REVIEW ARTICLE

Role of honey polyphenols in health

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Summary

Many bioactive phenolic compounds have been reported in hive products. This review discusses the occurrence and putative therapeutic applications of these phenolic compounds and is intended to be read by scientists, physicians, nutritionists, and other researchers interested in the rapidly developing science of honey and related products. In view of the information presented here, honey can be regarded as a rich source of phenolic bioactive molecules with promising potential benefits to health.

Keywords: Honey, polyphenols, cancer, antimicrobial, antioxidant, health.

Introduction

Honey is a sweet substance produced as a food source mainly from the nectar and secretions of plants by honey bees (Codex Standard for Honey, 2001). Honey is used to feed bees during the winter (Jaganathan and Mandal, 2009). For centuries honey has been used as food and as natural medicine, being prescribed by physicians of many ancient cultures for the treatment of a wide variety of ailments (Ransome, 1937). The art of apiculture and the benefits of honey have been known since the Egyptian first dynasty (Nicholson and Shaw, 2000), and ancient Greeks used honey as a sweetener (Brothwell and Brothwell, 1969). In Classical Greece, laws concerning apiculture were suggested and Plato included honey in his concept of a healthy diet (Skiadas and Lascaratos, 2001). The use of honey in folk medicine is thought to be as old as civilization, but in recent times there has been a renaissance in interest in its use as a medicinal product. The colour of honey can vary from clear to dark amber according to its floral source and mineral content and it has a close relationship with its flavour and quality (Jaganathan and Mandal, 2009). Honey may be viscous liquids or even solid with differing honeys identifiable by their colour, flavour, crystallization, and the presence of pollen grains in honey sediment (Alves da Silva et al., 2006).

Honey is mainly composed of water and sugar (about 96%) with the remainder being substances such as amino acids, enzymes, minerals, flavonoids, phenolic acids, ascorbic acid, carotenoid-like substances, organic acids, and several other compounds (White and Subers 1963; Tan et al., 1989; Alves da Silva et al., 2006). D-fructose and D-glucose are the predominant sugars but it is the former that occurs at higher concentrations. Sucrose occasionally exceeds 1% of the total sugar content while maltose may be found at levels three times higher than that of sucrose. The mineral fraction of honey is mainly composed of potassium and smaller amounts of magnesium, sodium, calcium, phosphorous, iron, managanese, cobalt and copper (Alves da Silva et al., 2006). Enzymes such as invertase, amylase, catalase and glucose oxidase are also present, and proline is the major amino acid constituent comprising about half the content of total free amino acids (White and Subers, 1963).

Citric and gluconic acids are also present in honey though malic, folic, lactic, succinic, butyric, acetic and formic acids have also been identified (Tan et al., 1989). Honey, depending on variety, is a poor source of vitamins with only a few honeys showing evidence of vitamins A, B2, C and B6 and carotenoid-like substances (Alves da Silva et al., 2006). Polyphenols, especially flavonoids and phenolic acids, are known to play an important role as antioxidants and honey is regarded as an important source of these compounds (Schramm et al., 2003; Viuda Martos et al., 2008b). The presence and concentrations of these phytochemicals in honeys can vary depending upon the floral source, the geographical and the climatic conditions. Consequently, polyphenols have been suggested as floral...
markers for the botanical authentication of unifloral honeys (Amiot et al., 1989; Jaganathan and Mandal, 2009). Pyrzynska and Biesaga (2009) discussed the analytical procedures for the analysis of phenolic acids and flavonoids in honey.

Polyphenols are the most important group of plant secondary metabolites and their chemical structures range from simple phenolic molecules to high molecular weight polymers of approximately 30000 Da (Bravo, 1998). All polyphenols have at least one hydroxyl group bound to an aromatic ring in the molecule and they are biosynthesised in plants by mainly the shikimate and the acetate pathways (Harborne, 1989). In general, apart from their ability to provide plants with colour, polyphenols have different functions in plants that include their ability to act as antimicrobial, antifungal, antioxidant activities, and chelation of toxic heavy metals (Harborne, 1993; Gould and Lister, 2005). Furthermore, much of the colours, flavour and taste of vegetable food and beverages are associated with the presence of polyphenols (Bravo, 1998).

According to the classification of Harborne (1989) polyphenols can be divided into at least ten different classes depending upon their basic chemical structure, but in honey phenolic acids and flavonoids are the most important. The flavonoid group may be further divided into thirteen classes (Harborne, 1988; Harborne, 1993) and more than 5000 flavonoids have been described since the late 1980s. Generally, polyphenols are divided into two major groups, the low- molecular- weight polyphenols comprising simple phenols and flavonoids, and the higher-molecular- weight polyphenols represented by tannins.

Simple phenols (Fig. 1 A) are those with a C6 carbon structure (such as phenol itself, cresol and thymol). Some have a C6-C1 structure, such as phenolic acids (for example, gallic, vanillic and syringic acids) and aldehydes (for example, vanillin). Those with a C6-C2 structure such as phenylacetic acids and acetophenones and the phenylpropanoid group with a C6-C3 structure are mainly represented by the hydroxycinnamic acids such as p-coumaric, ferulic and caffeic acids and their respective derivatives. Simple phenols, phenolic and phenylacetic acids can be found free in a large variety of plant species but their methyl and ethyl esters and glycosides can also occur in the free form and/or bound forms (Harborne, 1989; Bravo, 1998).

Flavonoids with a C6-C3-C6 structure represent the most widely distributed phenolic compounds in plants, and their carbon skeleton consists of an aromatic ring (A) fused to a heterocyclic ring (C) carrying an oxygen atom, and the other ring (B) is generally linked to number two carbon atom of the ring C (Fig. 1 B). In nature, they can be found as free aglycones although they usually occur as glycosides and their derivatives. At the same time, flavonoids are further divided and classified with respect to the degree of oxidation of the ring C into flavones (such as apigenin, luteolin and diosmetin), flavonols, (such as quercetin, myricetin and kaempferol), flavanones (such as naringenin and hesperidin), flavan-3-ols, (such as catechin and epicatechin), anthocyanidins and their glycosides (such as malvidin, cyaniding and pelargonidin). It is important to mention that flavones, flavonols and their glycosides are the most common flavonoids found in the plant kingdom (Bravo, 1998).

On the other hand tannins are molecules of intermediate to high molecular weight and have an important degree of hydroxylation. They are typically found in plants and can be classified in two large groups: hydrolysable tannins and condensed tannins; although there is a third group, the phlorotannins, which occurs in brown algae but are not consumed by humans (Ragan and

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Fig. 1. Basic structures of a simple phenol (A), a flavonoid showing the identification of its rings (B), and a condensed tannin or proanthocya-
nidin (C). NOTE: Fig. 1 (C) is based on one illustration appearing in: BRAVO, L (1998) Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. Nutrition Reviews 56 (11): 317-333.(Permission granted by: Blackwell Publishing Ltd., John Wiley & Sons Ltd.).
Hydrolysable tannins consist of molecules of either gallic acid or ellagic acid esterified to a polyol molecule such as glucose (Porter, 1989). These tannins can increase their molecular weight by consecutive esterification with other galloyl or ellagic molecules forming large polymers (Bravo, 1998). Further esterification with more gallic acid molecules is also plausible. This kind of tannin can be easily hydrolysed using diluted acids, alkalis, water and enzymes. Condensed tannins or proanthocyanidins are high-molecular-weight polymers, and the monomeric unit is a flavan-3-ol molecule such as catechin or epicatechin (Fig. 1 C). Oligomers such as dimers, trimers and tetramers of proanthocyanidins are well described but there are molecules with a degree of polymerization greater than 50. Molecular weights can reach values higher than 30000 Da (Würsch et al., 1984).

Since honey is a food product derived from plant nectar or plant exudate, it is an excellent source of various polyphenols. This review aims to clearly define the current state of knowledge of the phenolic composition of honey and evaluate its relevance to human health.

**Benefits and therapeutic properties of polyphenols in honey**

**Preliminary scope**

Studies into the biochemistry of polyphenols and their properties of pharmacological and therapeutic interest have been extensive. For example, flavonoids have important benefits in cardiovascular health, mainly on blood pressure and in the prevention of the damage due to lipid peroxidation of the low density proteins (Raj Narayana et al., 2001). Other therapeutic aspects of polyphenols are the protection of gastric mucus, liver mucus, anti-inflammatory and anti-neoplastic behaviour, antimicrobial activity (including the selective inhibition of some immunodeficiency viruses such as HIV-1 and HIV-2), and the biochemical effects on enzymes and hormones (Raj Narayana et al., 2001). Flavonoids, the most typical plant phenolics, have been the subject of many scientific researches. Havsteen (2002) produced a valuable contribution towards understanding the biochemistry and pharmacological potential of flavonoids, highlighting their interesting antiviral properties. He also remarked on current medical interest for the use of chemically pure flavonoids in the treatment of certain diseases, based on their effectiveness for inhibiting some enzymes, scavenging free radicals, and simulating the behaviour of hormones and neurotransmitters. Figure 2 shows some beneficial properties of the phenolic compounds.

Polyphenols can behave as antioxidants *in vivo* and *in vitro* because they function as terminators of free radicals and chelators of metal ions which could catalyse the lipid peroxidation (Bravo, 1998). The antioxidant activity of these molecules is due to a rapid donation of hydrogen atoms to stabilise the free radicals and the remaining phenoxy radicals can also react with any other radical to terminate the propagation route (Shahidi and Wanasundara, 1992). The chemical structure of polyphenols greatly influences their antioxidant activity (Bravo, 1998). Flavonoids, have one or more of some

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<td>Apigenin</td>
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structural features involved in antioxidant activity such as: an o-
diphenolic group in the B ring, a 2-3 double bond conjugated with
the 4-oxo function (in ring C), hydroxyl groups in positions 5 and 7
(in ring A) (Ratty and Das, 1988; Bors et al., 1990; Manach et al.,
1996). Some flavonoids present in honey are shown in Figure 3.
Table 1 summarises some of the phenolic compounds identified in
different types of honey using either high-performance liquid
chromatography (HPLC) or capillary electrophoresis (CE) techniques
with diode array detection (DAD) (Pyrzynska and Biesaga, 2009).

Generally, the antioxidant activity also correlates directly with
the degree of hydroxylation (Ratty and Das, 1988). In nature,
flavonoids usually occur as 3-O-glycosides and the presence of the
sugar moiety dramatically decreases the antioxidant activity of the
compound. Yet, free flavonoids, best known as aglycones, have
known antioxidant activity (Ratty and Das, 1988).

The role of polyphenols as antioxidant agents against radical
reactive species such as those belonging to the reactive oxygen
species (ROS) and reactive nitrogen species (RNS) groups is of
remarkable interest. Radicals belonging to ROS such as OH-
(hydroxyl), RCOO- (peroxyl) and RO· (alcohoxyl) are of major
concern in the study of the oxidative stress of living tissues (Ames et
al., 1993) since they can be scavenged by flavonoids (Shahidi and
Wanasundara, 1992). On the other hand, the highly reactive
nitrogen species peroxynitrite (ONOO-) has been investigated
regarding the ability of flavonoids, such as anthocyanins, to act as
scavengers (Haenen et al., 1997; Tsuda et al., 2000). Investigation
of the relationship between the chemical structure and the
antioxidant power (in terms of radical scavenging activity) of several
flavonoids demonstrated that this activity strongly depends on the
substitution pattern of the free hydroxyl groups in its base structure
(Ratty and Das, 1988; Bors et al., 1990; Manach et al., 1996; Bravo,
1998; Amic et al., 2003).

Kroon and Williamson (2005) discussed the benefits for health
connected to the intake of food rich in polyphenols and proposed
that the presence of polyphenolic substances in a balanced diet is
specially valuable. They further proposed that, just as recommended
daily intake values (RDI) exist for most micronutrients such as
vitamins and oligoelements, the evaluation of RDIs for various
polyphenols in food will also be possible in the not too distant future.

Functional foods, known as nutraceuticals, designed foods,
therapeutic foods and medicinal foods, fit the concept of optimal
nutrition (Berner and O’Donnell, 1998; Nagai and Inoue, 2004). In
fact, honey, propolis and royal jelly are considered among the foods
that possess the property of functionality, due to their naturally high
antioxidant potential and their anti-inflammatory properties (Ali et al.,
1991; Ali, 1995), associated with the presence of galangin (Raso et
al., 2001; Rosi et al., 2002a, 2002b), caffeic acid, phenethyl esters
(Ali, 1995), and chrysin (Mirzoeva and Calder, 1996; Martos et al.,
2003).

Table 1. Some identified phenolic compounds occurring in honeys (Pyrzynska and Biesaga, 2009).

<table>
<thead>
<tr>
<th>Type of honey</th>
<th>Analytical technique</th>
<th>Identified phenolic compounds</th>
<th>References</th>
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| Acacia, eucalyptus, lime, chestnut, | HPLC-DAD             | 4-hydroxybenzoic acid, protocatechuic acid, gallic acid, syringic acid, vanillic acid, p-
| heather, lavender, rosemary,        |                      | coumaric acid, caffeic acid, ferulic acid.                                                    | Dimitrova et al. (2007). |
| orange, sunflower and rapeseed honeys. |                      |                                                                                              |                |
| Australian Eucalyptus honey.        | HPLC-DAD             | Gallic acid, chlorogenic acid, caffeic acid, p-coumaric acid, ferulic acid, ellagic acid.     | Yao et al. (2004 a). |
| Citrus, thyme, rosemary, lavender   | CE-DAD               | Syringic acid, p-coumaric acid, caffeic acid, cinnamic acid, chlorogenic acid, ferulic acid, gallic acid. | Aljadi and Kamaruddin (2004). |
| honeys.                            |                      |                                                                                              |                |
| Eucalyptus honey.                   | HPLC-DAD             | Myricetin, tricetin, quercetin, luteolin, quercetin-3-methyl ether, kaempferol, pinocembrin, chrysin, pinobanksin, isorhamnetin, genkwanin. | Yao et al. (2004 b). |
| New Zealand and Australian          | HPLC-DAD             | Myricetin, tricetin, quercetin, luteolin, kaempferol, kaempferol-8-methyl ether, pinocembrin, chrysin, gallic acid, ellagic acid, chlorogenic acid, caffeic acid, p-coumaric acid, ferulic acid, syringic acid. | Yao et al. (2003). |
| Leptospermum honeys.                |                      |                                                                                              |                |
| Rosemary honey.                     | CE-DAD               | Kaempferol, ferulic acid, chrysin, pinocembrin, p-coumaric acid.                              | Dimitrova et al. (2007). |
Honey products have demonstrated antiviral properties (Amoros et al., 1992), including the inhibition of viral activation including HIV-1. This viral inactivation is thought to be due to the chrysin, acacetin and apigenin components (Critchfield et al., 1996). Other therapeutic properties of bee-products that have been reported include their anti-ulcer and antibacterial properties derived from the occurrence of flavonoids such as galangin and quercetin (Mirzoeva et al., 1997; Cushnie and Lamb, 2005). However, in honey there are other antimicrobial factors apart from polyphenols, such as the recently discovered methylglyoxal in manuka honey (Mavric et al., 2008; Adams et al., 2008), sugar content, hydrogen peroxide and bee defensin-1 (Kwakman et al., 2010). Indeed, it is important to note that not all antimicrobial properties can be attributed to polyphenols. Paradoxically honeys with the same phenolic profiles can either possess antibacterial activity or be totally devoid of any (Weston et al., 2000). Henriques et al. (2006) also studied the antibacterial activity of honeys that produce hydrogen peroxide. There is a substantial body of research on the antiproliferative effect of honey and its components on some cancers (Ghosh et al., 2005; Jaganathan et al., 2010a; Pichichero et al., 2010; Jaganathan et al., 2010b).

Finally, it is important to be aware that the bioavailability of dietary polyphenols is critical to realising their health benefits. Manach et al. (2004, 2005) reported that polyphenol bioavailability is dependent upon many variables including gut absorption, glucuronide excretion to the intestinal lumen, microbiota metabolism, liver and gut metabolism, plasma kinetics, a variety of metabolites in the bloodstream, bonding to albumin, cell assimilation and metabolism, accumulation in tissues and bile, and urinary excretion. Proanthocyanidins are abundant in the human diet but they are not well absorbed in the gut and the intake of flavonols, flavones and flavanols remains relatively small. In addition to their limited absorption and rapid elimination, final plasma concentrations of proanthocyanidins hardly ever exceed 1 µmol / L. Flavonoids with the highest bioavailability are flavanones and isoflavones reaching plasma concentrations in the vicinity of 5 µmol / L. Hydroxycinnamic acids are widely distributed in the diet at substantial levels but their bioavailability is poor due to esterification.

On account of these observations, honey has valuable properties which make it considered as an irreplaceable source of compounds with interesting therapeutic activities suitable to being part of a healthy diet.

The radical scavenging and antioxidant activities of honeys

Honey is regarded as a functional food largely due to the presence of phenolic compounds that are able to act as free radical scavengers, thus protecting cells and living tissues against oxidative stress. This oxidative stress has been associated with enhanced cellular ageing that is itself a feature of degenerative diseases such as cancer, cardiovascular disease and related diseases (Kinsella et al., 1993). Polyphenols in honey can scavenge hydroxyl, peroxyl and alcohoxyl radicals through their ability to act as a hydrogen donor and thus displaying their antioxidant properties.

Sánchez Moreno (2002) described diverse methods for the assessment of the free radical scavenging activity in food and biological systems. These reactive chemical species and free radicals include superoxide (O2·), hydrogen peroxide (H2O2), hypochlorous acid (HOCl), hydroxyl radical (HO·), peroxyl radical (ROO·) as determined by the TRAP (Total Radical Trapping Antioxidant Parameter), the ORAC (Oxygen Radical Absorbance Capacity) methods, the ABTS [2,2-azinobis-(3-ethylbenzothiazoline-6-sulphonate)], TEAC (Trolox Equivalent Antioxidant Capacity) method, the DPPH (2, 2-dpyhenyl-1-picrylhydrazyl) radical scavenging capacity assay, and the DMPD (N-N-dimethyl-p-phenylenediamine) method. Studies reporting the antioxidant power of honeys usually depend on the use of the DPPH method, although the ORAC method is increasing at a steady rate, together with those involving free radical scavenging mechanisms.

Beretta et al. (2005) proposed a standard analytical platform for the reliable assessment of the antioxidant activity of honey. Significant correlations were recorded among the results of the different methods used by the researchers. Principal component analysis grouped the analysed samples according to their antioxidant power and phenolic content. The authors emphasized the use of combined methods to either foresee or confirm the health benefits of honey in relation to their antioxidants’ concentration.

When the chemical composition and bioactivity of chestnut tree, rhododendron and multifloral honeys from Anatolia (Turkey) was investigated it was observed that chestnut-tree honey exhibited the highest polyphenolic content, the highest radical scavenging activity for superoxide, and the highest reducing power. Multifloral honey exhibited the highest scavenging activity for the reactive nitrogen species peroxynitrite (Küçük et al., 2007).

Baltrušaitytė et al. (2007a) studied the radical scavenging activity of Lithuanian honeys of different floral origin. Antioxidant power of these samples was remarkably widespread. The beneficial effects of bee products for health depend upon their source due to the strong variability in the antioxidant power. Further investigations have been recommended in order to elucidate connections between floral origin, phenolic composition and antioxidant activity as measures of the benefits of hive products on health.

The antioxidant activity of honey as phenolic content has been extensively studied. Research on the antioxidant activity of honeys from Yemen found that some Yemeni honeys contained significantly higher phenolic contents than other honeys, and the percentage antioxidant activities were higher than in the investigated non-Yemeni honeys (Al-Mamary et al., 2002). Based on these results, Yemeni honeys were found to be rich in antioxidant phenols with
antioxidant therapeutic potential (Al-Mamary et al., 2002).

Malaysian honeys were studied in relation to their polyphenolic content and antioxidant properties (Aljadi and Kamaruddin, 2004). Two of the most common Malaysian Apis mellifera honeys, namely Gelam and Coconut honeys, were studied regarding their phenolic content, radical scavenging activity (using the DPPH method), and total antioxidant power (using the Ferric Reducing Ability Plasma (FRAP) method). The data showed a significant correlation between the antioxidant activity of the honeys and their total phenolic contents. Gelam honey had a higher total phenolic content (21.4 μg/g) than Coconut honey (15.6 μg/g), as well as greater radical scavenging activity, water content and total antioxidant potential. These observations supported those of Frankel and colleagues (1998) that water content of honey and antioxidant activity were correlated (Aljadi and Kamaruddin, 2004).

In a study of crude Italian honeys, Millefiori honeys showed a higher flavonoid content than Acacia honeys in accordance with their greater antioxidant power (Blaza et al., 2006). In another study, the seven most common types of Slovenian honeys were studied in terms of their total phenolic content, antioxidant activity and colour (Bertoncelj et al., 2007). Honey samples were from acacia, lime, chestnut, fir, spruce, multifloral and forest (honeydew honey from coniferous trees). Analytical results showed that the total phenolic content and the antioxidant activity varied greatly among the different types of honey. Darker honeys (fir, spruce, forest) showed higher total phenolic content and higher antioxidant capacity than lighter honeys (acacia and lime). Total phenolic content ranged from 44.8 mg. gallic acid/Kg in acacia honey to 241.1 mg. gallic acid/Kg in fir honey. A significant correlation between the antioxidant activity and the phenolic content was also found. In accordance to these results, the polyphenolic composition and the antioxidant activity of Czech honeys, Lachman et al. (2010) suggested similarities between lime, rape and raspberry honeys, followed by floral honeys, while multifloral and honeydew honeys were remarkably different.

Oddo et al. (2008) studied the antioxidant activity of Australian honeys from Trigona carbonaria, a stingless bee from Australia and found that, when compared with honeys from different countries of the world, the flavonoid content was high (about 10.0 mg quercetin equivalents/100 g of honey). However, their phenolic content was lower (about 55.74 mg gallic acid equivalents/100 g of honey) than that recorded by Vit et al. (2008) for Czech A. mellifera honey. The Australian honey also displayed a higher total antioxidant activity than the Czech A. mellifera sample, while the radical scavenging activity was similar to that reported for floral and honeydews blends of Spanish honey (Oddo et al., 2008).

Honeys from the Czech Republic (Lachman et al., 2010) evaluated for their antioxidant activity and total phenolic composition. Forty honey samples of different types such as multifloral, lime, rape, raspberry, mixture and honeydew were studied. Total phenolics content ranged from 82.5 to 242.5 mg/Kg honey, those with the lowest content were lime honeys, whereas honeydew honeys exhibited the highest concentrations. The antioxidant activity values recorded using the FRAP, DPPH and ABTS methods demonstrated that floral honeys were the least active while honeydew honeys had the highest activity. The authors noted that the observed low activity of floral honeys was in accordance with the results of Al-Mamary et al. (2002), and was indicative of the presence of different phenolic compounds with different antioxidant activity. Raspberry honeys showed marked antioxidant activity which had also been reported by the results of Buňčová and Reblová (2008).

Gheldof and Engeseth (2002) and Gheldof et al. (2002) compared the scavenging activity of honey for oxygen radicals (3-17 Imol TE/g) to that of fruits and legumes (0.5-19 Imol TE/g).

The possible changes in the antioxidant power and the polyphenolic composition of honey when fermented into mead were another subject of research. It was found that pasteurisation of the starting musts did not induce any significant change in the antioxidant power of the resulting meads, although phenolic profiles had changed due to temperature (Wintersteen et al., 2005).

Free-radical scavenging activities of bee hive products and extracts, were examined from samples of multifloral honeys, monofloral honeys and honeydews. A high variability of the phenolic content was reported. Honeydew samples were the richest in phenolic compounds and showed a significant radical scavenging activity. However, it was observed that not all the activity of the samples accounted for the phenolic content. In fact, correlation between proline content and the radical scavenging capacity was found to be greater than that indicated by their total phenolic content. In this case scientists suggested giving more importance to the amino acid composition of honeys when evaluating their antioxidant power (Meda et al., 2005).

Kishore et al., (2011) evaluated the total phenolic content, the antioxidant and the radical scavenging activity of Asian honeys. They found a higher phenolic content in tulang honey (83.96 mg gallic acid equivalent /100 g of honey) than in Gelam, Indian forest and pineapple honeys, and observed strong correlations of the phenolic content with the antioxidant and radical scavenging activities. They also observed a significant peroxyxinite and superoxide anion scavenging ability from this honey.

Regarding research with cells, Blaza et al. (2007) studied the role of Italian honey flavonoids as agents against the oxidative damage to human red blood cells. This study investigated water and ether phenolic fractions from honeys to assess their phenolic and flavonoid contents and their antioxidant activities. Differences in their FRAP values were noted and it was concluded that hydrophilic polyphenols were mostly glycosides and water soluble high molecular weight polymers, whereas the lipophilic polyphenols were low-molecular weight flavonoids. The aqueous fractions showed the
highest antioxidant activity and the organic fraction showed activity against haemolytic agents and radicals involved in the lipid peroxidation of the cell membrane and this activity could in part be explained due to the higher liposolubility of these compounds.

Beretta et al. (2007) studied the protective effect of honey against hydrogen peroxide and peroxyl radicals able to damage endothelial cells and highlighted the synergistic action of honey antioxidants (mainly phenolic acids and flavonoids). This antioxidant activity had the ability to remove ROS that lead to oxidative stress of endothelial cells and thus lowering the risk of developing acute and chronic free-radical mediated pathologies such as atherosclerosis and cancer in vivo.

In the search of healing products based on honey, Van den Berg et al. (2008) studied the antioxidant and anti-inflammatory properties of honey in vitro and found that buckwheat honey was the most effective in reducing ROS such as hydroxy radicals (formed from superoxide anion produced by the polymorphonuclear neutrophils) and reactive nitrogen species such as peroxynitrite anion (formed from the nitric oxide released by macrophages) frequently found in wounds. Thus, this honey can help to reduce the inflammatory effects in a wound and the surrounding tissue, and help to improve wound healing due to its antibacterial and antioxidant properties.

The cytotoxic activity of Indian honey has recently been studied (Jaganathan et al., 2010b). Apart from flavonoids, phenolic acids such as di-hydroxybenzoic and cinnamic acids were found. This study observed that honey with the highest phenolic content and antioxidant activity increased numbers of 3T3 cells viability in a dose-dependent manner when cells were oxidative-induced to death. Moreover, it was found that this honey could induce apoptosis in cultured breast cancer cells (MCF-7) by arresting the cells at the sub-G1 phase (Jaganathan et al., 2010b).

It has also been demonstrated that an increase in the concentration of human plasma antioxidants was verified after the intake of food rich in them, such as buckwheat honey. Therefore, the antioxidant and reducing power of plasma increased significantly and it was advised to have a higher honey intake in order to increase the antioxidant defences in healthy adults (Schramm et al., 2003).

Ghel dof and Engeseth (2002) found that honeys from different floral sources can protect against the oxidation of lipoproteins in human plasma. Their results suggested that darker honeys such as buckwheat honey displayed more protection than lighter ones such as clover and acacia honeys.

The maintenance of the redox status of human plasma by flavonoids in Italian multifloral honeys was studied by Fiorani et al. (2006). Hydrophillic flavonoids were found to be remarkably more effective than lipophillic flavonoids in promoting the chemical reduction of the anion ferricyanide. However, the content of hydrophillic flavonoids was lower than that of lipophillic flavonoids, suggesting the presence of water-soluble phenolic polymers and sugars. HPLC-MS (liquid chromatography with mass detection) analyses of lipophillic flavonoids revealed the presence of high concentrations of the aglycones of quercetin, luteolin, kaempferol, fisetin, isorhamnetin, acacetin, chrysin, apigenin, galangin and tamarixetin. Cell-based assays demonstrated that lipophillic flavonoids developed greater protection for erythrocytes than hydrophillic ones, by passing through the cell membrane, accumulating in the cell and readily binding to haemoglobin. The antioxidant role of intracellular flavonoids was explained by a donor-electron mechanism to a trans-plasma membrane oxidoreductase (PMOR) which may consequently promote the reduction of extracellular oxidants.

Ghel dof et al. (2003) investigated whether the intake of honey could improve the human serum antioxidant status. After volunteers had consumed beverages of water, water with buckwheat honey, black tea, black tea with buckwheat honey and black tea with a sugar analogue of honey, it was found that those who had consumed water with buckwheat honey, significantly increased their plasma antioxidant capacity, when compared with subjects receiving the other beverages. Nevertheless, further studies on the bioavailability of honey phenolics and more long-term studies are required to better assess in vivo honey inhibition of plasma lipid peroxidation.

The antimicrobial and antiviral activity of honeys

The antimicrobial properties of honey have been known for millennia. Aristotle (384–322 BC) discussed the properties of different honeys and indicated pale honey for the treatment of sore eyes and wounds, while Dioscorides (ca. 50 AD) referred to a pale yellow honey form Attica as being the best for treating rotten and hollow ulcers. Honey has inhibitory effects against several types of bacteria such as Gram positive, Gram negative, aerobic and anaerobic bacteria (Molan, 1992).

There are several studies investigating the antimicrobial activity of honey. The antibacterial activity of honey is usually associated with the release of hydrogen peroxide, from the oxidation of glucose to glucolactone and then to gluconic acid in presence of the enzyme glucose oxidase (Adock, 1962; White and Subers, 1963). This activity is called peroxide-activity and constitutes, at variable extent, the mode of action of some honeys (Henriques et al., 2006). However, another antibacterial non-peroxide activity in honey is mainly due to their polyphenol content, sugar and other recently discovered factors. Firstly, non-peroxide antimicrobial activity of honey from stingless honeybees (Meliponinae) has been demonstrated as being important because antibacterial activity due to hydrogen peroxide might be reduced by the action of catalase present in human serum. (Temaru et al., 2007). Secondly, New Zealand manuka honey (Leptospermum scoparium (Myrtaceae)) have been studied regarding their antibacterial activity and its relationship with their phenolic
composition (Weston and Brocklebank, 2000), but in recent years Mavric et al. (2008) and Adams et al. (2008) described methylglyoxal as the dominant antibacterial compound of manuka honey. Atrott and Henle (2009) proved the close relationship between methylglyoxal content and the antibacterial activity in manuka honey. Moreover, Kwakman et al. (2010) characterized other antibacterial non-peroxide factors of honey such as bee defensin-1 along with methylglyoxal and sugar. Therefore, the antimicrobial activity of honey can have several explanations and not all the honeys behave similarly.

Regarding polyphenols, Burdock (1998) attributed the antibacterial properties of honey to the presence of aromatic acids and esters, whereas Takaisi and Schilcher (1994) said that pinocembrin, galangin and caffeic acid phenethyl ester can inhibit bacterial RNA polymerase. Moreover, Cushnie and Lamb (2005) suggested an antibacterial mechanism of action started by galangin; this involves degradation of the cytoplasmic membrane causing loss of potassium ions and the subsequent cell autolysis. Furthermore, Mirzeova et al. (1997) proposed another mechanism of action for quercetin, a flavonoid that may occur in honey. They suggested that quercetin may increase bacterium membrane permeability leading to electric potential dissipation and decrease in the synthesis of ATP. Kirmpal-Kaur et al. (2011) fractionated tualang honey into polar, acidic and basic fractions using the solid phase extraction technique (SPE) in order to evaluate their antibacterial properties against wound and enteric bacteria, and found that the acidic fraction enhanced the antibacterial properties of this honey. In an effort to identify the main phytochemicals with antibacterial activity present in the acidic fraction, the need for further investigations was acknowledged, although preliminary evidence indicated that these compounds could be polyphenols.

**The inhibition of microorganisms of clinical significance**

The recorded antimicrobial properties of honeys against some of the most important microorganisms from a clinical standpoint will now be described. Antimicrobial activity derived from the occurrence of polyphenols will be emphasised, although any other activity whose cause is not clearly defined will also be included.

Gram positive bacteria such as *Staphylococcus aureus*, the causal agent of a range of illnesses from skin infections to life-threatening diseases such as pneumonia and meningitis, did not grow in the presence of honeys produced by *A. mellifera* and *Tetragonisca angustula* bees in the Brazilian states of Paraná and Minas Gerais. In order to study this effect, honeys were analysed by high performance liquid chromatography (HPLC) and the antimicrobial activity was connected to phenolic compounds, such as 4-hydroxybenzoic acid (HBEN). These compounds occur in higher concentrations in propolis than in honey, and propolis was more effective against *S. aureus* than honey (Miorin et al., 2003). This bacterium has proved to be variable in susceptibility to different honeys. Turkish honeys from Anatolia showed a moderate inhibition towards some strains of *S. aureus* (Küçük et al., 2007), while Turkish rhododendron honeys partially inhibited the growth of this bacterium (Silici et al., 2010). Honey from stingless bees had powerful activity against *S. aureus* when compared to that exhibited by manuka honey produced by honeybees belonging to Apidae family (*A. mellifera, A. cerana*) (Temaru et al., 2007). Argentinean honeys from the province of Córdoba evidenced high activity against *S. aureus*, which was considered to be of remarkable clinical importance, since an increase in difficult-to-treat skin infections had been reported in the last decade and resistance against several antibiotics had developed (Basualdo et al., 2007). A study of the properties of several Cuban honeys demonstrated that Gram positive bacteria are more sensitive than Gram negative bacteria (Alvarez Suárez et al., 2010), with *S. aureus* the most sensitive bacterium (Alvarez Suárez et al., 2010). Honeys from *A. mellifera* produced in Thailand also showed inhibitory effects (Srisayam and Chantawannakul, 2010). Strains of *S. aureus* were found to be very sensitive to Spanish honeydew honeys (Pérez Martín et al., 2008) whereas in other studies using honeys from Galicia (northwest of Spain) two strains of the bacterium, including a difficult-to-treat strain in humans such as the methicillin-resistant *Staphylococcus aureus* (MRSA), exhibited different sensitivities (Gallardo-Chacón et al., 2008). South African honeys from indigenous *Leucospermum cordifolium* and *Erica* species showed poor antibacterial activity against this Gram positive bacterium (Basson and Grobler, 2008). Baltrušaitytė et al. (2007b) observed that Lithuanian honeys exhibited antibacterial effects on *S. aureus* and concluded that this was mainly due to the presence of hydrogen peroxide. Honeys produced in the Czech Republic are also antimicrobially effective with some honeydew honeys possessing the greatest effects (Vorlova et al., 2005). In a study with unifloral and multifloral Portuguese honeys, Henrques et al. (2005) analysed their antibacterial activity against a strain of *S. aureus*, and observed that all of the samples tested possessed peroxide activity except some honeys derived from *Lavandula stoechas* which revealed non-peroxide antibacterial activity. Recently, Isla et al. (2011) observed that algarrobo honey (*Prosopis nigra*) and a multifloral honey from the northwestern provinces of Argentina had activity against *S. aureus*. They identified at least five antibacterial compounds in the algarrobo honey and four compounds in the multifloral honey and found that most of them corresponded to flavonoids. One of these flavonoids was identified as pinocembrin. The authors also pointed out that the antibacterial activity of the analysed honeys might be mainly due to their phenol content because of the significant correlation observed between the phenolic content and the antibacterial activity.

Among the Gram negative bacteria, *Escherichia coli* is of great concern from a health point of view. It may cause life threatening gastric infections and diarrhoea, following consumption of
contaminated food, as well as other infections such as cystitis, meningitis, peritonitis and pneumonia. There are several studies on the antibiotic effect of honey towards *E. coli*. *E. coli* exhibited sensitivity to stingless honeybee honey (Temaru et al., 2007), Spanish honeys (Gallardo-Chacón et al., 2008), Cuban honeys (Alvarez-Suárez et al., 2010), and Thailand honeys (Srisayam and Chantawankul, 2010). Basualdo et al. (2007) demonstrated that *E. coli* can be inhibited by some Argentinean honeys while, Fangio et al. (2010) demonstrated the effectiveness of honeys produced in the province of Buenos Aires (Argentina) against this enterobacterium. The antimicrobial activity of these honeys was mainly non-peroxide and the presence of phytochemicals such as phenolic compounds was considered in the most active honeys (Fangio et al., 2010). Nevertheless, rhododendron Turkish honeys showed no inhibitory effect (Silici et al., 2010), and Basson and Grobler (2008) found poor antibiotic activity of South African honeys from indigenous *L. cordifolium* and *Erica* species. Some Czech Republican honeys were also tested for their antibacterial activity against *E. coli* and researchers concluded that honeydew honeys are the most effective (Vorlova et al., 2005). Recently, Brudzynski and Miotto (2011), in an investigation with twenty Canadian unheated honeys, quantified Maillard reaction-like products (MRLPs) and total phenol contents, apart from assessing the antioxidant activity using the ORAC method. One of their results indicated that both the recorded antioxidant activity and the content of MRLPs of these honeys mainly contributed to the antibacterial activity against *E. coli*. This antibacterial activity confirms the work of Rufian-Henares and de la Cueva (2009) who suggested that the antibacterial activity of coffee melanoidins against *E. coli* is due to their behavior as metal-chelators.

*Pseudomonas aeruginosa*, an important pathogenic bacterium which can cause several health disorders in humans including lung, urinary, tissue, blood and wound infections was studied in many published reports. Silici et al. (2010) showed that rhododendron honeys from Turkey have antimicrobial activity against *P. aeruginosa* when diluted at 50% and 75% in water. *A. mellifera* honeys produced in Thailand also inhibited the growth of this bacterium (Srisayam and Chantawannakul, 2010). Honey from stingless honeybees showed significant inhibitory effects on the growth of *P. aeruginosa* (Temaru et al., 2007). The bactericidal potency of Saharan honey against this pathogen was studied by Boukraa and Niar (2007) who reported that Saharan honey showed higher potency than Algerian honeys, probably due to antibacterial substances from the botanic flora occurring in the Sahara. This Gram negative and aerobic micro-organism was sensitive to some honeys produced in the province of Córdoba (Argentina) (Basualdo et al., 2007), but was the least sensitive in comparison with other bacteria (Alvarez-Suárez et al., 2010), while not sensitive to honey samples evaluated by Gallardo-Chacón et al. (2008).

*Helicobacter pylori*, can occur in the stomach, and is linked to the development of ulcers and many types of gastritis. There is evidence that honey can have inhibitory effects against this bacterium. Küçük et al. (2007) reported a moderate inhibitory effect by honeys harvested in Anatolia (Turkey), and studies conducted with manuka (*L. scoparium*) honey showed interesting antibacterial activity. We must remember that, as previously described, antibacterial activity of manuka honey is now mainly attributed to the occurrence of methylglyoxal (Mavric et al., 2008, Adams et al., 2008; Attrot and Henle, 2009). It has been suggested that this honey can also act by healing the gastric mucosa and stimulating epithelial cells growth.

*Bacillus cereus*, a Gram positive, aerobic and beta-haemolytic bacterium, is a food-borne pathogen for humans, whose growth results in the production of enterotoxins causing nausea, vomiting, abdominal cramps and diarrhoea. There are reports of the sensitivity of the bacterium towards some honeys. For example, some Thai honeys can inhibit growth of the bacillus (Srisayam and Chantawannakul, 2010), and similar activity was observed in studies using different honeys which included honey from Galicia (Spain) (Gallardo-Chacón et al., 2008). In contrast, *Bacillus cereus* was found to be resistant when rhododendron Turkish honeys were tested for their antibacterial activity (Silici et al., 2010).

Honeys produced in Anatolia (Turkey), in Cuba and in the Turkish Black Sea Region showed inhibition effects on strains of *Bacillus subtilis* (Küçük et al., 2007; Silici et al., 2010; Alvarez-Suárez et al., 2010), a Gram positive sporing bacterium occurring in soil which can contaminate food but rarely causes infections in humans.

Some other honey sensitive-pathogens described in the literature are *Bacillus anthracis* (anthrax), *Corynebacterium diphtheriae* (diphtheria), *Klebsiella pneumoniae* (pneumonia), *Mycobacterium tuberculosis* (tuberculosis), *Salmonella typhi* (typhoid fever), *Vibrio cholerae* (cholera) and different streptococci, among others. For example, *Klebsiella pneumoniae* was found to be sensitive to Argentinean (Basualdo et al., 2007), and Thai honeys (Srisayam and Chantawannakul, 2010). The growth of *Enterococcus faecalis* was inhibited by stingless honeybee honey (Temaru et al., 2007), and this bacterium also showed sensitivity to honey according to the research performed by Gallardo-Chacón et al. (2008).

In addition, other bacteria sensitive to different types of honey are *Staphylococcus epidermidis* (Basualdo et al., 2007; Baltrušaitytė, 2007b), *S. uberis* (Basualdo et al., 2007), *Pediococcus mirabilis* (Silici et al., 2010), *Aeromonas hydrophila* (Silici et al., 2010), *Micrococcus luteus* (Srisayam and Chantawannakul, 2010), *Streptococcus oralis* (Basson and Grobler, 2008), *Streptococcus anginosus* (Basson and Grobler, 2008), *Salmonella enterica ser. Typhimurium* (Vorlova et al., 2005; Gallardo-Chacón et al., 2008), *Shigella sonnei* (Gallardo-Chacón et al., 2008), *Listeria monocytogenes* (Vorlova et al., 2005; Gallardo-Chacón et al., 2008) and *Streptococcus mutans* (Basson and Grobler, 2008). Among yeasts, some *Candida* species were inhibited by Turkish honeys (Küçük et al., 2007).
The initial event in the development of bacterial infections of the gastrointestinal gut is the attachment of bacteria to the mucosal epithelial cells (Raupach et al., 1999) and the blocking of this event represents an interesting strategy for the prevention of diseases (Sherman et al., 1983; Leung and Finlay, 1991; O’Farrelly et al., 1992; Peralta et al., 1994). Ainaqdy et al. (2005) studied the antimicrobial activity of Omani honeys against Salmonella enteritidis and the ability of these honeys to prevent the bacterium from adhering to intestinal epithelial cells in vitro.

However, in spite of the antimicrobial activity, there are yeasts like Candida albicans and Saccharomyces cerevisae which showed resistance towards some honeys (Silici et al., 2010; Srisayam and Chantawannakul, 2010), while rhododendron honeys were not effective against strains of B. cereus, E. coli and Yersinia enterocolitica (Silici et al., 2010).

The bactericidal properties of honey led researchers to investigate its applications on cutaneous wound healing and the treatment of burns. Mohd Nasir et al. (2010) and Kirpal-Kaur et al., (2011) found that tualang honey (Koompassia excelsa) had important bactericidal and bacteriostatic effects in the treatment of burns by using dressings soaked with this honey. Also, non-toxicity of honey against tissue cell cultures of human keratinocyte and fibroblasts has recently been found in vitro. This kind of evidence may positively influence the choice of wound dressings in clinical prescriptions (Du Toit and Page, 2009).

Inhibition of viruses
Antiviral properties of honeys are also of great concern from a therapeutic point of view. Chritchfield et al. (1995) showed that some important flavonoids of honey such as chrys, acetin and apigenin can inhibit the human immunodeficiency virus (HIV-1) activation, via a probable mechanism involving the inhibition of viral transcription. Other researchers have demonstrated the inhibitory effects of chrysin against herpes simplex virus type 1 (HSV-1) (Lyu et al., 2005). Hu et al. (1994) observed that chrysin and apigenin have a significant antiviral activity against HIV-1 in acutely infected H9 lymphocytes. Apigenin also exhibited antiviral activity against influenza virus (H3N2) in vitro (Liu et al., 2008).

Molecular biological processes at DNA level are responsible for cell events that lead to the development of some phenomena such as carcinogenesis, and, in this line, binding studies of different flavonoids were undertaken. Apigenin, a cancer chemopreventive agent, has the highest affinity of ligand-DNA binding when compared to those of morine and naringin (Nafisi et al., 2008).

Chiang et al. (2005) observed that apigenin behaves as a potent antiviral substance against herpes virus type-2 (HSV-2), adenovirus (ADV-3), hepatitis B surface antigen (HBsA) and hepatitis B e antigen (HBeA).

Al-Waili (2004) studied the activity of honey on two types of herpes: labial and genital herpes. His results demonstrated that the topical application of honey on recurrent attacks of this viral disease was effective. This study reported that in the labial herpes the mean time of healing was 43% better than with the conventional treatment with acyclovir, while for genital herpes the mean healing time was improved around 59%. The authors remarked that some cases remitted completely after treatment with honey, although none of the attack remitted when using acyclovir. Honey has also demonstrated anti-Rubella activity in experiments performed on monkey kidney cell cultures infected with the Rubella virus (Zeina et al., 1996).

Finally, further investigations are required to study the relationship between the phenolic composition of honeys and their therapeutic properties, now that it has been proposed that honey from stingless bees may be used to manufacture pharmaceuticals, as well as nutritional supplements and cosmetics (Temaru et al., 2007).

Antitumour properties
Honey and its components have several applications in cancer therapy. There are a number of reports focusing on honey and some individual components undertaken in cell cultures, animal models and humans (Fig. 4) as described later in the text. So, for instance, the use of honey has revealed a significant inhibition of the proliferation in three human bladder cancer cell lines (T24, 253J and RT4) and one murine bladder cancer cell line (MBT-2). When researchers used between 1 and 25% of honey BrdU labelling index was significantly lower and the same was observed for the S-phase fraction when compared with control cells. In the in vivo studies, cancer cells were implanted subcutaneously in the abdomens of mice and tumour growth was significantly inhibited after intrasional injection of 6 and 12% of honey as well as after oral ingestion of honey (Swellam et al., 2003). In other research, honey was used in solution as treatment in W256 mammary carcinoma implants in Wistar rats, and a decrease in relative tumour weight was observed suggesting that honey modulated tumour growth (Tomasin and Cintra Gomes-Marcondes, 2011). Honey not only has antitumour properties, but has protective effects on the oxidative stress and carcinogenesis induced by carcinogenic compounds as methyl nitrosourea (MNU). In fact, one week after Sprague Dawely rats were injected with methyl nitrosourea one group of rats were given orally 5 g honey (containing 0.2 g of ground Nigella sativa seeds) per rat, per day. After six months the methyl nitrosourea injected in the control group produced a variety of oxidative stresses ranging from severe inflammatory reaction in lung and skin to colon adenocarcinoma, whereas honey and Nigella sativa together protected 100% (12/12) against effects of methyl nitrosourea (Mabrouk et al., 2002).

The antitumour effects of Eugenol, chrys and galangin have demonstrated antitumoural activity (Jaganathan et al., 2011). Eugenol, a natural compound available in honey, has antiproliferative...
effects in colon cancer cells (HT29, HT15) and increased the accumulation of cells at sub-G1 phase. Eugenol increased levels of ROS, DNA fragmentation and decreases mitochondrial membrane potential (MMP). Eugenol was found to be a potential chemopreventive agent against colon cancer cells (Jaganathan et al., 2011). Eugenol has not only antitumoural properties in this cell type, but also it has antiproliferative effects in other cells such as prostate or melanoma cancer cells (Ghosh et al., 2005, 2009). In animal models, this compound has demonstrated interesting results. So, when Ehrlich ascites carcinoma (EAC) cells were injected in female mice and then, either 0.2 ml (25% v/v) of honey or eugenol (from 80 to 120 mg/Kg) were administrated intraperitoneally, an inhibitory effect in tumour growth was reported of 30% with eugenol and close to 40% with honey. Another important compound with antitumoural properties is chrysin. This compound and honey (acacia honey) have antiproliferative effects in human (A375) and murine (B16-F1) melanoma cell lines. In this case honey and chrysin induced G0/G1 cell cycle arrest, and hence, chrysin has been considered as a potential candidate for cancer prevention and treatment (Pichichero et al., 2010). In other research, cell viability assay and flow cytometric analysis suggested that chrysin exhibited a dose-dependent and time-dependent ability to block, in G1 phase, rat C6 glioma cell line. It was demonstrated that expression of cyclin-dependent kinase inhibitor, p21, was significantly increased, and both cyclin-dependent kinase 2 and 4 (CDK2, CDK4) kinase activities were reduced by chrysin in a dose-dependent manner (Weng et al., 2005). Several individual compounds of honey have shown apoptotic effects. For instance, galangin is effective as an anti-proliferative and apoptotic agent in human myeloid cell lines (K562 and KCL22) and in imatinib mesylate-resistant myeloid cells (K562-R and KCL22-R). Galangin induced a decrease in Bcl-2 levels and markedly increased the apoptotic activity of imatinib in both imatinib sensitive and imatinib-resistant Bcr-Abl+ cell lines. These observations suggest that galangin is an interesting candidate for a combination therapy in the treatment of imatinib-resistant leukemias (Tolomeo et al., 2008). The honey components quercetin (Murakami et al., 2008), caffeic acid (Nagaoka et al., 2003), acacetin (Shen et al., 2010), kaempferol (Luo et al., 2010), and apigenin (Shukla and Gupta, 2010) have all been studied in relation to cancer.

Not all studies have been conducted on cell and animal models; in fact honey has also been evaluated in clinical cancer cases and with beneficial effects. Honey has been evaluated as a treatment for radiotherapy or chemotherapy, induced mucositis in humans (Motallebnajad et al., 2008; Rashad et al., 2009). Mucositis is a frequently encountered oral complication of both radiation and

Fig. 4. The benefits of honey against cancer at cell, animal and human levels.
chemotherapy of head and neck cancers. In the case of the research to assess the effect of honey against radiation-induced mucositis, Motallebnejad et al. (2008) performed a single blind clinical trial with forty patients with head and neck cancer and under radiotherapy treatment. Twenty of them were administered honey before, during and after radiation and the rest saline before and after radiation. Then, patients were evaluated weekly for mucositis and an important reduction in mucositis among honey-treated patients was found. In view of this result, it can be concluded that honey is an effective treatment in mucositis derived from cancer treatments. Another possible clinical use of honey is in the management of radiation-induced burns in women treated for breast cancer. In this case, women were treated with honey and pentoxifylline and so the area of burned skin was reduced by more than 25% with honey, so that patients underwent shorter radiotherapy treatments (Shoma et al., 2003).

Life Mel honey is a natural honey produced by bees that are fed a blend of different therapeutic herbs such as Calendula, Avena sativa, Echinacea, nettles, ginseng, red clover, Melissa and dandelion, among others. Their flavonoids, vitamins and minerals enrich Life Mel honey and each herb has a specific function to offset the adverse effect of drugs used in cancer patients undergoing chemotherapy. Neutropenia is a common side effect affecting cancer patients under chemotherapy treatments, consisting in a decrease of neutrophils in blood. The low levels of these blood cells put these patients at risk of infections. In fact, Zidan et al. (2006) observed that intake of Life Mel honey helped to prevent neutropenia induced by chemotherapy, and haemoglobin levels were high in 64% of the cases.

If we gather all of these results it is possible to believe that honey is an important source of interesting compounds for the treatment of cancer, and that it can be regarded as a functional food in the cancer field.

**Antiulcer and cardioprotective properties**

Of great interest are the antiulcer properties of honey and, also of propolis, described by Viuda Martos et al. (2008a, 2008b). These authors cited several sources regarding the relationship between the antiulcer action of honeys and their flavonoid content. The antiulcer capacity of honeys has been attributed to their many flavonoids (Gracioso et al., 2002, Batista et al., 2004, Hiruma-Lima et al. 2006). Flavonoids in bee hive products may inhibit the formation of gastric ulcers via various suggested mechanisms. For example, Speroni and Ferri (1993) deduced that these compounds increased the level of mucosal prostaglandins; Vilegas et al. (1999) added that apart from the formation of these prostaglandins, honey flavonoids can also inhibit acid secretions thus preventing ulceration. Another proposed theory to explain the development of gastric ulcers argues that the lesions are provoked by reactive oxygen species, and that the flavonoids in honey scavenge them and thus inhibit lipid peroxidation and so prevent tissue damage (Martin et al., 1998, Young et al., 1999, Duarte et al., 2001). Some studies confirmed the antiulcer activity of some flavonoids found in honey, such as kaempferol and quercetin (Leite et al., 2001, Yao et al., 2004 b, Orsolic and Basic, 2005, Fiorani et al., 2006), also hesperitin and naringin which were both found in orange honey (Ferreres et al., 1993, 1994; Kanaze et al., 2003).

The cardioprotective role of natural honey was studied by Rakha et al. (2008) in relation with the decrease of the vulnerability of the heart to several kinds of cardiac disorders and vasomotor dysfunction associated with hyperadrenergic activity. Hyperadrenergic activity may be caused by stress, emotion, and among physiological causes, there is evidence of a close association between palpitation, tachycardia, arrythmia, and the pheochromocytoma (an adrenaline-secreting tumour of adrenal medullary tissue). Adrenaline (epinephrine), a well-known drug widely used to maintain blood pressure, may cause side effects such as tachycardia, arrythmias, hypertension and oxidative stress. Natural wild honey can ameliorate the cardiac disorders induced by adrenaline injected in urethane-anesthetised rats probably thanks to its total antioxidant capacity and its great pool of enzymatic and non-enzymatic antioxidants involved in cardiovascular defense mechanisms.

The cardiovascular benefits of various flavonoids, their effects on blood pressure and the role played by some molecules such as quercetin and its glycosides in the prevention of the oxidative damage of low density lipoproteins (LDL) are fully described in the literature (Raj Narayana et al., 2001). Some honeys can protect LDL from oxidative damages (Ghelfdof and Engeseth, 2002; Ghdelfdof et al., 2003), and it is important from a clinical aspect, since oxidative modifications of LDL are considered critical in the onset of atherosclerosis (Esterbauer et al., 1992).

**Conclusions**

The phenolic composition of honey appears to have an important role in the health giving properties of bee hive products. Honey, together with other natural foods, seems to be an important component of the human diet.

Increasingly the amount of honey consumed in a well-balanced diet could help to improve the prevention of free radical related-diseases, as well as contributing to the management of more common infective disorders. Honey can also be considered as a natural alternative in the treatment of some herpes, and increasing interest amongst clinicians of the effects of flavonoids such as chrysin, acacetin and apigenin on HIV-1 virus is important.

In the cancer field, honey and some of its compounds, such as eugenol, chrysin and galangin have demonstrated prevention and treatment potential.
On account of its historical background of healthy properties and the increasing experimental knowledge, honey can be regarded, as a functional food which might be reasonably consumed throughout life. Nevertheless, further studies are required to determine and explore the mechanisms of flavonoid/polyphenol derived benefits and to possibly discover new and as yet unreported benefits of this natural product.

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