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NATURAL HONEY AS A POTENTIAL NUTRACEUTICAL SOURCE (REVIEW)

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Abstract

Honey, the sweet natural substance produced by honeybees is currently considered one of the nature's most powerful products. Natural honey can be regarded as a nutraceutical product due to its nutritional benefits and therapeutic promises. In addition to this, the use of honey as food and medicine has been embraced by different civilizations, from ancient times to the present, transcending the barriers of cultural and religious beliefs. The aim of the present review was to highlight and summarize some of the numerous medicinal attributes of honey, apart from its nutritional profile, that can contribute to its framing as nutraceutical agent. In this regard, it was proved that honey can promote metabolic and cardiovascular benefits, oral and bone health, haematological beneficial effects, anticancer activity. Moreover, evidence has been found for the use of honey as an alternative cure in several skin disorders.

Key words*: honey, medicinal properties, nutraceutical product.*

INTRODUCTION

In recent years, nutraceuticals have represented a growing field of interest for scientific research, due to both nutritive and therapeutic potentials. The term "nutraceutical" was originally coined by Stephen De Felice in 1989 and it derived from "nutrition" (a nourishing food or food component) and "pharmaceutics" (a medical drug) (De Felice, 1995; Brower, 1998; Mannion, 1998; Maddi et al., 2007). According to De Felice, a nutraceutical was described as, "a food that provides medical or health benefits, including the prevention and/ or treatment of a disease". The original definition has been reformulated throughout time, a nutraceutical being designated to possess physiological benefits, that provide protection against several disorders (Kalra, 2003; Sarin, 2012; Golla, 2018).

Natural honey can be considered a nutraceutical agent due to the fact that besides its nutritional value, it is widely appreciated for its therapeutic properties (Chua et al., 2014).

Honey represents a significant source of sugars, with a high nutritive value. It also consists of a minor class of compounds, such as enzymes, amino acids, proteins, polyphenols, organic acids, vitamins and minerals (Alvarez-Suarez et al., 2010; Da Silva et al., 2016).

A plethora of research documented honey's beneficial roles for medicinal purposes, namely metabolic and cardiovascular benefits (Busserolles et al., 2002; Agrawal et al., 2007; Ahmad et al., 2008; Bahrami et al., 2009), bone and oral health (Molan, 2001; English et al., 2004; Farid, 2009; Zaid et al., 2012; Hajizadeh et al., 2018), haematological beneficial effects (Chepulis, 2007; Beloor et al., 2010; Abioja et al., 2013), anticancer activity (Fernandez-Cabezudo et al., 2013; Aliyu et al., 2013; Spilioti et al., 2014). In addition to this, honey has been widely used in the treatment of wounds and numerous skin pathologies (e.g., eczema, dermatitis, burns, ulcers) due to strong antimicrobial and anti-inflammatory activities (Song and Salcido, 2011; Mayer et al., 2014; Oguz et al., 2018; Lukanc et al., 2018).

The present review aimed to summarize the numerous attributes of honey as food and as medicine, highlighting the need for its framing in the field of nutraceuticals.

HONEY AND NUTRITION

The wide array of compounds present in honey enhances its nutritional profile and promotes its use as food.

From a nutritional point of view, honey is mainly composed of sugars and water (White

and Doner, 1980; Bogdanov et al., 2008; Bradbear, 2009; Solayman et al., 2016).

The monosaccharides (fructose and glucose) represent the majority of the sugars detected in honey (75%), while disaccharides, trisaccharides and oligosaccharides make up the remaining 10 to 15% (Bogdanov et al., 2008; Da Silva et al., 2016).

Fructose is the prevalent sugar in acacia honey (Persano Oddo and Piro, 2004; Escuredo et al., 2014), while other monofloral honeys, such as rape honey (*Brassica napus*) or dandelion honey (*Taraxacum officinale*) recorded higher concentrations of glucose (Crane, 1990; Persano-Oddo and Piro, 2004).

These findings indicate that honey can be considered a genuine source of energy due to its high content of sugars. Furthermore, even though both fructose and glucose are monosaccharides, they possess distinct metabolism mechanisms. In this regard, Ajibola et al. (2012) showed that glucose is quickly absorbed into the blood system in order to provide energy, while the absorption of fructose takes place slower; but even so, fructose ensures energy for the individual, for a longer period of time than glucose does.

According to Santos-Buelga and González-Paramás (2017), the most abundant disaccharides detected in nectar honeys were maltose, isomaltose, kojibiose and turanose. Additionally, the reseach conducted by De la Fuente et al. (2011) revealed that sucrose derivates represent the majority of trisaccharides found in honey. Different studies emphasized increased amounts of the trisaccharides melezitose, erlose and raffinose in honeydew honey (Bogdanov et al., 2008; Rybak et al., 2013).

In addition, the oligosaccharides present in honey can display prebiotic effects, by stimulating both the *in vivo* and *in vitro* growth of bifidobacteria and lactobacilli populations in the gastrointestinal tract (Kajiwara et al., 2002; Sanz et al., 2005). Besides the sugars, honey is also constituted by other minor components, such as proteins, enzymes, amino acids, vitamins, minerals, organic acids, volatile and phenolic compounds (Viuda-Martos et al., 2008; Solayman et al., 2016). All these substances bring more value to the nutritive profile of honey and play a crucial role in the daily diet.

The honey's proteins originate predominantly from secretions of cephalic glands of honey bees, but they also derive from the nectar and pollen of flowers (White and Doner, 1980; Lee et al., 1998; Santos-Buelga and González-Paramás, 2017). Several factors such as, honey bee species, honeydew-producing insects, nectar and pollen source are thought to influence the mean protein content of honey (Lee et al., 1998). Furthermore, Escuredo et al. (2013) demonstrated that European honeydew and chestnut honeys recorded superior values concerning the protein content (1 g of proteins/100 g of honey) compared to eucalyptus (0.6%), blackberry or polyfloral honeys (0.7%). The major royal jelly protein 1 (MRJP1) represents the main protein found in honey and its average amount was 23.4% as compared with the total protein content (Bilikova and Simuth, 2010). Moreover, other evidences revealed that honey samples from different botanical and geographical origins, contained up to nine major royal jelly proteins (Simuth et al., 2004; Won et al., 2009; Bilikova and Simuth, 2010; Rossano et al., 2012).

The presence of enzymes in honey was reported a long time ago by White (1978). The α-glucosidase (invertase or saccharase) is found in the hypopharyngeal gland of the forager bee and it represents about 50% of the total protein of the gland, while amylase and glucose oxidase, each is estimated to represent 2-3% (Ohashi et al., 1999).

Other enzymes described in honey were catalase, acid phosphatase, proteases and esterases (Belitz et al., 2009). In general, enzyme activities are associated with the intensity of the nectar flow, such as the amount of nectar provided by the flowers or the concentration and composition of the nectar. Therefore, honeys obtained fom rich nectar sources, like acacia, frequently display decreased natural enzyme activities (Wehling et al., 2006).

Honey also contains amino acids (all of the nine essential amino acids and all of the non-essential amino acids, except asparagine and glutamine) (Iglesias et al., 2004). Proline is the predominant amino acid, representing 50-85% of this category, followed by phenylalanine

(Belitz et al., 2009). Several studies revealed that the sources which may provide the amino acids in honey are represented by nectar (Baker and Baker, 1986; Wunnachit et al., 1992), pollen (Marshall and Williams, 1987; Sing and Sing, 1996), or even the bees themselves, when discussing about proline (Ball, 2007; Truzzi et al., 2014).

The mineral content is variable, depending on the honey assortment. Therefore, it recorded lower values in light honeys (0.04%) than in the dark ones (0.2%) (Da Silva et al., 2016). Among the minerals described in honey, potassium is the most abundant one (Terrab et al., 2004; Da Silva et al., 2016; Kadri et al., 2017), followed by calcium, sodium or magnesium, depending on the honey type (González-Paramás et al., 2000; Atanassova et al., 2012; Mondragón-Cortez et al., 2013). Other macroelements and microelements identified in honey were iron, phosphorus, manganese, iodine, zinc, lithium, cobalt (Da Silva et al., 2016).

Honey contains low quantities of vitamins, most of them originating from the pollen grains (Ciulu et al., 2011). The predominant vitamin detected in honey is ascorbic acid, with mean amounts around 2 mg/100 g (Alvarez-Suarez et al., 2010a). Other vitamins discovered in honey include thiamine (B1), riboflavin (B2), nicotinic acid (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B8 or H) and folic acid (B9) (León-Ruiz et al., 2013; Da Silva et al., 2016).

Organic acids are another category of minor compounds that were reported in honey. They are mainly represented by gluconic, aspartic, butyric, citric, acetic, formic, fumaric, galacturonic, glutamic, glutaric, butyric, glyoxylic, 2-hydroxybutyric, α-hydroxyglutaric, isocitric, α-ketoglutaric, lactic, malic, malonic, methylmalonic, 2-oxopentanoic, propionic, pyruvic, quinic, succinic, tartaric, oxalic, levulinic, formic acids (Mato et al., 2007; Da Silva et al., 2016). Among them, the gluconic acid is the prevailing one in most honeys, excepting fir honey, where galacturonic acid has been mentioned as the predominant organic acid (Daniele et al., 2012).

The 600 volatile compounds found in honey provide its aroma and flavour qualities. They include hydrocarbons, aldehydes, ketones, fatty acids and other carboxylic acids, superior alcohols, esters, benzene and its derivatives, norisoprenoids, sesquiterpenes and its derivatives, sulphur and cyclic compounds (Manyi-Loh et al., 2011a; 2011b).

The phenolic compounds detected in honey can be classified into phenolic acids (e.g., vanillic, caffeic, syringic, p-coumaric, ferulic, ellagic, 3-hydroxybenzoic, chlorogenic, 4-hydroxybenzoic, rosmarinic, gallic and benzoic acids) and flavonoids (e.g., quercetin, kaempferol, myricetin, pinobanksin, pinocembrin, chrysin, galangin, hesperetin, apigenin, C and O-glycosyl derivatives and others) (Tomás-Barberán et al., 2001; Dimitrova et al., 2007; Trautvetter et al., 2009; Truchado et al., 2011; Da Silva et al., 2016). Moreover, evidences confirm that these polyphenols exert strong antioxidant activity by neutralizing free radicals (Rice-Evans, 1996; Gheldof and Engeseth, 2002; Khalil et al., 2012).

Overall, the above mentioned components identified in honey are responsible for its unique chemical composition, allowing honey to become one of the most important bee products, with high nutritive value and suitable for long-term storage.

HONEY AND MEDICINE

Haematology. In poultry, the red blood cell indices, such as haematocrit, erythrocyte and haemoglobin indices often record decreased values as a result of stress factors (Yahav and Hurwitz, 1996; Yahav, 1999).

In this regard, the basic immunosuppressive factors affecting broiler chickens on a daily basis, are considered to be the following ones: extreme environmental temperature, humidity, vaccination, feed and/or water deprivation, mycotoxins in feed, dust, ammonia, radiation, bacterial or viral exposure, overcrowding, failure to comply with the provisions related to transportation (Beloor et al., 2010; Abioja et al., 2013; Chikumba and Chimonyo, 2014; Olukomaiya et al., 2015).

In addition, Abioja et al. (2019) revealed that supplementing the drinking water with honey, in stressed broiler chickens, resulted in the improvement of the haematocrit (Ht), red blood

cell (RBC) count and haemoglobin (Hb) concentration. In a previous research, Obun et al. (2008) attested the efficiency of implementing a honey-based diet in broiler chickens and the amelioration of the haematological parameters, such as Ht, RBC and Hb concentration.

Furthermore, Adekunle et al. (2017) reported that the heterophyl/lymphocyte rate was not modified by a honey-based diet in chickens.

Other research highlighted the benefits of a honey-based diet on blood indices of adult rats. Thus, they observed an improved haemoglobin concentration, increased erythrocyte count and elevated haematocrit in the investigated animals (Ajibola et al., 2007).

An improved hematological profile in rats was also confirmed by Chepulis (2007), following a honeydew honey-based diet.

Metabolic and cardiovascular effects. Many studies have shown that honey can prevent metabolic and cardiovascular pathologies. For instance, it was demonstrated that honey decreases total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and enhances high-density lipoprotein cholesterol (HDL-C), in both healthy individuals and patients with high risk (Yaghoobi et al., 2008). Additionally, Al-Waili (2004a) emphasized that honey lowers triglycerides in patients with hypertriglyceridaemia and decreases low-density lipoprotein cholesterol (LDL-C) in patients with hyperlipidaemia.

Moreover, among the metabolic conditions that are thought to be involved in cardiovascular diseases is diabetes. Different studies highlight positive effects of honey in both healthy and diabetic patients (Agrawal et al., 2007; Ahmad et al., 2008; Bahrami et al. 2009). The study conducted by Erejuwa et al. (2011; 2012a) evaluated the effect of honey in diabetic rats. Their findings outlined a decrease of hyperglycaemia and dyslipidaemia in the investigated animals, probably due to the oligosaccharides detected in honey. In addition, Nemoseck et al. (2011) fed healthy rats with a diet containing 20% honey and observed significant decrease of triglycerides, body weight, food/energy intake, and epididymal fat weight, but not significantly glucose decrease, total cholesterol decrease, adiponectin, and C-reactive proteins.

In another research, Aluko et al. (2014) revealed the ability of honey to lower blood pressure in healthy male subjects. Hypertension represents one of the most important risk factors for premature cardiovascular diseases. Notably, Erejuwa et al. (2012b) underlined the antihypertensive effect of honey in experimental rats.

Some studies have shown that the metabolic and cardiovascular effects of honey could be associated with its valuable compounds, particularly flavonoids (Shen et al., 2012; Panchal et al., 2012).

Oral care. Scientific evidences suggest that honey is able to support oral health, due to its strong antibacterial properties. In this regard, there are studies which confirm the inhibitory effect of honey on the growth of some pathogens responsible for the development of dental caries (Steinberg et al., 1996; Molan, 2001a).

Furthermore, English et al. (2004) indicated that Manuka honey, a honey that gained a lot of attention due to its high antibacterial activity, could prevent the evolution of some inflammatory conditions, such as gingivitis and periodontal disease. Additionally, Manuka honey proved to combat the malodor of oral squamous cell carcinomas (Drain and Fleming, 2015).

Several studies emphasized the major role of honey in lowering the incidence of radio/chemotherapy-induced oral mucositis (Biswal et al., 2003; Samdariya et al., 2015; Rao et al., 2017).

A recent research also demonstrated the ability of honey to prevent radiation-induced xerostomia (Charalambous et al., 2017).

Bone health. Nowadays, osteoporosis is regarded as one of the most important threats for the population, being characterized by a decreased bone mass and a bone architectural degradation thus, compromising the bone vitality (Christiansen, 1991). Lately, honey has become an alternative cure in bone disorders. In this regard, Zaid et al. (2010) confirm that Tualang honey was able to produce an increase in bone density and to restore osteoporotic bone in female ovariectomized rats; this effect was probably due to honey's high content of

phenolic and flavonoid compounds (Jaganathan and Mandal, 2009) and due to its strong anti-inflammatory activity (Owoyele et al., 2011).

Another research conducted by Zaid et al. (2012) revealed that Tualang honey displayed better effects on the trabecular bone structure in the ovariectomized rats than calcium supplementation. Moreover, Farid (2009) discovered that the anti-osteoporotic effect of Tualang honey could be associated with the presence of calcium and gluconic acid in its composition, the latter one increasing the calcium absorption in bone and thereby, providing the bone mass strength (Ariefdjohan et al., 2008).

In a recent study, Hajizadeh et al. (2018) highlighted the efficacy of topical application of honey in mandibular bone defect healing in rats. Moreover, Sahin et al. (2018) discovered that grayanotoxin-containing honey, derived from *Rhododendron* spp. and *Kalmia* spp. enhanced the healing mechanisms of an artificial transverse fracture.

Anticancer activity. The potential anticancer activity of honey was evaluated in both *in vitro* and *in vivo* studies.

Hence, honey samples of different floral origins were tested against distinct human cancer cell lines (e.g., prostate, breast, endometrial, lung, skin, cervical, liver, bladder, kidney, oral squamous cell carcinoma, osteosarcoma) (Ghashm et al., 2010; Samarghandian et al., 2011; Morales and Haza, 2013; Aliyu et al., 2013; Spilioti et al., 2014).

Some *in vivo* investigations were performed on induced-cancer rats/mice (Mabrouk et al., 2002) or transplanted-cancer rats/mice (Oršolić et al., 2005). Moreover, Erejuwa et al. (2014) stated that honey supresses the evolution of cancer by stopping the most important stages of carcinogenesis, such as initiation, proliferation and progression.

According to Tomasin and Cintra Gomes-Marcondes (2011), honey is able to decrease cell proliferation in Walker 256 carcinoma. Likewise, the flavonoid and phenolic content of honey inhibits the cell cycle of colon (Jaganathan and Mandal, 2009), glioma (Lee et al., 2003) and melanoma (Pichichero et al., 2010) cancer cell lines in G0/G1 phase.

The overexpression of Bcl-xL in breast cancer patients is generally correlated with metastasis (Espana et al., 2004). Ahmed and Othman (2017) reported that Bcl-xL expression was stopped by Tualang honey at its intrinsic mitochondrial pathway.

Dermatological properties. The beneficial effects of honey on skin care have been documented since earliest civilizations. Therefore, honey has been widely used in several skin pathologies due to its antimicrobial, antioxidant, immuno-stimulatory and anti-inflammatory properties (Kwakman et al., 2008; Vandamme et al., 2013; McLoone et al., 2016; Pereira and Bártolo, 2016).

The main components of honey involved in the wound healing process are represented by hydrogen peroxide, glucose oxidase, gluconic acid, methylgloxal, polyphenols, as well as hygroscopicity, hypertonicity and lower pH (Al-Waili et al., 2011; Hadagali and Chua, 2014; Majtan, 2014; Devasvaran and Yong, 2016). In addition, available literature indicates the ability of honey in stimulating angiogenesis, granulation and epithelialization (Molan, 2001b), lymphocytes and phagocytes (Al-Waili et al., 2011), and in initiating the expression of tissue repair markers (Barui et al., 2011). It was reported a very low toxic effect of honey on keratinocytes and fibroblasts (Ranzato et al., 2012).

Mayer et al. (2014) showed that topical application of honey improved chronic venous leg ulcers within six weeks, in 25 patients. The healing effects of honey on experimental and traumatic wounds were also revealed by latest studies (Oguz et al, 2018; Lukanc et al., 2018).

Natural honey also manifested antifungal activity against *Malassezia* yeasts, proving its efficacy in seborrheic dermatitis treatment (Al-Waili, 2001; Gupta et al., 2004). Furthermore, a mixture consisting of honey, beeswax and olive oil revealed its beneficial effects in pityriasis versicolor, tinea cruris, tinea corporis, and tinea faciei and diaper dermatitis (Al-Waili, 2004b).

In general, honey can be applied alone in the treatment of wounds (Osuagwu et al., 2004; Khoo et al., 2010) or in combination with other products, such as aloe vera and milk or ascorbic acid (Farzadinia et al., 2016; Schencke et al., 2016).

CONCLUSIONS

Nowadays, the permanent change of modern society has led to the imminent need for natural products and health-promoting foods. Therefore, nutraceuticals have received extensive attention from the population due to both high nutritional value and ability to counteract the negative effects of many pathologies that threaten the quality of life.
Moreover, numerous evidences attested the enhanced nutritive profile and multiple therapeutic properties of honey. As a consequence, honey could easily be classified as a nutraceutical product due to its valuable characteristics and its worlwide recognition.

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