan ET AL., 2010).

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$_2$O$_2$) and non-peroxide components, i.e., the presence of phytochemical components like methylglyoxal (MGO) (Mavic et al., 2008). 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. Most types of honey generate H$_2$O$_2$ when diluted, because of the activation of the enzyme glucose oxidase that oxidizes glucose to gluconic acid and H$_2$O$_2$, which thus attributes the antimicrobial activity (Bang et al., 2003). But, in some cases, the peroxide activity in honey can be destroyed easily by heat or the presence of catalase. Besides H$_2$O$_2$, which is 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 (Simon et al., 2008). 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” (Simon et al., 2008). Several components are known to contribute the nonperoxide 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 (*L. scoparium*). Unlike manuka honey, the activity of ulmo honey is largely due to H$_2$O$_2$ production: 25% (v/v) solution of ulmo honey had no detectable antibacterial activity when tested in presence of catalase, while, at the same concentration the manuka honey retained its antibacterial activity in the presence of catalase (absence of H$_2$O$_2$). Neither type of activity is influenced by the sterilizing procedure of gamma-irradiation. Undiluted honey the acidity is a significant antibacterial factor. The antibacterial property of honey is also derived from the osmotic effect of its high sugar content and low moisture content, along with its acidic properties of gluconic acid and the antiseptic properties of its H$_2$O$_2$. A recent study examining the antimicrobial properties of honey in vitro found that H$_2$O$_2$, MGO and an antimicrobial peptide, bee defensin-1, are distinct mechanisms involved in the bactericidal activity of honey (Kwakman et al., 2010).

5.1.2. Antifungal effect

The synergistic action of starch on the antifungal activity of honey, a comparative method of adding honey with and without starch to culture media was used. *Candida albicans* has been used to determine the minimum inhibitory concentration (MIC) of five varieties of honey. The antifungal action of three single samples of South African honey (wabsbessie, bluegum and fynbos) against *Candida albicans* and found honey to inhibit on the growth of *C. albicans*, while the control, bluegum and fynbos honey produced only partial inhibition.

5.1.3. Antiviral effect

In addition to antibacterial and antifungal effects, honey has showed antiviral effect. Al-Waili (2004) investigated the effect of the topical application of honey on recurrent attacks of herpes lesions and con-
cluded that topical honey application was safe and effective in the management of the signs and symptoms of recurrent lesions from labial and genital herpes compared to acyclovir cream. Honey has also been reported to have inhibitory effects on rubella virus activity (Al-Waili et al., 2004).

5.2. Effect as antidiabetic agent

The prevalence of diabetes mellitus, estimated as 285 million people in 2010, is predicted to increase to 439 million people by the year 2030. The majority of this diabetic population will emerge from developing countries. Despite the availability of various classes of antidiabetic agents, diabetes mellitus remains a major cause of mortality and morbidity globally. As a result, there has been a considerable effort to search for more effective drugs. This has resulted in a renewed interest in research that investigates the health benefits of herbs and natural products including honey in the management of diabetes mellitus.

5.2.1. Antidiabetic effect of honey: Potential mechanisms of action based on the non-antioxidant constituents in honey

Considering that honey is reported to contain at least 181 substances (Gheldof et al., 2002), the exact mechanism of its antidiabetic effect is complex and therefore will necessitate detailed investigation (Erejuwa et al., 2010). Even though the mechanisms by which honey improves glycemic control and other diabetic profiles remain unclear, available evidence suggests that fructose in honey may modulate the hypoglycemic or antidiabetic effect of honey (Erejuwa et al., 2012). Certain varieties of honey have been reported to increase plasma concentrations of fructose in healthy humans. Similarly, evidence indicates that the fructose content of honey negatively correlates with glycemic index. Small amounts of fructose have been reported to reduce blood glucose through increased hepatic glucose uptake by activating glucokinase (Watford, 2002). The beneficial effect of fructose administration on glycemic control has also been documented in patients with type 2 diabetes mellitus. Evidence suggests that a number of oligosaccharides present in honey might play a role in the antidiabetic effect of honey. The oligosaccharides in honey may contribute to the antidiabetic effect of honey either via modulation of gut microbiota or through the systemic effects of oligosaccharides (Erejuwa et al., 2012).

5.2.2. Antidiabetic effect of honey: Potential mechanisms of action based on the free radical scavenging constituents and antioxidant effect of honey.

Compelling evidence implicates the role of oxidative stress in the pathogenesis and/or deterioration of glycemic control in diabetes mellitus. Increased glucose uptake in both skeletal muscle and adipose tissue enhances reactive oxygen species (ROS) generation and oxidative stress which in turn impairs glucose uptake and glycogen synthesis. Oxidative stress causes insulin resistance through impaired insulin signaling pathways such as interference with insulin receptor, insulin receptor substrate-1 and protein kinase B/Akt. Through its antioxidant effect honey might enhance insulin sensitivity in the liver and muscle thereby increase glucose uptake resulting in reduced hyperglycemia. A number of studies have shown that honey can scavenge free radicals (Deibert et al., 2010). So, honey supplementation may ameliorate oxidative stress in the pancreas, protect the pancreas against oxidative damage and thus enhance insulin secretion resulting in improved glycemic control. The antioxidant and free radical scavenging effects of honey may help to reduce the oxidative milieu and enhance antioxidant defenses in diabetes. The beneficial effects of antioxidants including honey in glycemic control have also been demonstrated (Lai 2008).

5.3. Effect as anticancer agent

Annually cancer is diagnosed in approximately 11 million people causing 7.6 million deaths worldwide. Cancer is a multistep process. It starts as an onset from a single transformed cell. Its genesis is characterized by the swift proliferation, invasion, and metastasis (Shishodia et al., 2003). The standard treatments against cancer are surgery, radiotherapy, and chemotherapy. These modalities are beset with serious side effects and costly too. These situations led to discovery of natural remedies and honey is proved to be one of the potential anticancer agents.

The phenolic contents of honey have been reported to have antileukemic activity against different types of leukemic cell lines (Abubakar et al., 2012). Its anticancer activity has been proved against various cancer cell lines and tissues, such as breasts (Fauzi et al., 2011), colorectal (Jaganathan and Mandal 2009), renal (Samarghandian et al., 2011), prostate, endometrial, cervical (Fauzi et al., 2011) and oral cancer (Ghashm et al., 2010). Honey potentiates the antitumor activity of chemotherapeutic drugs such as 5-fluorouracil and cyclophosphamide. Studies exhibiting anticancer effect of honey range from tissue cultures (Ghashm et al., 2010) and animal models to clinical trials. Polyphenols in honey are considered as one of the main factors responsible for the anticancer activity of honey (Abubakar et al., 2012).

5.3.1. Apoptotic activity

Honey induces apoptosis in various types of cancer cells via depolarization of mitochondrial membrane (Fauzi et al., 2011). Honey elevates caspase 3 activation level and poly (ADP-ribose) polymerase (PARP) cleavage in human colon cancer cell lines (Jaganathan and Mandal 2009) which is attributed to its high tryptophan and phenolic content. It also induces apoptosis by upregulating and modulating the expression of pro- and antiapoptotic proteins in colon cancer cell lines (Jaganathan and Mandal 2010). Honey generates ROS (reactive oxygen species) resulting in the activation of p53 and p53 in turn modulates the expression of pro- and antiapoptotic proteins like Bax and Bcl-2. Manuka honey exerts its apoptotic effect on cancer cells through the induction of the caspase-9 which in turn activates the caspase-3, the executor.
protein. Apoptosis induced by Manuka also involves induction of DNA fragmentation, activation of PARP, and loss of Bcl-2 expression. The apoptotic property of honey makes it a possible natural substance as an anticancer agent as many chemotherapeutics currently used are apoptosis inducers.

### 5.3.2. Antiproliferative activity

Honey and its several components (like flavonoids and phenolics) are reported to block the cell cycle of colon, glioma (Lee et al., 2003), and melanoma (Pichichero et al., 2010) cancer cell lines in G0/G1 phase. This inhibitory effect on tumor cell proliferation follows the downregulation of many cellular pathways via tyrosine cyclooxygenase, ornithine decarboxylase, and kinase (Lee et al., 2003). The results of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and the trypan blue exclusion assays have confirmed that anti-proliferative effect of honey is a dose- and time-dependent manner (Pichichero et al., 2010). Honey or its components mediate inhibition of cell growth due to its perturbation of cell cycle. Cell cycle is also regulated by p53 which is involved in tumor suppression. Honey is reported to be involved in modulation of p53 regulation.

### 5.3.3. Anti-Inflammatory and immunomodulatory activities

The literature shows that it reduces inflammation when applied in cell cultures, animal models, and clinical trials. Manuka, Pasture, Nigerian Jungle, and royal jelly honeys are found to increase IL-1β, IL-6, and TNF-α production. This immune modulatory and immune protective activity of honey is often linked to anticancer action. It has been shown that honey stimulates macrophages, T-cells, and B-cells to provoke antitumor effect (Attia et al., 2008). Sugars when ingested are slowly absorbed resulting in the formation of short chain fatty acid (SCFA) fermentation products (Kruse et al., 1999). It is a probable mechanism that the ingestion of honey may result in SCFA fermentation. Research has established that, either directly or indirectly, SCFA have immunomodulatory actions (Schley Field 2002). Thus, honey may stimulate the immune system via these fermentable sugars (Chepulis 2007). A sugar, nigerooligosaccharides (NOS), present in honey has been found to have immune potentiating activity (Muroasaki et al., 2002). Non sugar components of honey may also be responsible for immune modulation.

### 5.3.4. Antimutagenic activity

Mutagenicity, the ability to induce genetic mutation, is interlinked with carcinogenicity (Tsutui et al., 1997). Honey is shown to have a strong antimutagenic agent and hence has anticarcinogenic property (Saxena et al., 2012). The effect of honey on radiation (UV or γ) exposed *Escherichia coli* cells shows SOS response (SOS is an error prone repair pathway contributing to mutagenicity). A study was performed to knock out some important genes such as *umuC*, *recA*, and *umuD* involved in SOS mediated mutagenesis. These changes are significantly inhibited in the presence of honey confirming its strong antimutagenic effect.

### 5.4. Effect as weight management agent

With regard to obesity, several studies suggest that consuming honey may have a positive effect on regulating body weight (Chepulis and Starkey 2007), and Nemoseck et al. (2011), found significant evidence for this in an animal study in which honey-fed rats had significantly lower weight gain, adiposity, fat pad weight and total cholesterol, compared to sucrose-fed rats. This implies that honey could improve weight regulation and reduce blood-glucose level in humans, besides increasing the level of high-density lipoprotein cholesterol (HDL-C). Honey, which appears to confer high antioxidant activity and has a low glycaemic index, is postulated to reduce weight-gain in rats, compared to sucrose (Nemoseck et al., 2011). A research of Waili et al. (2008) showed that honey decreased total cholesterol and LDL-C in overweight healthy and overweight hyperlipidemic subjects. However, dietary fructose was increased from 3 to 20% of calories, at the expense of starch. Meanwhile, total cholesterol increased by 9%, and low-density lipoprotein (LDL-C) by 11% [139]. Another study performed by Chepulis and Starkey (Chepulis and Starkey 2008) demonstrated that weight gain was substantially reduced in honey-fed rats compared with those fed a sucrose-based diet. This agrees with the earlier work of Chepulis, which showed that honey reduced weight-gain in a short-term feeding, compared with sucrose (Chepulis and Starkey 2008).

### 5.5. Impact on infants

The application of honey in infant nutrition used to be a common recommendation during the last centuries and there are some interesting observations. Infants on a diet with honey had better blood formation and a higher weight gain than when a diet without honey was applied. Infants had a higher weight increase when fed by honey than by sucrose, and showed less throw up than the sucrose controls. When infants were fed on honey rather than on sucrose an increase of haemoglobin content, a better skin colour and no digestion problems were encountered. Infants on honey diet had a better weight increase and were less susceptible to diseases than infants fed normally or when given blood building agents. The positive effects of honey in infant diet are attributed to effects on the digestion process. One possible cause is the well-established effect of oligosaccharides on *B. bifidus*. When fed on a mixture of honey and milk infants showed a regularly steady weight gain and had an acidophlic microorganism flora rich in *B. bifidus*. Another experiment with honey and milk showed that infants were suffering less frequently from diarrhoea, and their blood contained more haemoglobin compared to those on a diet based on sucrose sweet-
ened milk. Honey fed infants had an improved calcium uptake, and lighter and thinner faeces (Bianchi 1977). However, there is a health concern for infants regarding the presence of Clostridium botulinum in honey.

5.6. Honey for gastrointestinal diseases

Any factors that may cause the digestive system to malfunction are likely to trigger gastroenteritis, and these factors may be divided into biological factors (bacterial, viral and parasite infections) and non-biological factors (drugs, chemicals, toxins secreted by bacteria, improperly prepared food, life styles etc.) Bacterial gastroenteritis has a high incidence rate worldwide. Bacterial gastrointestinal diseases are usually caused by, but not limited to, infection by Gram-negative bacilli e.g. Enterobacteriaceae, Campylobacter spp., Helicobacter spp. and related organisms, and Clostridium spp.

The use of honey for treating gastroenteritis, peptic ulcers or gastritis can be traced back to the ancient era. Honey has been used for the treatment of veterinary diarrhoea. Kandil et al. (1987) also reported that the number of ulcers caused by aspirin, a non-steroidal anti-inflammatory drug (NSAID), in 10 rats was significantly decreased in the group treated with floral honey (3 cf. 10), whereas it was less significantly decreased if treated with honey from sugar-fed bees (8 cf. 10) or increased in those given saline (15 cf. 10). Another research carried out a similar study, in which the healing rate of honey against ulcers caused by another non-steroidal anti-inflammatory drug, indomethacin, in the rats was reported to be 70% (Ali 1995). The same author also reported that honey prevented ulceration from being caused by indomethacin (Ali et al., 1990). A group of researchers reported that mice infected with E. coli O157:H7 or S. typhimurium had a lower mortality in the group injected with 7 month old Egyptian clover honey than in the control group (E. coli: 0% cf. 86.6%; S. typhimurium: 40% cf. 93.3%), whereas the reduction in the mortality was less significant in the honey being stored over a long term. A clinical trial in humans with a relatively large sample size was reported and in this study 169 infants and children admitted into hospital suffering from gastroenteritis were assigned into two groups (in each group there were 18 patients with bacterial diarrhoea). One group was treated with honey whilst the other was treated with the standard oral rehydration therapy (ORT; a 2% solution of glucose and electrolyte). The treatment with honey solution revealed a statistically significant reduction in the duration of bacterial diarrhoea (58 hours cf. 93 hours), and gave no increase in the duration of non-bacterial diarrhoea. In another clinical trial (Salem 1981), 45 patients with dyspepsia were given no treatment other than 30 ml of honey solution before meals three times daily. After the treatment the number of patients passing blood into faeces declined from 37 to 4, the number of patients with dyspepsia from 41 to 8, the number of patients with gastritis or duodenitis from 24 to 15, and the number of patients with duodenal ulcer from 7 to 2.

Another important gastrointestinal pathogen is Helicobacter pylori (H. pylori) and it colonizes 50% of the world’s population (Kusters et al., 2006). H. pylori infection consequences can be listed as follows: gastroduodenal ulcer disease, chronic gastritis, and gastric adenocarcinoma. It has traditionally been confirmed that successful eradication of H. pylori can reduce the recurrence rate of duodenal ulcer, early gastric cancer, and meta chronic carcinoma (Kato and Asaka 2012). In an in vitro assay, 8 commercial honey brands sold in Muscat, Oman, were tested for anti-H. pylori activity by asurface diffusion method and in combination with amoxicillin or clarithromycin. The results demonstrated that all of them had anti-H. pylori activity, but no synergy was observed, either with honey and clarithromycin or honey and amoxicillin (Nzeako and Al-Namaani 2006). These data suggest that a triple regimen with these honeys could help to eliminate the bacteria. Recently, in an effort to find the active compounds of honey, two studies were performed. In the first one, 3 honeys from different regions of South Africa were tested for anti-H. pylori activity. “Pure Honey” presented the minimal inhibitory effect (73.3%) at 750 mL/L, so it was extracted with different organic solvents (n-hexane, diethyl ether, chloroform or ethyl acetate). All extracts demonstrated anti-H. pylori activity at concentrations ≥10%, but the chloroform extract had the lowest MIC95 value, ranging from 0.156-500 mL/L, depending on the strain (Manyi-Loh et al., 2010). This suggests that all extracts could contain compounds that are inhibitory for the bacteria. In the second work, a bioguided fractionation of a honey extract from Golden Crest Honey was undertaken. The highest antibacterial activity was exhibited by fraction GCF3, with an MIC = 5 mg/mL (Manyi-Loh et al., 2012). This value is very high compared to commercial antibiotics (for amoxicillin, the MIC = 0.015 to 0.12 μg/mL for ATCC 43504, according to Clinical and Laboratory Standards Institute guidelines).

6. Effect of honey on probiotics

According to the Food and Agriculture Organization and the World Health Organization (FAO 2001), probiotics are “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”. Honey has been reported to reveal a potential prebiotic activity (Sanz et al., 2005; Rosendale et al., 2008) and this is thought to be due to oligosaccharides in the honey. Several researchers have shown that honey may reveal positive effects on the normal flora, although some of the results may not always agree with others due to several experimental factors such as the floral source of the tested honey and the microbial flora examined. Ezz El-Arab et al. demonstrated that the colon bifidobacteria and lactobacilli counts in male Swiss albino mice were markedly increased in the group receiving food supplemented with a monofloral (cotton) honey even when the mice had administered ochratoxin A (10 ng/kg by weight/day) or aflatoxins (1 μg/kg by weight/day), although the concentration of the honey in the diet was not clearly noted (Ezz El-Arab et al., 2006). An-
other study compared the stimulative effect of 5% honey on the growth of intestinal bifidobacteria with fructooligosaccharide (FOS), galactooligosaccharide (GOS) and inulin, and found them to be equivalently effective (Kajiwara et al., 2002). Shamala et al. (2000) also noted that Lactobacillus acidophilus and L. plantarum had higher viable counts in a medium with a diluted honey (equivalent to 1% sugar concentration; floral source unknown) than in a medium with sucrose (1%) or a mixture of glucose (0.5%) and lactose (0.5%). An in vivo study conducted in the same study, also showed that viable counts of lactic acid bacteria from both small and large intestines of rats fed with honey were markedly higher than those from rats fed with sucrose. On the other hand, Varga reported that none of the 1%, 3% and 5% (w/v) acacia honeys added in yoghurt had stimulatory or inhibitory effect in the yoghurt (Varga 2006). However, so far there is no report showing that honey is detrimental to the normal flora, perhaps due in part to the antibacterial activity of the reported honey not being as significant as that of manuka honey.

7. Conclusion

Due to variation of botanical origin honey differs in appearance, sensory perception and composition. It contains mainly carbohydrates. The glycemic index of honey varies from 32 to 87, depending on botanical origin and on fructose content. The main nutrition- and health relevant components are the carbohydrates, which make it an excellent energy source especially for children and sportsmen. Besides its main components, the carbohydrates fructose and glucose, honey contains also a great number of other constituents in small and trace amounts, producing numerous nutritional and biological effects: antimicrobial, antioxidant, antiviral, antiparasitic, antiinflammatory, antimutagenic, anticancer and immunosuppressive activities. Microbial resistance to honey has never been reported and so makes it a very promising alternative therapeutic. Manuka honey has been widely researched and its antibacterial potential is renowned worldwide. The potency of honeys, such as Tualang honey, against microorganisms suggests its potential to be used as an alternative therapeutic agent in certain medical conditions, particularly wound infection. Many studies reported that honeys other than the commercially available antibacterial honeys (e.g., manuka honey) can have equivalent antibacterial activity against bacterial pathogens. The growth of bacterial species that cause gastric infections, such as S. typhi, S. flexneri and E. coli, are inhibited by Tualang honey at the low concentrations. The Tualang honey has been reported to be effective against E. coli, S. typhi and S. pyogenes, and thus, when taken orally in its pure undiluted form, this honey may help speed up recovery from such infections. Even manuka honey also reported to be a potential therapeutic for gastrointestinal disorders. Honey is effective when used as a substitute for glucose in oral rehydration and its antibacterial activity shortened the duration of bacterial diarrhoea. Currently, the emerging antimicrobial resistance trends in human wound bacterial pathogens are a serious challenge. Thus, honey with effective antimicrobial properties against antibiotic-resistant organisms such as MRSA and MDR P. aeruginosa, Acinetobacter spp. and members of the family Enterobacteriaceae, which have been associated with infections of burn wounds and in nosocomial infections, is much anticipated.

Overall, the unpredictable antibacterial activity of non-standardized honey may hamper its introduction as an antimicrobial agent due to variation in the in vitro antibacterial activity of various honeys. At present a number of honeys are sold with standardized levels of antibacterial activity, of which the best known is manuka (Leptospermum) honey as well as Tualang (Koombassi excelsa) honey. The medical-grade honey (Revamil, medihoney), which has the potential to be a topical antibacterial prophylaxis because of its broad-spectrum bactericidal activity, or to be a treatment for topical infections caused by antibiotic-resistant as well as antibiotic-sensitive bacteria, should be considered for therapeutic use. Moreover, mountain, manuka, capsillano and eco-honeys have exhibited inhibitory activity against H. pylori isolates at concentration 10% (w/v), demonstrating that locally produced honeys possess excellent antibacterial activity comparable to the commercial honeys. Therefore it is necessary to study other locally produced but yet untested honeys for their antimicrobial activities.

Additionally, the unexpected tolerance of probiotics to the antibacterial activity of honey (e.g. manuka honey) may also help improve many medical conditions as honey could be used therapeutically without disturbing their growth. This may be helped by the prebiotic action of honey on probiotics. It was found that probiotics are not only relatively resistant to the antibacterial activity of the manuka honey than are enteropathogens, but also their growth is stimulated by the honey compared with the control group in a plain medium. This suggests the possibility that honey may stimulate the ability of probiotics to compete with pathogens. In addition to that many therapeutic properties like gastrointestinal disorders, cardiovascular problems, antidiabetic properties, anticancer properties and so on, overlap with honey. Based on these facts, it can be hypothesized that a conjugated therapeutic product of honey and probiotics can perform faster in improving a medical condition than only honey.

Conflict of Interest:

We declare that we have no conflict of interest

References


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