Saudi Journal of Biological Sciences 25 (2018) 320–325

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Honey: Single food stuff comprises many drugs

Shahid Ullah Khan [a], Syed Ishtiaq Anjum [b,*], Khaista Rahman [c], Mohammad Javed Ansari [d], Wasim Ullah Khan [e], Sajid Kamal [f], Baharullah Khattak [g], Ali Muhammad [a], Hikmat Ullah Khan [c]

[a] Huazhong Agricultural University, Wuhan 430070, PR China
[b] Department of Zoology, Kohat University of Science and Technology, Kohat 26000, Pakistan
[c] Department of Biotechnology, Quaid-i-Azam University, Islamabad, Pakistan
[d] Department of Plant Protection, College of Food and Agriculture Sciences, King Saud University, Riyadh, Saudi Arabia
[e] School of Chemistry and Chemical Engineering, Sun Yat- Sen University, Guangzhou 510275, PR China
[f] School of Biotechnology, Jiangnan University, Wuxi 214122, PR China
[g] Department of Microbiology, Kohat University of Science & Technology, Kohat 26000, Pakistan

ARTICLE INFO

Article history:
Received 16 June 2017
Revised 16 July 2017
Accepted 14 August 2017
Available online 16 August 2017

Keywords:
Honey
Physical properties
Chemistry
Medicinal value
Mechanism of action

ABSTRACT

Honey is a natural food item produced by honey bees. Ancient civilizations considered honey as a God gifted prestigious product. Therefore, a huge literature is available regarding honey importance in almost all religions. Physically, honey is a viscous and jelly material having no specific color. Chemically, honey is a complex blend of many organic and inorganic compounds such as sugars, proteins, organic acids, pigments, minerals, and many other elements. Honey use as a therapeutic agent is as old as human civilization itself. Prior to the appearance of present day drugs, honey was conventionally used for treating many diseases. At this instant, the modern research has proven the medicinal importance of honey. It has broad spectrum anti-biotic, anti-viral and anti-fungal activities. Honey prevents and kills microbes through different mechanism such as elevated pH and enzyme activities. Till now, no synthetic compound that works as anti-bacterial, anti-viral and anti-fungal drugs has been reported in honey yet it works against bacteria, viruses and fungi while no anti-protozoal activity has been reported. Potent anti-oxidant, anti-inflammatory and anti-cancerous activities of honey have been reported. Honey is not only significant as anti-inflammatory drug that relieve inflammation but also protect liver by degenerative effects of synthetic anti-inflammatory drugs. This article reviews physico-chemical properties, traditional use of honey as medicine and mechanism of action of honey in the light of modern scientific medicinal knowledge.

Contents

* Corresponding author.
E-mail addresses: ishtiaq@kust.edu.pk, ishtiaq11@gmail.com (S.I. Anjum).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2017.08.004

1. Introduction

Honey is a super saturated solution or semi-solid natural product synthesized from necter of flower by honey bees (Aljadi and Kamaruddin, 2004; Dashora et al., 2011; Hilary et al., 2017). Honey bees collect nectar, secretion of flowers or other living parts of plants and excretions of plant sucking insects. Honey bees then transform these substances by combining with specific substances of their own. These are deposited, dehydrated and kept in the honey comb for ripening and maturing(Alimentarius, 2001). Honey is the oldest food stuff. It has been used as a major sweetener in the ancient world until sugar cane was cultivated. This is why since ancient times humankind introduced honey and honeybees with much gratitude for their value (Samarghandian et al., 2017; Dewey, 2004).

1.1. Physical properties of honey

Different physical parameters like color, pH, enzyme activity, ash contents, electrical conductivity and even taste of honey varies with honeybee species, geographical origin and presence of impurities (Terrab et al., 2003). The color of honey varies from pale yellow to darkish red to black depending upon plant source. The darkness mostly occurs due to change in temperature (Lawal et al., 2009). The tendency of granule formation is the character of honey which makes it differ from other sweeteners (Bogdanov et al., 2004). Like other physical parameters, the pH of honey also indicates the purity or crudeness of honey but it depends upon the geography of the area. The pH range for Pakistani honey is about 2.4–4.7 (Khaliq UrrRhman et al., 2013). Moisture is the most important determinant of honey solidity. High moisture content is additionally a novel property of honey and is generally ranges from 13–20% (White and Honey, 1978; Jaafar et al., 2017). Like other Newtonian fluids, viscosity of honey depends upon its moisture content and temperature. At 24 °C with 18.9% moisture, the viscosity of honey is approximately 9.9 psa (Zaitoun et al., 2001; Sopade et al., 2003; Yanniotis et al., 2006). Beside all these properties, honey is resistant to spoilage on account of its high sucrose contents. Therefore, it was used as a preservative for other food substances (Lawal et al., 2009).

2. Chemistry of honey

Like physical properties, the chemistry of honey also varies depending upon the geography and purity of the sample. There is no standard scale globally. However, generally honey has a content of 80–85% carbohydrates, 15–17% water, 0.3% proteins, 0.2% ashes and minor quantities of amino-acids, phenols, pigments and vitamins (Bogdanov et al., 2008; Miguel et al., 2017). Beside these other components are also found in minor concentration. The trace elements of honey were determined in mg kg^{-1} as following: Ca (221.9), Mg (54.15), K (579.6), Na (351.4), Fe (8.3), Cu (0.2), Cr (0.5), and Pb (1.1) (Serra, 1989). Cantarelli et al. (2008) analyzed different varieties of honey from different parts of Argentina. They identified a vast range of trace elements in different samples of honey. The major trace elements in μg g^{-1} of honey were: P (1.17–100.66), Fe (1.13–10.32), Al (0.02–13.04), Mn (0.07–0.68), Zn (0.14–3.87), Cu (0.05–0.68), Ca (18.60–136.14), Mg (6.01–46.57), Na (6.10–89.98) and K (90.92–1955.75).

The concentration of trace elements in honey samples collected from Spain, Italy, Turkey and Egypt were also in the same range (Cantarelli et al., 2008). The concentration of trace elements was found in a vast range in honey samples collected from different regions of Poland especially Lead (Pb) ranged from 0.007 to 1.21 mg kg^{-1} (Rostkowski and Omieljaniuk, 1989). Different methods were used to identify diverse elements in honey. Lvanov (1989) developed a method to identify sugars in honey containing lower levels of reducing sugars and higher levels of sucrose (Lvanov, 1989). Similarly Navel methods have been employed to identify the ascorbic acid, nitrogen and protein contents of honey (Men et al., 1989; Siegfried, 1989).

The carbohydrate components of honey contain various types of mono and disccharides. The average concentration of Fructose, Glucose, Sucrose and reducing sugars are 38.38%, 30.31%, 1.31% and 76.65% respectively. Irrespective of the origin or variety of honey, Fructose/Glucose ratio remains the same (i.e. 1.23) (White et al., 1996). Beside these, more than 22 other sugars have been found in honey in which dextrose and laevulose are major ones. Ten disaccharides have been identified in honey including Maltose, Sucrose, Maltulose, Turanose, Isomaltose, Laminaribiose, Nigerose, Kojibiose, Gentiobiose and B-trehalose. Some trisaccharides are also found in honey such as Maltotriose, Erlose, Melezitose, Centose 3-α5 Isomaltosylglucose, l-Kestose, Isomaltotriose, Panose, Psopanose and Theanderose. All these sugars are present in very small quantities (Bogdanov et al., 2004).

The total polyphenol and vitamin C contents in different honey varieties are similar. The polyphenol contents of the honey samples from south Nigeria was found to be in the range of 36.26–102.80 mg 100 g^{-1} with an average of 65.31 mg 100 g^{-1}, while vitamin C contents were observed to be within the range of 13.89 and 27.32 mg 100 g^{-1} with an average of 21.15 ± 3.99 mg 100 g^{-1}. A variety of phytochemicals, as well as other substances including organic acids, vitamins, and enzymes; some of which may serve as sources of dietary antioxidant are also present in honey (Gheldof and Engeseth, 2002; Cantarelli et al., 2008). About 8–11 proteins have been found in various honey sources among which four proteins are common to all varieties of honey. These are originated from honey bee instead of the feeding substance. Honey's proteins are mainly in the form of enzymes (Omafuvbe and Akanbi, 2009). The honey bees add different enzymes during the process of honey ripening. The enzymes added include diastase (amylase), which digest starch to maltose and is relatively stable to heat and storage, and invertase (saccharase or α-glucosidase), which catalyses the conversion of sucrose to glucose and fructose. The invertase also catalyses many other sugar conversions and is mainly responsible for the sugar patterns of honey. Glucose oxidase and catalase are two other enzymes added by the honey bees, which regulate the production of hydrogen peroxide H_2O_2. The H_2O_2 produced serve as one of the anti-bacterial factor of honey (Amir et al., 2010). The differences observed between the total protein contents of honey samples may be attributed by the botanical origin of the honey. Later on it was reported that the diastase and the invertase enzymes differ in wide limits depending on the botanical origin of honey (Khalil et al., 2014). The range of protein contents of honey reported by Bosi and Battalglini is 0.01–0.04 g

100 g^{-1} with proline, lysine, phenylalanine, aspartic acid and glutamic acid as the most abundant amino acids observed (Kamal et al., 2002). The ash content of honey from Nigeria, Pakistan, Bangladesh Argentina, Spain, Turkey and Algeria was <0.6 g 100 g^{-1} (White, 1975; Oddo et al., 1999; Gheldof et al., 2002; Buba et al., 2013).

3. Medicinal value of honey

The concept of using honey as a medicine started at least six thousand years ago (Ball, 2007). The earliest written records on papyri and Sumerian clay tablets clearly demonstrate that honey was used as a medicine before 1900–1250 BC by Egyptians (StomfayStitz and Kominos, 1960). The scientist and philosopher Aristotle (384–322 BC) discussed honey as being a good cream for sore eyes and wounds (Aristotle, 350 BC), while Dioscorides (50 AD) described honey as being good for all rotten and hollow ulcers, sunburn (spots on the face), coughs and inflammation of the throat, and tonsils (Dioscorides et al., 1934). The ancient Greeks were using honey for the treatment of fatigue. Their athletes were utilizing a mixture of honey and water before major athletic events (Willson and Crane, 1975). Zumla and Lulat reviewed that Ancient Chinese, Greeks, Egyptians, Assyrians and Romanians were also using honey to treat their wounds and gut infections (Zumla and Lulat, 1989). More recently, it was found that honey plays a versitale biological perforrmance such as anti-bacterial fungicidal antioxidant. The favorable facts on the anti-oxidant, anti-bacterial, anti-fungicidal, hepatoprotective are recurrently available in the scientific literature. In principle, honey is a valuable supplement for healthy population (Denisow and Denisow-Pietrzyk, 2016). Recent advances in research, literature highlighted that honey has potential biological activities with promising health promoting properties (Muhammad et al., 2016).

All religious books and literature have mentioned honey as a valuable medicine and food (Ajibola et al., 2012). However in modern science, despite its long history as medicine, it was not recognized as therapeutic agent until the recent past. It is due to an incomplete understanding of its mechanism and range of activity (Blair et al., 2009). In 21st century more research is being done on the medicinal use of honey. Now it is rapidly becoming a part of modern medicine (Majtan and Majtan, 2010).

3.1. Honey as a medicine in infectious diseases

The resistance of microbes to modern anti-microbial drugs is a serious problem globally. Scientists are trying to overcome this problem by developing such drugs, to which microbes have no or less resistance. Additionally the drug should have broad spectrum activity. Recently it was reported by Meo and his coworkers that, honey plays a key role in modern medicine development. The nutritional quality of honey is highly effective and show potential properties against reactive oxegen species, inflammation, infectious agents like bacteria and fungi as well as coughs reducing and wound curing characteristics. Honey also plays a major role to improve the reproductive system likes concentration of serum testosterone, sperm count and fertility (Denisow and Denisow-Pietrzyk, 2016; Meo et al., 2017a; Muhammad et al., 2016). Only honey is such a natural food item which is having all these properties.

The following are some of the important medicinal uses of honey in infectious diseases in the light of modern research.

3.2. Antibacterial activities of honey

In 1982, it was first reported that honey has antimicrobial activity. Later on extensive work has been carried on a large number of honey varieties; which showed antimicrobial activity. One of the well-known honey varieties is Manuka (*Leptospermum scoparium*), which has been reported exhibits inhibitory effect against 60 bacterial species. These species include aerobic and anaerobic; Gram-positive and Gram-negative bacteria (Mandal and Mandal, 2011). Research has been carried out on Malaysian Tualang honey, which exhibited broad spectrum activity against enteric bacteria. It was also demonstrated that it could be used effectively to relieve different kinds of wounds (Tan et al., 2009). Similarly work has done on Egyptian honey that has the capability to exhibits *S. typhimurium*and *E. coli* O157:H7 (Amiot et al., 1989). It wasreported that several numbers of honey sample collected from different geographical area and the antimicrobial effects were similar of all sample but considerable variations were found in their composition. Its means that honey contain drug multi-resistance pathogen activity (Noori et al., 2013).

Many varieties of honey from different from plant origin have shown antimicrobial activity, e.g. honey, from Erica (*Erica arborea*); Canola (*Brassica napus*); Castaña (*Castanea sativa*); Abeto (*Pinaceaseabies*); Acacia (*Fabaceae acacia*), and from multi-floral honey. Different honey types have also been reported from diverse geographical origin like Brazil, Ethiopia, New Zealand, Iran, India and Pakistan to have potent antibacterial activity (Soler et al., 1995; Miorin et al., 2003; French et al., 2005; Khalil et al., 2014; Mulu et al., 2017).

The antibacterial mechanism of honey is not fully understood till now (Cooper, 2014; Bradshaw, 2011). However, it is proposed by many researchers that honey inhibit bacterial growth due to a number of different factors. High sugar concentration, low pH, hydrogen peroxide generation, proteinaceous compounds, phenolic compounds, or other unidentified components present in the honey provide antimicrobial activity (Mundo et al., 2004). The higher concentrations of sugars provide osmolarity to honey which is a well-known antimicrobial factor of honey. The low humidity content of honey, leads to aw (water activity) values between 0.56 and 0.62. This hinders the growth of almost any microorganism except certain osmophilic yeasts and bacteria. Several studies concluded that the sugar concentration of honey is the only factor responsible for its antibacterial effect (White et al., 1963; Mundo et al., 2004; Visavadia et al., 2008). Many researchers have demonstrated that protein contents are the main source for providing antimicrobial activity.

The first report about the antimicrobial activity of enzyme glucose oxidase present in honey was proposed by White et al. (1963). According to them, when it is diluted to 50%, it leads to a subsequent increase in the quantity of gluconic acid and hydrogen peroxide, which inhibits the growth of *S. aureus* (Cooper et al., 2002). The glucose oxidase has been considered as an important factor for honey activity. However glucose oxidase does not interact directly with the microorganisms. This enzyme is recognized as an antimicrobial agent given the fact that its products contribute directly to antimicrobial activity (Mohrig, 1968). Lysozyme has also been reported as an antimicrobial agent in honey. This enzyme hydrolyzes the β-1, 4 linkage between the residues of N-acetylmuramic acid and N-acetyl-D-glucosamine in the peptidoglycan of the bacterial wall (Molan, 1992). Lysozyme was found to be present in 71 honey samples. Other studies revealed its absence in some samples of honey (Casteels-Josson et al., 1994; Bogdanov et al., 2008).

More recently it was reported that not only the enzymes but other proteins biomolecules present in honey, contribute to antimicrobial activity of honey (Casteels-Josson et al., 1994). Such biomolecules consist of antimicrobial peptides, such as bee defensin-1, also known as royalisin. This peptide was previously identified in bee haemolymph (Klaudiny et al., 2005). It is also present in the head and thoracic section of bees and in royal jelly (the main food of queen bee larvae) It has been reported that bee

defensin-1 shows a powerful activity against gram-positive bacteria, including *B. subtilis*, *S. aureus*, and *Paenibacillus* larvae (Kwakman et al., 2011; Kwakman and Zaat, 2012). But still the mechanism of action has not been described in detail. This peptide can be considered an antimicrobial agent of honey (Majtan et al., 2012). Furthermore, it was found that the synergistic effect of honey and propolis inhibit the antimicrobial activity of single and mixed microbial culture (Noori et al., 2012).

MRJP1 (Major Royal Jelly Protein 1) is a multifunctional protein that acts as a precursor of short antimicrobial peptides jelleines is also present in honey (Eick et al., 2014). Most recently it has been identified that methylglyoxal component of honey kills *P. gingivalis* (a common pathogenic bacteria of mouth), therefore honey can be used for oral disease treatment (Zeina et al., 1996).

3.3. Antiviral activities of honey

A number of studies suggest that some varieties of honey have strong activity against certain viruses (Shahzad and Cohrs, 2012; Watanabe et al., 2014) A. In 1996, Zeina suggest that honey has effective role against rubella virus (Sankum et al., 2002). Similar study on royal jelly suggested strong antiviral activity against herpes simplex virus (HSV) (Hashemipour et al., 2014). The antiviral activity of royal jelly is greater than honey (Izuta et al., 2009).

The mechanism of antiviral activity of royal jelly has been ascribed to the impact of 10-HAD (10-Hydroxy-2-Decenoic Acid). This fatty acid stimulates white blood cells (WBCs), resulting in the adhesion of WBCs to viruses such as HSV and hepatitis viruses, leading to their destruction (Shahzad and Cohrs, 2012). Pure clover and Manuka honey have anti-Varicella Zoster virus (VZV) activities. It can prevent skin infection but its mechanism of action is not still known (Zareie, 2011). Research carried out in University of Waikato described the antiviral activity of honey against Respiratory Syncytial Virus (Feás and Estevinho, 2011).

3.4. Anti-fungal activities of honey

Fungi are abundantly differentiated in nature and environmentally essential symbionts on earth, forming mycorrhizas with around 66% of all plant species and occurring in basically all biological communities (Helgason et al., 2007). Many species of fungi are more pathogenic than bacteria. Candadia is among the most pathogenic and opportunistic species of phylum fungi. The cases of Candadia infection are elevating day by day. The increased use of antifungal agents resulted in development of resistance to the synthetic drugs presently available. It makes necessary to discover new classes of antifungal compounds, to cure fungal infections. Natural products have been traditionally used in the treatment of diseases, as these consist of many active compounds. Honey being one of these products (Molan, 2002).

Honey may have a large variance in therapeutic components depending on its origin. The floral source of honey plays an important role in its biological properties (Molan, 2002). It has proven that some varieties of honey have anti-fungal activities against some species of yeast including candadia (Kacaniova et al., 2009). It wasinvestigated that jujube honey has a potential antifungal propertiy against *C. albicans* and also capable to stop the development of *C. albicans* biofilms and interrupt the developed biofilms (Ansari et al., 2013).

The antifungal activity of honey is due to many characteristics but a study revealed that the ethanolic extract of honey is having strong antifungal activity as compare to pure honey or any other solvent extract (Khosravi-Darani et al., 2013). Recently it has been proven that different plant extracts in combination with honey synergize the anti-fungal properties of honey. This will help in future to use honey in combination with many other natural products for treating fungal diseases (Swellam et al., 2003).

3.5. The anti-tumor and anti-oxidant properties of honey

Different studies indicated that honey can be used as natural medicine for treating cancer (Attia et al., 2008; Pichichero et al., 2010; Fernandez-Cabezudo et al., 2013) A study concluded that honey showed in vitro anti-proliferative effect in bladder cancer cells used T24, RT4, 253J and MBT2 bladder cancer cell lines (Lee et al., 2003). Similar study showed that honey has caffeic acid phenyl esters (CAPE) which arrest cell growth in the sub G1 phase of cancerous cell cycle and induce apoptosis of cells by activation of caspase-3 by CAPE protein (Oršolić et al., 2005). Moreover studies also suggested that the anti-tumour effect of honey mostly depends upon the time of application. It is likely that polyphenolic components present in honey, stimulate host anti-tumour defense system. Even in the presence of a tumour, the nutritive constituents of honey prevail. It is possible that honey promotes tumour growth since it contains a mixture of vitamins, minerals and amino acids, as well as a large amount of glucose. In addition, its high osmolarity induces an outflow of lymph. This enhances nutrification and oxygenation, and its acidity favors release of oxygen from hemoglobin in the capillaries of adjacent tissues (Shati and Alamri, 2010).

Honey has remarkable reactive oxygen species (ROS) scavenging activities. This effect might be due to the phenolic content and the lipid metabolism-enhancing effect of honey (Elmenoufy, 2012). This is a beneficial effect of honey, which has the ability to counteract the oxidative damage and protect liver and kidney tissues (Beretta et al., 2010).

3.6. Honey cure Inflammatory, hepatic and many more problems

Honey can act as anti-inflammatory agent. It can be used in the management of wounds healing (Postmes and Vandeputte, 1999). In vivo study of honey on injured tissue showed that honey reduces the amount of wound exudate. This is most likely a consequence of honey's anti-inflammatory properties (Molan, 2002). A decrease in inflammatory cells has been found in animal models following honey application on full-thickness burns. Similar findings have been reported in animal studies comparing ampicillin and nitro fuazone in treating infection of full-thickness wounds (Reyes-Gordillo et al., 2007). It has been reported that honey inhibited enzymes involved in inflammation such as cyclooxygenase-1 and cyclooxygenase-2. It also decreased the amount of poten inflammatory compounds including prostaglandins such as PGE2 (prostaglandin E2), PGF2α (prostaglandin F2α) and thromboxane B2 in plasma (Erguder et al., 2008).

The protective and therapeutic effects of honey in liver disorders have also been identified. Honey can prevent damage of liver due to bile duct obstruction (Adeleye and Opiah, 2003). Other studies indicated that honey has protective role against certain drugs mediated hepatotoxicity (Zeina et al., 1996). Traditionally honey has been used for treatment of cough in both, children and adults (Croft, 1990). Therefore honey is being used as a key ingredient in many cough syrups (White and Honey, 1978). Al-Wailiand his coworkers reported the clinical research of honey that honey has a great impact in the human health status. They described that honey has many biological activities rather then antimicrobial activities (Al-Waili et al., 2013). Honey reduced the cardiovascular risk factors and has many effects on several metabolic factors. Recently clinical research was also carried out about honey and concluded that honey provide a defensive effect from lead-induced blood, hepatic renal toxic effects (Fihri et al., 2016).

Honey also has therapeutic effects in Hey fever and diabetes mellitus (as it reduces glucose level in blood) (Sirnik et al., 1978). It is also used for treatment of cardiovascular disorders and high level of High Density Lipids in blood (Onyesom, 2004). It is a good appetizer and is used for treating disorders related to digestive tract (Ladas and Raptis, 1999). It is also used against alcohol abuse (Ladas and Raptis, 1999), constipation (laxative agent) (Küplülü et al., 2006), and some types of allergies (Bogdanov, 2014). More recently, it is reported that honey decreased the level of diabetes mellitus and also reduced the level of those compounds which involved in the development of diabetes mellitus. Honey also has a property of antioxidant and anti-inflammatory (Meo et al., 2017b) However, honey contains *Clostridium botulinum*spores. If used for infants, it is risky for their health because of poor immunity against *Clostridium botulinum* (Küplülü et al., 2006).

4. Conclusion

Honey is not food stuff only but a combination of many medicinally important chemicals either from plant or honey bee. Therefore, honey is used in drug manufacturing in modern medicinal companies. The combined effect of honey and plant extracts has opened a door for developing a safe and highly potent natural drug against contagious diseases like tuberculosis, tetanus, influenza, hepatitis and human immune deficiency syndrome. Beside these all, it will also overcome the serious problem of microbial resistance to synthetic antimicrobial drugs. Therefore it is still an open window for researchers to work on it and contribute to the science of this prestigious God gifted product.

Acknowledgments

The author has been supported by the Chinese Scholarship Council for his PhD study.

References

Adeleye, I., Opiah, L., 2003. Antimicrobial activity of extracts of local cough mixtures on upper respiratory tract bacterial pathogens. West Indian Med. J 52 (3), 188–190.
Ajibola, A., Chamunorwa, J.P., Erlwanger, K.H., 2012. Nutraceutical values of natural honey and its contribution to human health and wealth. Nutr. Metab. 9 (1), 61.
Al-Waili, N., Salom, K., Al-Ghamdi, A., Ansari, M.J., Al-Waili, A., Al-Waili, T., 2013. Honey and cardiovascular risk factors, in normal individuals and in patients with diabetes mellitus or dyslipidemia. J. Med. Food 16 (12), 1063–1078.
Alimentarius, C., 2001. Revised codex standard for honey. Codex Stan 12, 1982.
Aljadi, A., Kamaruddin, M., 2004. Evaluation of the phenolic contents and antioxidant capacities of two malaysian floral honeys. Food Chem. 85 (4), 513–518.
Amiot, M., Aubert, S., Gonnet, M., Tacchini, M., 1989. Les composés phénoliques des miels: Étude préliminaire sur l'identification et la quantification par familles. Apidologie 20 (2), 115–125.
Amir, Y., Yesli, A., Bengana, M., Sadoudi, R., Amrouche, T., 2010. Physico-chemical and microbiological assessment of honey from Algeria. Electron. J. Environ., Agric. Food Chem. 9 (9), 1485–1494.
Ansari, M.J., Al-Ghamdi, A., Usmani, S., Al-Waili, N.S., Sharma, D., Nuru, A., Al-Attal, Y., 2013. Effect of jujube honey on candida albicans growth and biofilm formation. Arch. Med. Res. 44 (5), 352–360.
Attia, W.Y., Gabry, M.S., El-Shaikh, K.A., Othman, G.A., 2008. The anti-tumor effect of bee honey in Ehrlich ascite tumor model of mice is coincided with stimulation of the immune cells. Egypt. J. Immunol. 15 (2), 169–183.
Ball, D.W., 2007. The chemical composition of honey. J. Chem. Educ. 84 (10), 1643.
Beretta, G., Gelmini, F., Lodi, V., Piazzalunga, A., Facino, R.M., 2010. Profile of nitric oxide (no) metabolites (nitrate, nitrite and n-nitroso groups) in honeys of different botanical origins: Nitrate accumulation as index of origin, quality and of therapeutic opportunities. J. Pharm. Biomed. Anal. 53 (3), 343–349.
Blair, S., Cokcetin, N., Harry, E., Carter, D., 2009. The unusual antibacterial activity of medical-grade leptospermum honey: Antibacterial spectrum, resistance and transcriptome analysis. Eur. J. Clin. Microbiol. Infectious Dis. 28 (10), 1199–1208.
Bogdanov, S., 2014. Propolis: composition, health, medicine: a review. Bee Product Sci., 1–40
Bogdanov, S., Jurendic, T., Sieber, R., Gallmann, P., 2008. Honey for nutrition and health: a review. J. Am. Coll. Nutr. 27 (6), 677–689.
Bogdanov, S., Ruoff, K., Oddo, L., 2004. Physico-chemical methods for the characterisation of unifloral honeys: a review. Apidologie 35 (Suppl. 1), S4–S17.
Bradshaw, C.E., 2011. An in vitro comparison of the antimicrobial activity of honey, iodine and silver wound dressings. Biosci. Horizons 4 (1), 61–70.
Buba, F., Gidado, A., Shugaba, A., 2013. Analysis of biochemical composition of honey samples from north-east nigeria. Biochem. Anal. Biochem. 2 (3), 139.
Cantarelli, M., Pellerano, R., Marchevsky, E., Camiña, J., 2008. Quality of honey from Argentina: study of chemical compositтion and trace elements. J. Argentine Chem. Soc. 96 (1–2), 33–41.
Casteels-Josson, K., Zhang, W., Capaci, T., Casteels, P., Tempst, P., 1994. Acute transcriptional response of the honeybee peptide-antibiotics gene repertoire and required post-translational conversion of the precursor structures. J. Biol. Chem. 269 (46), 28569–28575.
Cooper, R., Molan, P., Harding, K., 2002. The sensitivity to honey of gram-positive cocci of clinical significance isolated from wounds. J. Appl. Microbiol. 93 (5), 857–863.
Cooper, R., 2014. Honey as an effective antimicrobial treatment for chronic wounds: is there a place for it in modern medicine? Chronic Wound Care Manage. Res. 1, 15–22.
Croft, L.R., 1990. Honey and hay fever: a report on the treatment of hay fever with honey. LR Croft.
Dashora, N., Sodde, V., Bhagat, J., Prabhu, K.S., Lobo, R., 2011. Antitumor activity of dendrophthoe falcata against ehrlich ascites carcinoma in swiss albino mice. Pharm Crops 2, 1–7.
Denisow, B., Denisow-Pietrzyk, M., 2016. Biological and therapeutic properties of bee pollen: a review. J. Sci. Food Agric. 96 (13), 4303–4309.
Dewey, M., Caron, 2004. Honey. Mid Atlantic Apiculture Rsearch and Extension consortium publications.
Dioscorides, P., Goodyer, J., Gunther, R.T., 1934. The Greek Herbal of Dioscorides. University Press.
Eick, S., Schäfer, G., Kwieciński, J., Atrott, J., Henle, T., Pfister, W., 2014. Honey–a potential agent against porphyromonas gingivalis: an in vitro study. BMC Oral Health 14 (1), 24.
Elmenoufy, G.A., 2012. Bee honey dose-dependently ameliorates lead acetate-mediated hepatorenal toxicity in rats. Life Sci. J. 9 (4), 780–788.
Erguder, B.I., Kilicoglu, S.S., Namuslu, M., Kilicoglu, B., Devrim, E., Kismet, K., Durak, I., 2008. Honey prevents hepatic damage induced by obstruction of the common bile duct. World J. Gastroenterol. 14 (23), 3729–3732.
Feás, X., Estevinho, M.L., 2011. A survey of the in vitro antifungal activity of heather (erica sp.) organic honey. J. Med. Food 14 (10), 1284–1288.
Fernandez-Cabezudo, M.J., El-Kharrag, R., Torab, F., Bashir, G., George, J.A., El-Taji, H., Al-Ramadi, B.K., 2013. Intravenous administration of manuka honey inhibits tumor growth and improves host survival when used in combination with chemotherapy in a melanoma mouse model. PLoS One 8 (2), e55993.
Fihri, A.F., Al-Waili, N.S., El-Haskoury, R., Bakour, M., Amarti, A., Ansari, M.J., Lyoussi, B., 2016. Protective effect of morocco carob honey against lead-induced anemia and hepato-renal toxicity. Cell. Physiol. Biochem. 39 (1), 115–122.
French, V., Cooper, R.A., Molan, P.C., 2005. The antibacterial activity of honey against coagulase-negative staphylococci. J. Antimicrob. Chemother. 56 (1), 228–231.
Gheldof, N., Engeseth, N.J., 2002. Antioxidant capacity of honeys from various floral sources based on the determination of oxygen radical absorbance capacity and inhibition of in vitro lipoprotein oxidation in human serum samples. J. Agric. Food Chem. 50 (10), 3050–3055.
Gheldof, N., Wang, X.-H., Engeseth, N.J., 2002. Identification and quantification of antioxidant components of honeys from various floral sources. J. Agric. Food Chem. 50 (21), 5870–5877.
Hashemipour, M.A., Tavakolineghad, Z., Arabzadeh, S., Iranmanesh, Z., Nassab, S., 2014. Antiviral activities of honey, royal jelly, and acyclovir against hsv-1. Wounds: Compendium Clin. Res. Pract., 26(2), 47–54.
Helgason, T., Merryweather, J.W., Young, J.P.W., Fitter, A.H., 2007. Specificity and resilience in the arbuscular mycorrhizal fungi of a natural woodland community. J. Ecol. 95 (4), 623–630.
Hilary, S., Habib, H., Souka, U., Ibrahim, W., Platat, C., 2017. Bioactivity of arid region honey: an in vitro study. BMC Complement. Altern. Med. 17 (1), 177.
Izuta, H., Chikaraishi, Y., Shimazawa, M., Mishima, S., Hara, H., 2009. 10-hydroxy-2-decenoic acid, a major fatty acid from royal jelly, inhibits vegf-induced angiogenesis in human umbilical vein endothelial cells. Evidence-Based Complement. Altern. Med. 6 (4), 489–494.
Jaafar, K., Haidar, J., Kuraydiyyah, S., Ghaddar, T., Knio, K., Ismail, B., Toufeili, I., 2017. Physicochemical, melissopalynological and antioxidant properties of artisanal honeys from Lebanon. J. Food Sci. Technol. 54 (8), 2296–2305.
Kacaniova, M., Melich, M., Knazovicka, V., Felsociova, S., Sudzinova, J., 2009. The antimicrobial activity of honey and propolis against yeasts candida species. Sci. Papers Anim. Sci. Biotechnol. 42 (2), 167–173.
Kamal, A., Raza, S., Rashid, N., Hameed, T., Gilani, M., Qureshi, M.A., Nasim, K., 2002. Comparative study of honey collected from different flora of pakistan. Online JB Sci. 2, 626–627.
Khalil, A.T., Khan, I., Ahmad, K., Khan, Y.A., Khan, J., Shinwari, Z.K., 2014. Antibacterial activity of honey in north-west pakistan against select human pathogens. J. Tradit. Chin. Med. 34 (1), 86–89.
Khaliq UrrRhman, A.H., Ullah Shafqat, Ullah Imdad, Zai Muhammad, 2013. Phytochemical analysis and chemical composition of different branded and unbranded honey samples. Int. J. Microbiol. Res., 4(2), 132–7.
Khosravi-Darani, K., Khaksar, R., Esmaeili, S., Seyed-Reihani, F., Zoghi, A., Shahbazizadeh, S., 2013. Antifungal and anti-bacterial synergistic effects of mixture of honey and herbal extracts. Zahedan J. Res. Med. Sci. 15 (8), 30–33.

Klaudiny, J., Albert, Š., Bachanová, K., Kopernický, J., Šimúth, J., 2005. Two structurally different defensin genes, one of them encoding a novel defensin isoform, are expressed in honeybee apis mellifera. Insect Biochem. Mol. Biol. 35 (1), 11–22.
Küplülü, Ö., Göncüoğlu, M., Özdemir, H., Koluman, A., 2006. Incidence of clostridium botulinum spores in honey in turkey. Food Control 17 (3), 222–224.
Kwakman, P.H., de Boer, L., Ruyter-Spira, C., Creemers-Molenaar, T., Helsper, J., Vandenbroucke-Grauls, C., Zaat, S., Te Velde, A., 2011. Medical-grade honey enriched with antimicrobial peptides has enhanced activity against antibiotic-resistant pathogens. Eur. J. Clin. Microbiol. Infectious Dis. 30 (2), 251–257.
Kwakman, P.H., Zaat, S.A., 2012. Antibacterial components of honey. IUBMB Life 64 (1), 48–55.
Ladas, S.D., Raptis, S.A., 1999. Honey, fructose, absorption and the laxative effect. Nutrition 15 (7–8), 591–592.
Lawal, R., Lawal, A., Adekalu, J., 2009. Physico-chemical studies on adulteration of honey in nigeria. Pak. J. Biol. Sci.: PJBS 12 (15), 1080–1084.
Lee, Y.-J., Kuo, H.-C., Chu, C.-Y., Wang, C.-J., Lin, W.-C., Tseng, T.-H., 2003. Involvement of tumor suppressor protein p53 and p38 mapk in caffeic acid phenethyl ester-induced apoptosis of c6 glioma cells. Biochem. Pharmacol. 66 (12), 2281–2289.
Lvanov, T., 1989. Experiments on bee keeping. Kubratovo. Bulg. Zhivotnovud. Nauki 25, 96–103.
Majtan, J., Klaudiny, J., Bohova, J., Kohutova, L., Dzurova, M., Sediva, M., Bartosova, M., Majtan, V., 2012. Methylglyoxal-induced modifications of significant honeybee proteinous components in manuka honey: possible therapeutic implications. Fitoterapia 83 (4), 671–677.
Majtan, J., Majtan, V., 2010. Is manuka honey the best type of honey for wound care? J. Hosp. Infect. 74 (3), 305–306.
Mandal, M.D., Mandal, S., 2011. Honey: Its medicinal property and antibacterial activity. Asian Pac. J. Tropical Biomed. 1 (2), 154–160.
Men, R., Liu, S., Yan, S., 1989. Determination of ascorbic acid in food using photochemical generation of iodine. Fenxi Huaxue 17, 903–905.
Meo, S.A., Al-Asiri, S.A., Mahesar, A.L., Ansari, M.J., 2017a. Role of honey in modern medicine. Saudi J. Biol. Sci. 24, 975–978.
Meo, S.A., Ansari, M.J., Sattar, K., Chaudhary, H.U., Hajjar, W., Alasiri, S., 2017b. Honey and diabetes mellitus: Obstacles and challenges–road to be repaired. Saudi J. Biol. Sci. 24, 1030–1033.
Miguel, M., Antunes, M., Faleiro, M., 2017. Honey as a complementary medicine. Integrative Med. insights, 12.
Miorin, P., Levy Junior, N., Custodio, A., Bretz, W., Marcucci, M., 2003. Antibacterial activity of honey and propolis from apis mellifera and tetragonisca Angustula against staphylococcus aureus. J. Appl. Microbiol. 95 (5), 913–920.
Mohrig, W., 1968. Lysozym als antibakterielles agens im bienenhonig und bienengift. Acta Biol. Med. Germanica 21 (13), 85–95.
Molan, P.C., 1992. The antibacterial activity of honey: 1. The nature of the antibacterial activity. Bee World 73 (1), 5–28.
Molan, P.C., 2002. Re-introducing honey in the management of wounds and ulcers-theory and practice.
Muhammad, A., Odunola, O.A., Ibrahim, M.A., Sallau, A.B., Erukainure, O.L., Aimola, I. A., Malami, I., 2016. Potential biological activity of acacia honey. Front. Biosci. (Elite Ed.) 8, 351–357.
Mulu, A., Tessema, B., Derbie, F., 2017. In vitro assessment of the antimicrobial potential of honey on common human pathogens. Ethiopian J. Health Dev. (EJHD) 18 (2).
Mundo, M.A., Padilla-Zakour, O.I., Worobo, R.W., 2004. Growth inhibition of foodborne pathogens and food spoilage organisms by select raw honeys. Int. J. Food Microbiol. 97 (1), 1–8.
Noori, A., Al-Ghamdi, A., Ansari, M.J., Al-Attal, Y., Salom, K., 2012. Synergistic effects of honey and propolis toward drug multi-resistant staphylococcus aureus, escherichia coli and candida albicans isolates in single and polymicrobial cultures. Int. J. Med. Sci. 9 (9), 793.
Noori, A., Al Ghamdi, A., Ansari, M.J., Al-Attal, Y., Al-Mubarak, A., Salom, K., 2013. Differences in composition of honey samples and their impact on the antimicrobial activities against drug multiresistant bacteria and pathogenic fungi. Arch. Med. Res. 44 (4), 307–316.
Oddo, L.P., Piazza, M.G., Pulcini, P., 1999. Invertase activity in honey. Apidologie 30, 57–66.
Omafuvbe, B., Akanbi, O., 2009. Microbiological and physico-chemical properties of some commercial nigerian honey. Afr. J. Microbiol. Res. 3 (12), 891–896.
Onyesom, I., 2004. Effect of nigerian citrus (citrus sinensis osbeck) honey on ethanol metabolism. S. Afr. Med. J. 94 (12).
Oršolić, N., Terzić, S., Šver, L., Bašić, I., 2005. Honey-bee products in prevention and/or therapy of murine transplantable tumours. J. Sci. Food Agric. 85 (3), 363–370.
Pichichero, E., Cicconi, R., Mattei, M., Muzi, M.G., Canini, A., 2010. Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression. Int. J. Oncol. 37 (4), 973–981.
Postmes, T., Vandeputte, J., 1999. Recombinant growth factors or honey? Burns: J. Int. Soc. for Burn Injuries, 25(7), 676.
Reyes-Gordillo, K., Segovia, J., Shibayama, M., Vergara, P., Moreno, M.G., Muriel, P., 2007. Curcumin protects against acute liver damage in the rat by inhibiting nf-κb, proinflammatory cytokines production and oxidative stress. Biochim. Biophys. Acta (BBA)-General Subjects, 1770(6), 989-996.
Rostkowski, J., Omieljaniuk, N., 1989. Determination of lead content in honey in poland. Bromatol. Chem Toksykol. 25, 319–327.
Samarghandian, S., Farkhondeh, T., Samini, F., 2017. Honey and health: A review of recent clinical research. Pharmacogn. Res. 9 (2), 121.
Sankum, M., Kuntaruk, S., Chantawannakul, P., Tragoolpua, Y.,, 2002. Effect of royal jelly against herpes simplex virus type 2 infection. Poster presented at: Thai society of virology conference; april 26-may 1, Bangkok, Thailand.
Serra, B., 1989. A study of physicochemical properties of eucalyptus honey in Spain. An. Bromatol. 41, 41.
Shahzad, A., Cohrs, R.J., 2012. In vitro antiviral activity of honey against varicella zoster virus (vzv): a translational medicine study for potential remedy for shingles. Transl. Biomed. 3 (2).
Shati, A.A., Alamri, S.A., 2010. Role of saffron (crocus sativus l.) and honey syrup on aluminum-induced hepatotoxicity. Saudi Med. J. 31 (10), 1106–1113.
Siegfried, R., 1989. Determination of protein and total nitrogen using fp-228 in comparison with other methods. Fresenius Zeitschrift fur Analytische Chemie 335 (5), 489–492.
Sirnik, V., Koch, V., Golob, T., 1978. The influence of honey on the digestibility of nutritive substances for albin rats (l'influence du miel sur la digestibilité des substances nutritives chez le rat albinos). In: IIIe Symposium International d'Apitherapie, 11–15 Septembre 1978, Portoroz, Yougoslavie, pp: 286–290.
Soler, C., Gil, M., Garcia-Viguera, C., Tomás-Barberán, F., 1995. Flavonoids patterns of French honeys with different floral origin. Apidologie 26 (1), 53–60.
Sopade, P.A., Halley, P., Bhandari, B., D'Arcy, B., Doebler, C., Caffin, N., 2003. Application of the williams–landel–ferry model to the viscosity–temperature relationship of australian honeys. J. Food Eng., 56(1), 67–75. Available from <http://www.sciencedirect.com/science/article/pii/S0260877402001498>. https://doi.org/10.1016/S0260-8774(02)00149-8.
StomfayStitz, J., Kominos, S.D., 1960. Uber bakteriostatische wirkung des honigs. Zeitschrift fur lebensmittelunteruchung und forschung. 113, 304–309.
Swellam, T., Miyanaga, N., Onozawa, M., Hattori, K., Kawai, K., Shimazui, T., Akaza, H., 2003. Antineoplastic activity of honey in an experimental bladder cancer implantation model: in vivo and in vitro studies. Int. J. Urol. 10 (4), 213–219.
Tan, H.T., Rahman, R.A., Gan, S.H., Halim, A.S., Asma'Hassan, S., Sulaiman, S.A., Kirnpal-Kaur, B., 2009. The antibacterial properties of malaysian tualang honey against wound and enteric microorganisms in comparison to manuka honey. BMC Complement. Altern. Med. 9 (1), 34.
Terrab, A., González, A.G., Díez, M.J., Heredia, F.J., 2003. Characterisation of moroccan unifloral honeys using multivariate analysis. Eur. Food Res. Technol. 218 (1), 88–95.
Visavadia, B.G., Honeysett, J., Danford, M.H., 2008. Manuka honey dressing: An effective treatment for chronic wound infections. Br. J. Oral Maxillofac. Surg. 46 (1), 55–56.
Watanabe, K., Rahmasari, R., Matsunaga, A., Haruyama, T., Kobayashi, N., 2014. Anti-influenza viral effects of honey in vitro: potent high activity of manuka honey. Arch. Med. Res. 45 (5), 359–365.
White, J., Honey Jr, 1978. Honey. Adv. Food Res. 24, 288–374.
White, J., White, Jr., Mary, L., Riethof, Mary, Subers, H., Irene, Kushnir, 1996. Eastern utilization research and development division, agricultural research service, philadelphia, pa. Composition of american honeys tech bull 1261, ars usda.
White Jr, J.W., 1975. Physical characteristics of honey. Honey: A Comprehensive Survey. E. Crane, ed.
White, J.W., Subers, M.H., Schepartz, A.I., 1963. The identification of inhibine, the antibacterial factor in honey, as hydrogen peroxide and its origin in a honey glucose-oxidase system. Biochim. Biophys. Acta (BBA)-Specialized Section Enzymol. Subjects, 73(1), 57–70.
Willson, R., Crane, E., 1975. Uses and products of honey. In: Crane E. (Ed,), Honey: A Comprehensive Survey.
Yanniotis, S., Skaltsi, S., Karaburnioti, S., 2006. Effect of moisture content on the viscosity of honey at different temperatures. J. Food Eng., 72(4), 372–377. Available from <http://www.sciencedirect.com/science/article/pii/S0260877405000208>. https://doi.org/10.1016/j.jfoodeng.2004.12.017.
Zaitoun, S., Ghzawi, A.A.-M., Al-Malah, K.I.M., Abu-Jdayil, B., 2001. Rheological properties of selected light colored jordanian honey. Int. J. Food Prop. 4 (1), 139–148. http://dx.doi.org/10.1081/JFP-100002192.
Zareie, P.P., 2011. Honey as an Antiviral Agent Against Respiratory Syncytial Virus. University of Waikato.
Zeina, B., Othman, O., Al-Assad, S., 1996. Effect of honey versus thyme on rubella virus survival in vitro. J. Altern. Complement. Med. 2 (3), 345–348.
Zumla, A., Lulat, A., 1989. Honey–a remedy rediscovered. J. R. Soc. Med. 82 (7), 384.