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REVIEW ARTICLE

Towards a better understanding of the therapeutic applications and corresponding mechanisms of action of honey

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Abstract Honey is a bee-derived supersaturated solution composed of complex contents mainly glucose, fructose, amino acids, vitamins, and minerals. Composition of honey may vary due to the difference in nectar, season, geography, and storage condition. Honey has been used since times immemorial in folk medicine and has recently been rediscovered as an excellent therapeutic agent. In the past, honey was used for a variety of ailments without knowing the scientific background and active ingredients of honey. Today, honey has been scientifically proven for its antioxidant, regulation of glycemic response, antitumor, antimicrobial, anti-inflammatory, and cardiovascular potentiating agent. It can be used as a wound dressing and healing substance. Honey is different in color, flavor, sensory perception, and medical response. Apart from highlighting the nutritional facts of honey, we collected the finding of the published literature to know the mechanism of action of honey in different diseases. This review covers the composition, physiochemical characteristics, and some medical uses.

Keywords Honey · Medicine · Composition

Introduction

Recently, there has been increasing interest among the consumer, food industry, and researchers in functional foods. The previous concept of "adequate nutrition" consisting of a balanced amount of nutrients (protein, carbohydrate, lipids, minerals, and vitamins) has now been replaced by "optimal nutrition" which include, in addition to the above concept, the potential of the food to promote health and general wellbeing and reduce the risk factors of certain diseases (Viuda-Martos et al. 2008). This is the reason that the functional food is also known as therapeutic food, nutraceuticals, superfoods, designed food, or medicinal food (Nagai and Inoue 2004). The market for functional foods is increasing at fasting speed all over the world. A functional food may be natural or artificial by eliminating or modifying some of the basic components. Some of the important functional foods are omega-3 fatty acids, vitamins, prebiotics, probiotics, synbiotics, fiber, phytochemicals, bioactive peptides, and others (Viuda-Martos et al. 2008). Among the foods fulfilling the characteristics of functional food include honey, propolis, and royal jelly.

Honey is sweet and viscous syrup produced by the honeybee (*Apis mellifera*). Honey is probably the first natural sweetener ever discovered in human history. Currently, honey is used as one of the most nutritious food supplements and a medicinal agent, ranking it as a potential nutraceutical compound all over the world (Cortes et al. 2011). By definition, honey is a viscid, aromatic liquid obtained from plant nectars, collected by the honeybees, composed of different complex substances such as sugars, amino acids, enzymes, minerals,

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and vitamins with multiple beneficial health benefits. The flavor, composition, and other characteristics vary with floral nectars, regional and climatic changes (Umesh Hebbar and Rastogi 2008). Honey could be classified as floral when derived from the nectar of the flowering plants or non-floral if obtained from the secretions of plants or mixed when both types are involved (Manyi-Loh et al. 2001; Plutowska et al. 2011). Due to this categorization, consequently, the chemical composition of honey differs in physiological characteristics such as acidity, color, electrical conductivity, proline content, pH, ash, etc. (Manyi-Loh et al. 2001).

Honey is a food having moisture ranges from 16 to 18%. Due to low water and high osmotic contents, honey is safe from microbial contamination and can be stored for a reasonable period at room temperature without the need of any preservative. However, due the presence of osmophilic yeast, fermentation may occur (Bhandari et al. 1999). The relationship between human and honey exists since Stone Age as the only available natural sweetener. Man risked life to climb and fought the bees to reach honey (Bogdanov et al. 2008). The initial written proof on the discussion of honey as drug and ointment dates back from 2100 to 2000 BC. The aim of the present review is to discuss the composition and some essential nutrients of honey and the important medical uses.

Composition

Honey is a complex mixture of carbohydrates, water, and other minor components (Garcia et al. 1986; Cortes et al. 2011). The composition of honey is influenced by the regional and climatic condition and type of flower as unifloral and polyfloral (Cortes et al. 2011). By composition, honey is composed of 82.4% carbohydrates, 17.1% water, and 0.5% amino acids; vitamins; minerals; and other minor compounds (Garcia et al. 1986; Montenegro and Fredes 2008; Cortes et al. 2011). Different heavy metals have been isolated from honey which can be related to the geographical and botanical origin (Cortes et al. 2011).

Alvarez-Suarez et al. (2010) reviewed that honey is a supersaturated solution of approximately 181 substances. Before the production of industrial sugar, honey was considered as the major carbohydrate sweetener (Bogdanov et al. 2008; Alvarez-Suarez et al. 2010). In many human societies, honey is being used as a nutrient as well as a medicine (Bogdanov et al. 2008). The specific color, aroma, flavor, and texture depend upon the type of flower, plants, and honeydew. Other factors include the physiological behavior of bee and their foraging habits, climatic conditions, and post-collection processing. Honey is produced almost all over the world. The honey production is approximately 1.2 million tons annually, and it is less than 1% of the total sugar produced in the world (Bogdanov et al. 2008). The consumption of honey varies from country to country. Honey consumption in China and Argentina is 0.1 to 0.2 kg per capita. In the European union, the honey consumption is 0.3–1.8 kg per capita annually.

According to a report, about 600 compounds have been isolated from honey. Generally, the compounds in honey may be derived directly from the plant source, conversion of the plant compounds by the metabolism of the bee, or from storage, heating, handling, and environmental and microbial contamination (Manyi-Loh et al. 2001). The chemical families to which the isolated chemicals belong include hydrocarbon, furan and pyran, aldehyde, benzene and its derivatives, norisoprenoids, alcohol, ketone, terpenes, sulfur, acid, ester, and cyclic compounds. The volatile compounds in honey vary due to the storage condition and the temperature at which the honey has been stored. In addition, the floral composition and geographical location greatly influence the composition of honey. The changes in the organic compounds of honey during storage could be due to two reasons: during storage, the heat labile compounds may be destroyed and volatile compounds are produced by the non-enzymatic action (Manyi-Loh et al. 2001).

Honey is nutritious syrup composed of a variety of contents. A brief discussion of some of the important compounds is presented here.

Carbohydrate

Because of its high nutritional quality and unique flavor, honey has become the most increasingly acceptable sweetener by consumers as a substitute of other sweeteners (Cortes et al. 2011). The major sugars in honey are glucose, fructose, and monosaccharide in addition to 25 different kinds of oligosaccharides (Siddiqui 1970; Doner 1977). The principle oligosaccharides include maltose, turnose, sucrose, trehalose, panose, palatinose, 6-kestose, and 1-kestose (Bogdanov et al. 2008). Honey should not be considered as a complete food according to human standard rather as a food supplement. The fructose and glucose of honey can be quickly utilized as an instant energy source soon after digestion by the human body. A daily dose of 20 g honey can fulfill about 3% requirement of energy.

Protein, enzymes, and amino acids

Honey contains approximately 0.25% protein, mainly consisting of enzymes and amino acids. The major enzymes of honey are diastase, invertase, and glucose oxidase. The intake of honey for the human consumption as a protein source is not sufficient as the recommended daily requirement (Bogdanov et al. 2008).

Vitamins, minerals, and other compounds

Honey contains varying amounts of minerals and trace elements like sodium, calcium, potassium, magnesium, phosphorous, zinc, copper, iron, manganese, chromium, and selenium (Bogdanov et al. 2008). The important vitamins include phyllochinon, thiamine, riboflavin, pyridoxine, niacin, pantothenic acid, and ascorbic acid.

Polyphenols

The phenolic compounds separated from honey can be grouped as flavonoles (fisetin, quercetin, galangin, myricetin, kaempferol), flavanones (hesperidin pinobanksin, naringin, pinocembrin naringenin), flavones (luteolin genkwanin, apigenin, wogonin, tricetin, acacetin), phenolic acid (gallic acid, p-hydroxybenzoic acid, caffeic acid, vanillic acid, p-coumaric acid, syringic acid, cinnamic acid, ferulic acid, chlorogenic acid, rosmarinic acid, and derivatives), coumarins (coumarin), and tannins (ellagic acid) as documented by Abubakar et al. (2012).

Flavoring agents

The aroma profile is one of the most important characteristics for the evaluation of authenticity and organoleptic quality of a food product. From the consumer point of view, the flavor of honey is the most important criterion. The aroma of the honey most depends upon the volatile and other semi-volatile organic compounds (Jerković et al. 2006). Depending upon the botanical origin, the taste, flavor, and color may vary. Sugar is the major flavoring agent. The aroma mainly depends on the quantity and the type of amino acids. The aroma of the honey has been associated with different kinds of phenolic compounds isolated from different types of honey (Bogdanov et al. 2007). Polyphenols present in honey are about 56–500 mg/kg depending upon the type of honey (Al-mamary et al. 2002). The important phenols in honey are quercetin, chrysin, galangin, luteolin, and apigenin (Tomas-Barberan et al. 2001). Generally, mild colored honey is also mild in flavor while dark color represents a more pronounced flavor (Castro-Várquez et al. 2003; Kaskonienė et al. 2008).

Contamination of honey

Honey is contaminated by environment, heavy metals, antibiotic, and pesticides (Bogdanov 2006). Some of the plants used by bees contain poisonous substances such as diterpenoids and pyrrazolidine (Edgar et al. 2002; Bogdanov et al. 2008). Common clinical signs of honey poisoning include vomiting, nausea, stomach pain, headache, unconsciousness, and blurred eye sight.

Honey has a variety of nutritional and health benefits. Some of the pharmacological properties of honey in different disease conditions along with the possible mechanism of action are elucidated below.

Oral use of honey

Glycemic regulation

The glycemic regulation of honey is the most important characteristics which is one of the essential mechanisms through which the organisms maintain their internal milieu. For many decades, there have been increasing interest in controlling blood glucose disorders and controversial results have been documented (Cortes et al. 2011). Some authors have considered honey as useless due to large contents of sugar (White 1978). Others have reported encouraging results by posing honey as a potential nutritional supplement to cure pathologies of glucose homeostasis (Al-Waili 2004; Ahmad et al. 2008).

The exact mechanism through which the honey acts to produce hypoglycemic action is not fully understood. Many such contents in honey as zinc, copper and antioxidants, fructose, and glucose may probably play an important role (Fredes and Montenegro 2006; Montenegro and Fredes 2008; Yaghoobi et al. 2013). It has been suggested that the slow absorption of saccharides in the intestine is triggered by the presence of glycemic carbohydrates in honey (Vosloo 2005; Ahmad et al. 2008). The fermentable and non-fermentable carbohydrate components present in the natural honey may modulate the intermediary metabolism in the intestines (Shamala et al. 2000; Chow 2002; Ahmad et al. 2008). According to another view, the sugar of honey is poorly absorbed from the intestinal lumen and so is less likely to be available in the blood stream (Agrawal et al. 2007). The hypoglycemic effect of honey has also been linked to the insulin-like effect of hydrogen peroxide present in honey (Hayes and Lockwood 1987). The insulin-like activity of honey has been associated with some other compounds added by the hypopharyngeal glands of honeybee. It has also been postulated that the glycemic effect is due to the decreasing level of prostaglandin (one of the main physiological inhibitors of insulin) and nitric oxide (stimulates the increase of insulin secretion) as suggested by Yaghoobi et al. (2013), Cheng et al. (2003), and Smukler et al. (2002). Some compounds such as chrysin and chrysin-derived substances could act as hypoglycemic agents in diabetes cases (Shin et al. 1999). Other compounds such as flavonol and myricetin have been linked to stimulation of lipogenesis and glucose transport in adipose tissue (Ong and Khoo 1996). In addition, some other substances such as kaempferol, isorhamnetin-3-O-beta-D-glucoside, apigenin, quercetin, and kaempferol 3-neohesperidoside have hypoglycemic and insulinomimetic effect (Fang et al. 2008; Viuda-Martos et al. 2008; Montenegro et al. 2009).

Antimicrobial effect

Honey has been used as an antiseptic agent since the time of Aristotle (Molan 2001). It has been suggested that the wound-healing effect of honey is due to its antibacterial activity. Honey has been known to have antimicrobial (Molan 1992, 1997; Bogdanov et al. 1997), antiviral, and antiparasitic effects (Kilicoglu et al. 2006). Antibacterial effect against *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Streptococcus pneumoniae* type β, *Staphylococcus aureus*, and *Vibrio cholerae* and antifungal activity against *Candida albicans* (Montenegro et al. 2009) have been documented.

The major effect of honey against bacteria is due to the low quantity of water which inhibits the growth of bacteria. In addition, glucose oxidase and hydrogen peroxide are also involved in the antibacterial activity (White et al. 1963). Furthermore, chemical compounds such as aromatic acids, phenolics, and flavonoids and low pH are responsible for antibacterial activity (Molan and Russell 1988; Weston et al. 1999; Cushnie and Lamb 2005). The peroxide activity however is destroyed by factors such as heat, light, and storage (Bogdanov 1997) which determine the antibacterial activity of honey. In addition, Cortes et al. (2011) summarized several factors that serve the function of the antibacterial action of honey including hydrogen peroxide, resulting from the glucose and oxygen in the presence of hydrogen peroxide, the high sugar contents producing high osmotic effect, the presence of diverse organic acids such as gluconic acid, and the non-peroxidic substances like polyphenols. These compounds vary from honey to honey, depending upon plants from which the bees collect the nectar (Cooper 2007). The antibacterial activity of honey may also be due to its high sugar content which increases the osmotic pressure and ultimately destroys the pathogens. Even under dilute conditions of honey with water, it showed an inhibitory effect against many bacteria during wound infection (Simon et al. 2009). Recently, Halstead et al. (2016) found the antimicrobial characteristics of Surgihoney by preventing the biofilm and concluded that it is a superior form of the medical honey.

The antiviral effect of honey has been documented in adult patients in herpetic lesions and pain management in genital and labile herpes (Al-Waili 2004). In another study, it was reported that topical application of honey is superior to acyclovir in itchiness (Al-Waili 2004). Honey has also been used in zoster patients with the hope to prevent secondary bacterial infection of the skin (Simon et al. 2009).

In a report, the antibacterial effect of honey has been attributed probably to the presence of high osmotic pressure, hydrogen peroxide, non-peroxide factors (phytochemicals), and acidity (pH), in addition to low protein content, bee defensin-1, low redox potential, viscosity, and increased phagocytic activity (Arvanitoyannis et al. 2005; Kwakman et al. 2010). The very high viscosity and low water content contribute to the antibacterial effect (Halawani and Shohayeb 2011). In another report, the antibacterial effect of honey was associated with the presence of gluconic acid as the most prevalent acid, which is produced by the oxidase activity of glucose in the presence of water and oxygen (French et al. 2005). The low pH of honey mainly due to the presence of organic acids such as hexadecanoic acid, formic, propionic, gluconic, acetic, which inhibit the growth of the bacteria (Osmojasola 2002). The antibacterial activity of honey has largely been attributed to hydrogen peroxide. This compound is released slowly without any ill effect on tissue and produce hydroxyl- and superoxide-free radicals, which act against the microbes (Olaitan et al. 2007). The antibacterial activity of honey may depend upon the concentration of hydrogen peroxide since its amount can be destroyed by heat and light or degraded by the action of ascorbic acid, catalase, and metal ion. In such a circumstance, the antibacterial activity may be lesser or eliminated (Olaitan et al. 2007). Some honey can retain the antibacterial activity, even in the presence of catalase, light, and heating, and are commonly known as non-peroxide honey. A special honey known as Monuka honey has been known for its antibacterial activity to prevent methicillin-resistant *S. aureus* (MRSA) strains (Russell et al. 1990). This antibacterial activity originates not from the hydrogen peroxide but due to the presence of dicarbonyl compound methylglyoxal, a highly cytotoxic metabolite. Furthermore, Monuka honey was useful in the clinical cases of dental plaque, dermatophytes, and gingivitis (Brady et al. 1997).

Pure honey has antibacterial activities against Shigella and Salmonella species, enteropathogenic *E. coli*, and *Helicobacter pylori* as reviewed by Alvarez-Suarez et al. (2010). Critchfield et al. (1996) reported that chrysin, apigenin, and acacetin inhibited the activation of HIV-1 probably through the inhibition of viral transcription. Other flavonoids such as quercetin and rutin exhibited antiviral activities against HSV, poliovirus, syncytial virus, and sindbis virus (Selway 1986; Middleton and Chithan 1993). The proposed mechanism of honey for the antiviral effect is due to inhibition of viral polymerase and the binding of viral capsid proteins and viral nucleic acid (Selway 1986).

Antioxidant activity

Reactive oxygen species (ROS) are produced during the enzymatic reaction in the cell. These ROS are normally neutralized by the endogenous antioxidant defense system; however, if the production is larger than the internal capacity, then oxidative stress occurs. Scientists are more interested to explore natural sources to prevent or reduce the impact of oxidative stress on cell (Chand et al. 2016; Naz et al. 2016).

Clinical conditions such as diabetes, hyperlipidemia, and hypertension are associated with high production of ROS. Due to the sweet taste of honey, reluctant consumers may more readily consume it compared to plant-origin antioxidants. Several studies have reported that honey can reduce oxidative stress (Beretta et al. 2007a, b; van den Berg et al. 2008). Honey has been known to possess significant antioxidant activity due to the presence of catalase, ascorbic acid, oxidase, flavonoids, carotenoid derivatives, phenolic acids, organic acids, amino acids, and Maillard reaction products (Al-Mamary et al. 2002; Beretta et al. 2005). Some of the polyphenols of honey like caffeic acid phenethyl ester, quercetin, kaempferol, chrysin, pinobanksin, galangin, acacetin, pinocembrin, caffeic acid, and apigenin have been documented as powerful polyphenols (Jaganathan and Mandal 2009). The antioxidant activity of the phenol of honey has been correlated similar as 1 mM alpha-tocopherol (Al-Waili 2003); however, the antioxidant capacity of honey depends upon the plant origin.

In a study, honey consumed at the rate of 1.5 or 1.2 mg/kg body weight increased the body antioxidant activity such as vitamin C, β-carotene, uric acid, and glutathione reductase (Khalil and Sulaiman 2010). In a report, honey caused an increase in the antioxidant capacity in terms of blood vitamin C, carotene, uric acid, and glutathione reductase (Al-waili 2003). In a study, the protective effect of native honey was elucidated in the form of quenching cumoperoxyl radicals, lipophilic cumoxyl, and complete inhibition of cell membrane oxidation (Beretta et al. 2007a, b). These compounds exert their antioxidant effect through reduction or removal of ROS, thus reducing the incidence of pathologies associated with the damage produced by the free radicals (Beretta et al. 2007a, b). However, the exact mechanism through which honey acts against the free radicals is not fully understood. The most postulated theories in favor of the possible mechanism of action include hydrogen donation, free radical scavenging, inhibition of enzymatic action involving initiation reaction, interference with propagation reaction, metal chelating, and acting as a substrate for free radicals and ROS (Havsteen 2002; Middleton et al. 2000; Viuda-Martos et al. 2008). In addition, the phytochemicals have been associated with the antioxidant effect of honey (Bergman et al. 1983). It has been documented that the darker color of honey has more antioxidant potential.

The flavonoids are known to possess antioxidant effect and reportedly scavenge free radicals including superoxide, singlet oxygen, and lipid peroxy radicals (Husain et al. 1987; Robak and Gryglewski 1988; Kandaswani and Middleton 1994). A native honey showed protective peroxyl radicals induced by 1,1-diphenyl-2- picrylhydrazyl and hydrogen peroxide due to the phenolic acids and flavonoids (Beretta et al. 2007a, b). Thus, it is concluded that the phytochemicals present in honey may improve the antioxidant status given that the increasing intake of sweetener in the world, the substitution of honey as a sweetener, could result in an enhanced antioxidant defense (Al-Waili 2003).

Cardiovascular protective effect

Ischemic heart disease (IHD) is one of the most important causes of death and incurs more economic losses than any other diseases worldwide. Myocardial infarction (MI) and arrhythmias are serious manifestations of IHD. In management of such diseases, the drugs used have certain limitations; hence, there is a strong tendency towards the natural products with less adverse effects. Natural honey has been applied for medical purposes since ancient times. Yochum et al. (1994) documented that flavonoids are phenolic compounds known for their antioxidant effect by protecting low-density lipoprotein (LDL) and subsequently prevent coronary heart disease (CHD). Some of the important phenols like caffeic acid phenethyl ester (CAPE), quercetin, kaempferol, acacetin, and galangin in honey have promising pharmacological effect in cardiovascular diseases (Khalil and Sulaiman 2010). Quercetin, an important flavonoid, inhibited Ang II-induced hypertrophy in cultured rat aortic smooth muscle cells (RASMCs), reduced the blood pressure and endothelial dysfunction, and enhanced endothelium-dependent aortic vasodilation-induced acetylcholine (Khalil and Sulaiman 2010). In another study, quercetin decreased the risk of development of cardiovascular disease and delayed or reduced the severity of hypertension, cardiac hypertrophy, and vascular dysfunction (Carlstrom et al. 2007). Mode of delivery, however, is critical in delivering protective effect in cardiovascular diseases.

Acacetin, another flavone, is an anti-atrial fibrillation agent and delayed human atrial rectifier K^+ current, transient outward K^+ current, and prolonged action potential duration in atrial cells of the human heart (Gui-Rong et al. 2008). In a study on dogs, a dose of 5 mg/kg acacetin prolonged effective refractory period in atria and maintained QT interval (Khalil and Sulaiman 2010). Caffeic acid derived from propolis of honeybee hives may potentially reduce blood pressure and heart rate. Kaempferol, another phenol of honey, improved the relaxation of coronary artery rings in porcine in which contraction was induced by 9,11-dideoxy-9α, 11α-methanoepoxy prostaglandin F2α (Xu et al. 2006). In another study, kaempferol increased the antiapoptotic protein and Bcl-2 and decreased the proapoptotic protein and downregulated the expression of XBP-2, GRP78, IRE1-alpha, CHOP, endoplasmic reticulum (ER), stress proteins IRE1-alpha, ATF-6alpha, and phosphor-eIF-2alpha (Kim et al. 2008).

Galangin has antioxidative properties in the endothelial tissue and prevents heart disease through prevention of lipid peroxidation. In addition, it has also a protective effect on other antioxidants such as vitamin C, vitamin E, and flavonoids. In epidemiological studies, quercetin has been shown to have antioxidant flavonol, which can reduce the incidence of heart stroke and coronary heart disease (Randi et al. 2007). Regular flavonoid intake is linked with a reduced incidence of heart-associated diseases. During coronary heart failure, the effect of honey is associated with its antithrombotic, antioxidant, anti-ischemic, and vasorelaxant effects. The protective effect of honey in heart diseases is achieved through improving vasodilatation, decreasing the platelet adhering and clot formation, and preventing low-density lipoprotein cholesterol (Khalil and Sulaiman 2010). The ingestion of 75 g natural honey in comparison with the artificial honey (fructose and glucose) showed reduction in risk factors of cardiovascular factors such as insulin, C-reactive protein, cholesterol, triglyceride, and low-density lipoprotein and elevated high-density lipoprotein in honey consumption group (Al-waili 2004). It is pertinent to note that in the era of cardiovascular disease, honey has been used only in the experiments in animals focusing on honey's effect in reduction of the risk factors such as hyperlipidemia and production of free radicals (Chepulis 2007; Eteraf-Oskouei and Najafi 2013).

Topical applications of honey

Antitumor activity

The International Agency for Research on Cancer (IARC) reported that globally, 12.7 million people have been diagnosed with cancer (Abubakar et al. 2012). The conventional therapies including chemical agents and surgical interventions are not very successful to check the increased incidence of most cancers. Polyphenol of honey has chemically prevented the different stages of cancer including tumor initiation and promotion through inactivation of carcinogen, inhibition, cell cycle arrest, arresting apoptosis and differentiation, reduction of angiogenesis, antioxidation, or combination of these factors (Fresco et al., 2006).

Quercetin (3,3′,4′,5,7-penta-hydroxyflavone) has been demonstrated to inhibit HL-60 cells with the dose of 10 and 80 μM (Kang and Liang 1997). The antiproliferative effect of quercetin is associated with its inhibitory effect on membrane tyrosine protein kinase (TPK) or cytosolic protein kinase C (PKC) in HL-60 cells. Csokay et al. (1997) demonstrated that quercetin inhibited leukemia in human cell through the process of apoptosis (caspase activation), arresting the process of differentiation and cell cycle (G2/M) (Lee et al., 2006). Kaempferol and galangin (3,5,7-trihydroxyflavone) showed a dose-dependent growth inhibition effect on HL-60 cells with significant disruption in the cell cycle of the affected cells (Bestwick et al. 2007). A dose-dependent effect on HL-60 was reported by apigenin (40,5,7-trihydroxyflavone) through disruption of DNA fragmentation and a time- and dose-dependent increase in the release of cytochrome c elevation of caspases 3 and 9 (Wang et al. 1999). Apigenin was found to induce a caspase-dependent apoptosis; activation of caspases 3, 7, and 9; induction of mitochondrial injury; activation of c-jun-NH2-kinase (JNK); inactivation of Akt; and downregulation of Akt and Mcl-1, in cancerous cells.

The effect of acacetin was demonstrated to inhibit the growth of T cell leukemia Jurkat cell in humana in a dose-dependent manner with activation of caspases 3, 8, and 9; enhanced expression of cytochrome c; phosphor-FAF1, FADD, and Apaf-1; and increased activity of Bax and reduction in expression of Bcl-2 (Watanabe et al. 2012). Two important flavonoids, fisetin and wongonin, can prevent the anticancer properties of HL-60 cells in a dose-dependent fashion (Lee et al. 2002). Wogonin, apigenin, and chrysin can sensitize human T cell leukemia virus type 1, downregulate c-FLIP mRNA expression, and enhance TRAIL-R2 expression, which may further facilitate TRAIL-induced apoptotic death in cancer cells (Ding et al. 2012).

The antiproliferative effect of caffeic acid phenethyl ester (CAPE) was demonstrated in HL-60 cells through inhibition of DNA and RNA and protein synthesis (Chen et al. 2001). Chen et al. (2001) further confirmed the apoptotic effect of CAPE in human myeloid leukemic cell line (HL-60) in a dose- and time-dependent manner after treatment. In addition, changes such as inhibition of Bcl-2 and stimulation of Bax and cleavage of caspase 3 were reported (Chen et al. 2001). In another study, COPE induced mitochondria-mediated apoptosis in U937 cells and significant elevation of the cytochrome c in affected cells (Jin et al. 2008). Chrysin (5,7-dihydroxyflavone) is another naturally occurring flavonoid in honey, which has demonstrated anticancer effect by apoptosis in U937 cells and increased proteolytic cleavages of PLC-γ1 and DEVD-pNA (Woo et al. 2004).

Luteolin, another flavonoid, exhibited anticancer properties by cell shrinkage, appearance of apoptotic bodies, chromatin condensation, cytoplasmic blebbing, and appearance of DNA ladder pattern, disruption of mitochondrial membrane potential, release of cytochrome c in the treated cells (Ko et al. 2002; Cheng et al. 2005). Hesperidin, a honey flavone, exerts anticancer effects in wild-type p53-positive human upregulation of Bax protein expression and downregulation of Bcl-2 and XIAP during the treatment of NALM-6 cells.

Polyphenol such as carnosol, rosmarinic, and carnosic acid showed antileukemic activity and increased the antioxidant activity and phase II detoxifying enzymes by activation of genes (Valdés et al. 2012). Ellagic acid demonstrated dose-dependent cell growth inhibition and apoptosis by chromatin condensation, nuclear shrinkage, and nuclear fragmentation in HL-60 cells (Hagiwara et al. 2010).

Glucose and fructose of honey contains the antitumor and antimutagenic activities of honey by depressing Trp-p-1 (3-amino-1,4-dimethyl-5H-pyridol [4,3-b] indole) (Wang et al. 2002). Oral dose of honey induced a significant antimetastatic in mammary carcinoma in mice anaplastic colon adenocarcinoma (Orsolic et al. 2003). There is an increasing demand in novel anticancer agents with rising number of cases worldwide. Most of the therapeutic agents exert their action through apoptosis, cell cycle arrest, and inhibition of cell growth. Most of the phenolic compounds isolated from honey also use one of the same pathways for the induction of anticancer effect. However, further experiments are needed to elucidate the role of crude honey against leukemia by using cell line or animal models in clinical and epidemiological studies. Growing number of evidence has demonstrated the anticancer effect of honey. The full mechanism is though still needed to be understood; the anticancer effect of honey is largely related to its interference inducing apoptosis and anti-inflammatory, antiproliferative, and antimutagenic effect. Honey is also involved in stimulating the immune system. Further, some questions are still to be answered such as why sugar is carcinogenic, while honey is anticancer which is largely composed of sugars.

Anti-inflammatory effect

The anti-inflammatory effect of honey has been pointed out for the last 30 years. Blood thromboxane and PGF2α were reduced in response to ingestion of 70 g of honey (Al-Waili and Boni 2003). In addition, the anti-inflammatory effect of honey has also been observed in inflammatory bowel disease (Bilsel et al. 2002). The anti-inflammatory effect has been linked to the reduction of free radicals produced at the site of inflammation and antibacterial or direct anti-inflammatory effect. Honey has also remarkable ability to improve the immune system by promoting human peripheral blood B and T lymphocytes and neutrophils (Abuharfeil et al. 1999). In addition, tumor necrosis factor-alpha, interleukin-1β, and interleukin-6 have been found to be stimulated in monocytic cell culture when honey was consumed (Tonks et al. 2003). Moreover, honey supplementation enhanced antibody production in rats against thymus-dependent and independent stimulated antigen (Al-Waili and Haq 2004).

The inflammatory effect of honey has been observed in microscopic studies in animal models by a reduced number of white blood cells (Molan 1998). As a result of reduced inflammation, edema and exudates are prevented by honey, which subsequently decrease pain through reduction in the prostaglandin mediated by the inflammatory process (Simon et al. 2009). A wound causes the production of protease activity which can eliminate the healing process. The anti-inflammatory action of honey eliminates the process and promotes healing. In addition, the anti-inflammatory activities of honey are linked with the reduction of bacterial load, promoting debriding and ultimately preventing the inflammatory reaction (Simon et al. 2009).

The anti-inflammatory effect of honey has been linked with different flavonoids that inhibit the development of inflammation. One of the important flavonoids is galangin which is capable of inhibiting cyclooxygenase (COX) and lipo-oxygenase activity, reducing the expression of cyclooxygenase-2 (COX-2) and limiting the action of polygalacturonase (Viuda-Martos et al., 2008). Another compound of caffeic acid phenethyl ester (CAPE) showed the anti-inflammatory effect through inhibiting the production of arachidonic acid from the cell membrane causing suppression of cyclooxygenase-1 (COX-1) and inhibits COX-2 (Mirzoeva and Calder 1996). Chrysin, a flavonoid present in honey, exhibited anti-inflammatory effect by suppression of pro-inflammatory activities of COX-2 and inducible nitric oxide synthase (iNOS) (Woo et al. 2005).

Burns and wound healing

Empirical evidences have shown that honey has been used to treat wounds and burns since the time immemorial. Honey characteristically makes an ideal wound dressing, moisturizes injured tissue, soothes inflammation, and prevents microbial load and gauze sticking (Molan 2006). Emerging evidence suggested that honey interacts with the cellular interaction and promotes angiogenesis, granulation, and epithelialization; enhances phagocytosis; expresses tissue repair markers; stimulates lymphocytes; and triggers epithelial-mesenchymal transition in keratinocytes (Molan 2001; Al-Waili et al. 2011; Barui et al. 2011; Ranzato et al. 2012).

Due to the numerous properties, honey is an appropriate wound-healing agent probably due to the antimicrobial substances such as hydrogen peroxide released by peroxidase, an important enzyme produced by the bees into the nectar (Wijesinghe et al. 2009). The wound-healing characteristics of honey are also due to its antibacterial activity against Gram-positive bacteria such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci (Cooper et al. 2002). Honey also produces a physical barrier on the wound surface owing to its high viscosity which prevents bacterial penetration and colonization (Efem 1988). In addition, it provides a moist environment which prevents the tearing of newly formed tissue when the dressing is removed (Wijesinghe et al. 2009). Furthermore, due to the deodorizing characteristics, it controls the malodor of the wound infected with anaerobic bacteria (Molan 1999; Dunford et al. 2000).

Stewart (2002) reported that application of Medihoney eliminated the odor and reduced the pain and bleeding of an ulcer on the back of knee to ankle. In another study, Richards (2002) reported that a bilateral leg ulcer treated with Medihoney healed in a 6-month period. Several other studies also reported healing of wounds located in different regions of the leg with application of honey (Dunford et al. 2000; Alcaraz and Kelly 2000). In addition, Anoukoum et al. (1998) reported the healing of 14 cases of gangrene in the genital and perineum with an average healing time of 28.7 days. Mphande et al. (2007) reported that honey was more effective in comparison with sugar in promoting wound healing and reduction of bacterial contamination and pain during dressing changes and motion. Topical application of honey accelerated wound healing, reduced antibiotic uses, and eradicated bacterial infections in postoperative wound infection following cesarean section (Al-Waili 2005). Honey dressing is economically advantageous to the patients, reducing the hospital stay, surgical costs, and dressing materials.

The evidence of wound healing in animal models is more convincing since animals are free from bias of behavior in the healing process. The process of anti-inflammatory effect helps in the granulation and epithelialization in reducing pain and edema (Al-Waili et al. 2011). In addition, moist healing reduces the hypertrophic scarring and stimulates granulation, epithelialization, and granulation, which ultimately helps in speeding up the process of healing (Molan, 2006). By applying honey, the epithelial cells produce a certain type of growth factor such as tumor necrosis factor (Tonk et al. 2007). It has been documented that 5.8 kDa, a certain factor of honey, can trigger a stimulatory response in macrophages, which produce growth factor that affect epithelialization and fibroblast regeneration (Simon et al. 2009). Another mode of action of wound healing is processed through the increased production of nitric oxide and reduced prostaglandins (Al-Waili et al. 2011). It has also been suggested that the wound-healing effect is associated with the acidic nature of which reduce the pH at the site of the wound and off load oxygen from the hemoglobin into the capillaries. Reduction in protease activity in the wound is suppressed by the non-neutral pH of the honey (Simon et al. 2009). The protease activity in the wound is linked with slowing of the healing process by stopping the production of growth factor like fibronectin which is involved in the activation of fibroblasts and epithelial cell migration.

Honey in dermatology and skin care

Honey has been used as one of the oldest used remedies in skin care and management. Histological evidence has revealed that honey has been used for eye cosmetics, vaginal irrigation due to its antibacterial activity, and sweetening breath (Burlando and Cornara 2013). In addition, it has been used as a binder in a paste and vehicle in cream and lotions, skin moisturizer, lip softener, face mask, and hair dye (Cavallo et al. 2008). Honey has also been used to maintain wrinkles; in softening and cleaning cream for pimples; and in anti-age face mask with other ingredients like yogurt, lemon, avocado, and egg yolk (Oumeish 1999; Burlando and Cornara 2013). According to traditional Chinese medicine, honey has been used to remove discoloration, freckles, and scars and improve the general appearance of the skin (Oumeish 1999). In India and Pakistan, honey has been used for skin smoothing, spot removal, face protection, and the removal of freckles (Ahmad et al. 2008). Due to the antibacterial activity of honey (low pH, the release of hydrogen peroxide, low water content), it has been used as vaginal candidosis, superficial mycoses, athlete's foot, and ringworm (Molan 1992).

The dermatological characteristics of honey are mainly due to the presence of hydrogen peroxide and methylglyoxal. Honey is special for would dressing and is also useful in the treatment of dandruff, diaper dermatitis, pityriasis, tinea, seborrhea, hemorrhoids, psoriasis, and anal fissure (Burlando and Cornara 2013). In cosmetic formulations, honey acts as humectant, soothing, emollient, hair conditioning effects, retards wrinkle formation, keeps the skin juvenile, prevents pathogen infections, and regulates pH. Honey-based products include hydrating creams, after sun, lip ointments, cleansing milks, shampoos and conditioners, and tonic lotions. The mechanism of action is due to the antioxidant effect, induction of cytokines, and expression of matrix metalloproteinase and epithelial-mesenchymal transition (Burlando et al. 2013).

Rosacea is an incurable skin disease characterized by facial rash affecting about 3% of the global population (Fingleton et al. 2013). Some topical applications have been suggested to reduce the severity of the disease; however, they are mostly infective in prolonged use due to wide side effects (van Zuuren et al. 2011). The efficacy of kanuka honey in this condition was attributed to a wide range antibacterial effect and anti-inflammatory and healing of damaged skin (Leong et al. 2012). Holt (2015) suggested that New Zealand kanuka honey can effectively treat rosacea condition and reduce antibiotic resistance. Recently, Braithwaite et al. (2015) reported that the mixture of 90% medical-grade kanuka honey and 10% glycerine demonstrated clinical efficacy in randomized controlled trial.

Conclusion

Honey is one of the oldest natural products; however, its biological and medical benefits have not been fully assessed. This review has clearly demonstrated that honey is a low-cost remedy for a number of medical ailments with no side effects. There are many discrepancies in the published research regarding the effect of using honey in different conditions.

Factors such as species, type of nectar, geographical location, storage, and processing conditions may affect the outcome of the honey. More randomized trials are required comparing different kinds of honey to create a strong body of evidence to pinpoint recommendation for medical use. Despite the interesting evidence, the topic merits future research to specify the mechanisms of action. The interaction of different polyphenols in honey has yet to be fully understood. Further research trials are needed using cell lines, animals, and clinical and epidemiological studies. In addition, some precaution much be observed while using honey to avoid problems with people who suffer from bee allergy allergens.

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