Pharmaceutical Applications of Honey

14

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Abstract

Currently, researchers are oriented to the use of several natural products as alternatives in curing various ailments. Among natural products, honey occupies a great position as a sweetening agent as well as a magic remedy for a large list of diseases. Several studies had been conducted on different types of honeys. At first, most of the studies were focused on the use of honey as a natural antimicrobial. Afterwards, many pharmaceutical applications have been knocked. The well-known anti-inflammatory, antioxidant, and antimicrobial characteristics of honey suggest its use to promote wound healing, relief oxidative stress in case of cardiovascular diseases and cure several infectious and inflammatory diseases. Honey has proved its effectiveness in eradication of multidrug resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), controlling blood sugar in diabetic patients, accelerating healing of wounds and chronic ulcers, improving cough and asthma, treatment of different types of cancers, and reducing symptoms associated with periodontal diseases.

Keywords

Honey · Antimicrobial · Antioxidant · Anti-inflammatory · Wound · Cough · Diabetes

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14.1 Introduction

Honey is considered as a treasure trove of nature. Since antiquity, honey had been used as a cure for several diseases as well as a dietary supplement. Benefits of Honey were mentioned in the holy books, Papyrus and even engraved in stones (Pathare et al. 2015). Honey originating from a single flower is termed as monofloral honey and that produced from more than one flower is termed as polyfloral honey. There are numerous types of honey related to its botanical origin. The composition of each honey type varies with its floral source, geographical origin and season of collection as well. That's why some honeys can exert certain therapeutic activities while others cannot. About 80% of honey is fructose and glucose. Other components of honey include proteins, vitamins, minerals, flavonoids, and phenolic acids (Sakač et al. 2019). This chapter will shed light to the possible biological activities of honey and its major pharmaceutical applications in reducing symptoms of some diseases such as wounds and chronic ulcers, cough, asthma, dental problems, diabetes, and cancer. Table 14.1 shows some currently available pharmaceutical products of honey.

14.2 Honey as Antimicrobial Agent

Development of microbial resistance is the major health problem that threatens human being and livestock as well (Levy and Marshall 2004). The rapid emergence of multidrug resistance gave a warning alarm for scientists to look for new antimicrobial agents or seek in the past for ancient remedies thought to have antimicrobial activity and reevaluate their efficacy as antimicrobials. Among these remedies is the bee's honey that has been used for long time for its nutritional and therapeutic values (Mandal and Mandal 2011). Table 14.2 shows some examples of microbial pathogens that proved sensitivity to honey.

14.2.1 Honey as Antibacterial

Bee's honey has proven to have antibacterial activity against various array of bacterial pathogens either gram positive e.g., *Staphylococcus aureus*, *Bacillus anthracis*, *Streptococcus pneumonia*, *Streptococcus mutans,* and *Enterococcus faecalis* or gram negative e.g., *Escherichia coli*, *Salmonella typhi, Shigella species, Proteus species, Pseudomonas aeruginosa, Klebsiella pneumoniae, Helicobacter pylori, Haemophilus infleunza* and *Vibrio cholerae* (Abeshu and Geleta 2016).

14.2.1.1 Mechanisms Exerted by Honey as Antibacterial

The mechanism by which honey exerts its antibacterial activity is multifactorial, that's why resistance to honey is not detected in tested bacterial isolates (Cooper et al. 2010). Also, resistance to honey is minimized by its antimutagenic and

Table 14.1 A list of some available pharmaceutical products of honey

Product	Category	Manufacturer
Manuka honey	Nutritional and health benefits	Honeybee Centre
Magnificent Manuka honey soap bar	Cleansing and antibacterial for skin and hair	
Clover honey and lavender soap bar		
Wedder spoon Manuka lozenges (with eucalyptus and menthol or with ginger and Echinacea	Soothing the irritated tissues of the throat	
Day time soothing syrup with UMF™ 10+ Manuka honey	Soothing irritated throats and cough	Comvita
Night time soothing syrup with UMF™ 10+ Manuka honey		
Chewing vitamin-fortified candy from honey and wax	Substitute for chewing gums	
Skin therapy cream	Skin care products	Natural beauty
Manuka honey hydrating cream		
Clarify and illuminate cleanser		
Orange honey blossom extraordinary beauty oil		
Simple Manuka hand cream		
Honey infused hair mask	Hair care products	Gisou
Honey infused hair conditioner		
Honey infused hair wash		
Honey infused hair perfume		
Honey infused hair oil		
Revamil wound dressing	Wound and burn care products	Oswell Penda Pharmaceuticals
Revamil melginate wound dressing		
Revamil collagen wound dressing		
Revamil wound gel		
Revamil balm wound ointment		
Medihoney antibacterial wound gel		Comvita

antiproliferative activity. Previous studies reported that bacterial cells exposed to Manuka honey do not proceed in the normal cell division cycle but slowed down its division rate. This may be due to affection of honey to a genomic site in the bacteria that is important in cell division (Abdel-Azim et al. 2019).

Honey has numerous components that act individually to inhibit bacterial growth or coincide together to strengthen its power against bacteria. Mechanisms for antibacterial activity of honey can be summarized as follows:

– Honey has high osmolarity that originates from the high sugar content of honey. Most of bacteria cannot survive the high osmolarity.
– The pH of honey is low (in the acidic range), so it doesn't suit the growth of most bacterial pathogens which favors neutral pH (Mandal and Mandal 2011).

Table 14.2 Examples of some microbial pathogens that are sensitive to honey

Type of honey	Organism	Reference
Manuka honey	MRSA, *Escherichia coli, Salmonella typhi Enterobacter aerogenes*	Lusby et al. (2005), Visavadia et al. (2008)
	Helicobacter pylori	Mandal and Mandal (2011)
	Bacillus subtilis	Kwakman et al. (2011)
	Infleunza virus	Watanabe et al. (2014)
	Respiratory syncytial virus	Zareie (2011)
Heather honey "Erica species"	*Candida albicans, Candida krusei, Cryptococcus neoformans*	Feás and Estevinho (2011)
Tualang honey	*Stenotrophomonas maltophilia Acinetobacter baumannii*	Tan et al. (2009)
	Aspergillus niger, C. albicans	Hamid et al. (2018)
Ulmo honey	*Ps.aeruginosa,* MRSA, *Escherichia coli*	Sherlock et al. (2010)
Iranian honey	*C. albicans, C. krusei, C. glabrata, C. tropicalis*	Shokri and Sharifzadeh (2017)
Acacia honey, Kelulut honey	*Aspergillus niger, C.albicans*	Hamid et al. (2018)
Medihoney	*C. albicans, C. krusei, C. dubliniensis*	Irish et al. 2006)
Turkish honey	Fluconazole-resistant *C. albicans, C. krusei* and *C. glabrata*	Koc et al. (2009)
Croatian honey (Fir honeydew honey, Mint honey)	MRSA, *Acinetobacter baumannii*	Gobin et al. (2018)

- The low water content of honey along with its high osmolarity cause dehydration of the surrounding medium and bacteria as well and further bacterial cell lysis (Mandal and Mandal 2011).
- The glucose oxidase enzyme secreted by the honeybee in the nectar will be activated by body fluids to convert glucose into gluconic acid and hydrogen peroxide. The peroxide species activate cytokine production as a consequence to neutrophils activation and thus increase the inflammatory response that help bacterial killing (Vandamme et al. 2013).
- The antibacterial activity of honey may correlate to its anti-quorum sensing activity (Wang et al. 2012) which in turn affects expression of virulence genes and biofilm formation (Jenkins et al. 2014).
- Polyphenolic compounds such as flavonoids can affect bacterial growth through disruption of cell membrane function, inhibition of bacterial DNA synthesis by impairing DNA gyrase enzyme, and blocking of cell metabolism (Cushnie and Lamb 2005).
- Bee defensin-1 in the bee saliva may be transferred to honey during eructation process. This compound has strong antimicrobial activity against gram positive bacteria (Kwakman et al. 2010).
- Bee propolis may be present in raw honey and it is known for its antimicrobial activity (Campos et al. 2014).

14.2.1.2 Revamil Honey Versus Manuka Honey as Antibacterial

The antibacterial activity of honey is not a constant value against bacterial pathogens where it varies greatly with the type of honey used and the species of the bacteria. The variation in the antibacterial activity of honey is usually associated with variation in its botanical source, geographical source, weather conditions, and honey processing. All these parameters result in different chemical composition of honey even different quantities of the same components. So, some types of honey are known to have potent antibacterial activity while others have little activity. Stingless bee honey experienced inhibitory effect to the growth of gram positive and gram negative bacteria which suggests adding it as ingredient in pharmaceutical preparations (de Queiroz Pimentel et al. 2013). The antibacterial effect of this type of honey is enhanced by the diffusion of antibacterial components from propolis in the pots where it is stored (Campos et al. 2014).

There are two types of medically graded honeys that have proven their potent activity as antimicrobials, Manuka honey and Revamil honey. These two types undergo sterilization by gamma radiation to eliminate bacterial spores that may contaminate them during processing (Kwakman et al. 2011). Although effective as antimicrobial but the mechanism is limited to their chemical composition. Manuka honey originates from Manuka flower present in New Zealand. The nectar of this flower is characterized by the presence of high concentrations of dihydroxyacetone which is meanwhile converted to the effective antibacterial methylglyoxal. The mechanism suggested by this chemical is its interaction with guanine residue in RNA or DNA resulting in impairment of DNA and protein synthesis (Krymkiewicz et al. 1971). In addition to methylglyoxal Manuka honey was found to stimulate immune system to release certain mediators such as TNF-α, IL-1β, and IL-6 which help clearance of microbial infections. Manuka honey is usually assigned to a UMF value (Unique Manuka Factor) that indicates its antimicrobial potency (Tonks et al. 2007).

Revamil honey is produced under controlled process where bee colonies are kept in adjustable conditions. The controlled production process ensures that its chemical composition and further therapeutic values will be maintained. Revamil acts as antibacterial through its two major components: hydrogen peroxide and bee defensin-1. Absence of these components in manuka honey explains the difference in their antibacterial mechanism. Both honeys show potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa*, *E. coli,* and *Bacillus subtilis*. Although Revamil showed its bactericidal activity in shorter time, Manuka honey maintained its bactericidal activity even with very high dilutions against food spoiling bacteria and in this case it is more suitable to use Manuka honey in food preservation to protect against food spoiling microbes rather than Revamil honey (Kwakman et al. 2011).

14.2.2 Honey as Antifungal

Fungal infections represent a major threat to public health. *Candida albicans* comes in the first place as an opportunistic pathogen that can cause a wide range of diseases starting with oral and vaginal candidiasis to the most serious invasive condition candidemia. It is now extended to other candida species to generally affect human health (Perlin 2009). In addition to remarkable toxicity, conventional antifungal agents are now worthless against most fungal infections. This can be attributed to the improper use of antifungals which lead to emergence of resistant fungal species (Pappas et al. 2004). Researchers realized the urgent need for new antifungal agents that combine both effective therapeutic activity and minimal side effects and then natural products have shed the light to start considering as a medicament, among which is honey.

Several reports demonstrated the effective antifungal activity of honey against multiple fungal pathogens including *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *Cryptococcus neoformans,* and *Trichosporon* species (Khosravi et al. 2008; Koc et al. 2009; Feás and Estevinho 2011). The polyphenolic compounds in honey affect its antifungal power, and these compounds vary with respect to type and concentration to the botanical origin of honey. In this regard, good antifungal activity of Rhododendron honey was observed compared to that of orange honey (Andrade et al. 1997).

Irish group limited effectiveness of honey as antifungal to topical applications which limits its value for treatment of systemic fungal infections. Honey has good role in systemic fungal infections through its clearance and protection of different body entrances such as mouth and vagina and even indwelling medical devices from contaminants. The other problem that faces honey for use in treatment of oral or vaginal candidiasis is its dilution by human body fluids. This can be overcome through its formulation as oral chewable tablets or vaginal suppositories or continuous addition of honey on infected area to maintain high concentration above the MIC value all over the therapeutic period (Irish et al. 2006).

14.2.3 Honey as Antiviral

Several problems are associated with the use of the conventional antiviral drugs in therapy. These problems can be summarized in rapid emergence of drug resistance due to high incidence of viral genetic mutations, prohibition of drug intake during pregnancy and breast feeding, toxic side effects, and even the high cost (Hashemipour et al. 2014). As a result, developing new antiviral drugs with minimum toxicity and lower drug resistance remains the priority for virologists. Scientists now focus on natural products seeking its medicinal value. The nutritional value, safety, and availability of bee's honey make it among the first products to explore its medical value. Several studies had been conducted on the antiviral potential of honey. Honey possessed antiviral activity against common viruses such as rubella virus (Zeina et al. 1996), varicella zoster virus (Shahzad and Cohrs 2012), herpes simplex-1 virus

(Al-Waili 2004), and influenza viruses (Watanabe et al. 2014). Moreover, the duration for viral diarrhea is much decreased when honey is administered compared to the conventional antiviral drugs (Andualem 2013). The mechanism by which honey exerts its antiviral activity is not fully understood. However, it was suggested that the anti-influenza activity of different honey samples was partly due to rutin and chrysin (Watanabe et al. 2014). On the other hand, manuka honey demonstrated the highest anti-influenza activity that may be attributed to its content of methylglyoxal that had shown good antiviral activity in foot and mouth viral infection (Ghizatullina 1976).

14.3 Honey and Wound Healing

Wound is a breach in human body caused accidentally or through surgical operation. The wound area is characterized by the presence of damaged tissue, low oxygenation, and impaired blood circulation (Porth 2017). Based on duration for complete cure, wounds can be divided into acute wounds that are healed within 8–12 weeks and chronic wounds that do not respond to treatment within the proposed period of healing but getting worse. Rapid management of wounds is an important measure in diabetes, obesity, and elderly patients (Lu et al. 2018). Since ancient times, honey was used in wound treatment due to its physical and chemical properties. Honey has several mechanisms that are employed together to help rapid healings of wounds, described as follows and in Fig. 14.1.

1. Antimicrobial activity:
   The antibacterial and antifungal properties of honey select for its use in treatment of wounds. Wounds are at high risk for being infected. The reported

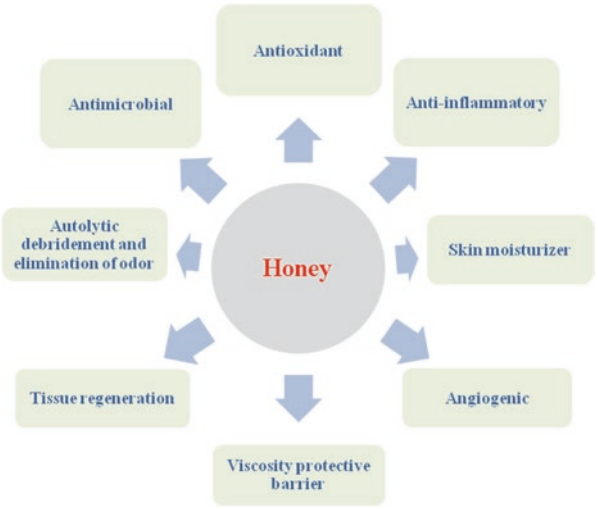

Fig. 14.1 Mechanisms employed by honey in wound healing

peroxide and non-peroxide activity of honey against common bacterial pathogens isolated from wound infections assures its importance in wound clearance from any possible microbial contaminants (Singh et al. 2012).

2. Skin moisturizing capacity:

   Maintenance of wound tissues moisturized is very essential in wound healing process. Moisture can enhance tissue oxygenation (Kurhade et al. 2013), stimulate blood circulation, stop tissue necrosis (Korting et al. 2011), decrease possibility for scar formation (Atiyeh et al. 2003), and reduce the chance for secondary microbial infections (Kurhade et al. 2013). Honey is known for its skin moisturizing capacity. The hydroxyl groups in chemical structures of different honey components such as sugars and proteins (Boateng et al. 2008), vitamins and minerals (Vanhanen et al. 2011), sorbitol, glycerin and propylene glycol (Draelos 2010), all these components contribute to honey's moisturizing effect. In addition, high osmolarity withdraws water from the surroundings to hydrate wound tissues (Alvarez-Suarez et al. 2010).
3. Honey acts as a protective barrier on wound tissues to prevent its microbial contamination (Hananeh et al. 2015).
4. Honey enhances blood circulation in wound tissues and allows for tissue regeneration through stimulating the growth of the outermost epithelial layer and the connective tissue. The increase in tissue growth that occurs upon oral administration of honey seems to be due to growth factor component rather than nutritional or environmental factors (Al-Waili et al. 2011).
5. Anti-inflammatory activity:

   Inflammation of wound tissues occurs due to invasion by a foreign matter e.g., bacteria and fungi or degeneration of tissues (Molan 1999). During inflammation, macrophages augment the production of inflammatory mediators such as nitric oxide, cytokines, and prostaglandins. These mediators cause cytotoxic effect to the target cells, but excessive production of such mediators can cause tissue damage (Kim et al. 2013). Therefore, anti-inflammatory drugs are given during therapeutic treatment of wounds. Unfortunately, the known anti-inflammatory drugs were found to decrease wound healing either by their destructive effect on the tissues (nonsteroidal anti-inflammatory drugs, e.g., aspirin) or prevention of tissue regeneration (corticosteroids e.g., dexamethasone) (Krischak et al. 2007). Honey has anti-inflammatory activity through inhibition of cyclooxygenases and prevention of overproduction of inflammatory mediators (Erguder et al. 2008). These effects are brought about by the phenolic compounds in honey. Another indirect effect of these phenolic compounds is being as antiradical compounds that protect tissues from the cytotoxic effect of inflammatory mediators. Consequently, honey can reduce swelling in wound area and in this case, better oxygenation and nutritional supplementation can reach wound tissues and encourage its growth (Molan 1999).
6. Debridement of a wound is an essential step in treatment process as necrotic tissue helps growth of infective microbes that can cause extended damage to the surrounding tissue. Honey helps removal of necrotic tissue through autolytic debridement of the wound which eliminates wound odor (Vandamme et al. 2013).

7. Antioxidant activity:

   In the first stage of wound healing, overproduction of nitric oxide leads to production of hydrogen peroxide and reactive oxygen species (ROS) (Ju et al. 2012). These species cause harm to the wound and distant body organs through activation of cellular and humoral mediated immune mechanisms (Closa 2013). Antioxidants can counteract these harmful effects by two possible mechanisms.

   (a) Enzymatic removal of free radicals through its conversion to stable harmless molecules, e.g., peroxidases, catalase, and superoxide dismutase (Ahmad et al. 2010).
   (b) Nonenzymatic removal of ROS which blocks their damaging activity and even prevents their formation by the cell, e.g., vitamin C, tocopherol, and phenolic compounds (Ahmad et al. 2010).

   Honey can improve wound healing through its antioxidant properties where it contains a wide variety of phenolic compounds that can act as antioxidant for the nonenzymatic removal of free radicals. In addition, some enzymes in honey e.g., peroxidase can also, clear the ROS and protect the cells from the destructive effect of these free radical species (Khalil et al. 2011).

Wound dressing is a crucial step that has a great effect on the healing process. Wound dressings were applied to the wound to protect the damaged tissues from being infected (Henry et al. 2019). Currently, wound dressings are loaded with active compounds that can accelerate the healing process. Several factors can control the choice of the suitable wound dressing. Patient relief, duration of application, infected wounds, sterility of dressing, ease in application or removal of dressing and the cost, all mentioned factors guide the physician to select the most suitable wound dressing (Henry et al. 2019). Honey is effectively used in wound dressing for first- and second-degree burns, diabetic ulcers, and leg ulcers. Being nontoxic, nonirritant, and easily applied and removed make honey dressing more comfortable to use than any other dressings (Bulman 1955). For pediatric patients, Revamil gel and gauze are selected as the most suitable wound dressing for the patient comfort where this type of dressing doesn't stick to wounds so it does not cause any pain in its removal (Henry et al. 2019).

14.4 Honey and Respiratory System

14.4.1 Honey and Cough

Many factors can trigger coughing reflex. The most common factors are the upper respiratory tract infections (URTIs) and inhalation of an allergen (Landau 2006). Cough is considered an annoying symptom that bothers both the sick child as well as his parents. Most symptoms of URTIs can be resolved within 1 week but cough may last for several weeks. When a family has a child with persistent cough, it

means there is a lack of sleep and disturbance of life regimen to all family members where there is a high possibility for absence from school or work for the sick child and his parents, respectively (Ayazi et al. 2017).

Many drugs that are usually prescribed for controlling cough in children demonstrate undesirable side effects. Children given dextromethorphan were unable to sleep normally and those given diphenhydramine were drowsy (Paul et al. 2004). Appearance of such side effects necessitates searching for a safe alternative natural remedy. Since ancient times, honey is used to relief common cold symptoms with special regard to cough. Being cheap, available, and safe to use, honey is then recommended by the world health organization (WHO) for curing cough and other URTIs-related symptoms (World Health Organization 2001). Several studies were conducted to evaluate the effect of honey on number of coughing episodes and its severity. Honey proved to be effective in decreasing number of coughing episodes compared to over-the-counter drugs dextromethorphan and diphenhydramine (Oduwole et al. 2018). The combination of honey and coffee has proven good activity in curing post-infectious persistent cough where the damaged nerve endings by mucosal irritation and desquamation were recovered and mucosal tissue became coalescent (Raeessi et al. 2013). The mechanism by which honey causes cough sedation is proposed to be through its sweetness that induces excess saliva secretion leading to liquefaction of mucous in the affected airways and reduction of larynx irritation then relief of cough episodes (Paul 2012). Another explanation for the sedative effect of honey on cough was illustrated by Eccles. He supposed that there is possibility for interaction between sweet tasting nerve fibers and cough initiating nerve fibers. This interaction originates mainly from their anatomical relationship (Eccles 2006).

14.4.2 Honey and Asthma

Asthma is a common chronic respiratory illness that affects the lower respiratory tract (LRT) and is usually the result for exposure to allergens (Cianciosi et al. 2018). The disease manifestations include inability to breathe, chest constriction, and early morning and night coughing (Balaha et al. 2012). These manifestations result from the inflammatory cell response, the structural changes of airways, goblet cells hyperplasia, excessive mucous secretion, and blood vessels expansion. Augmentations in thickness of epithelial and subepithelial layers are the main changes in airway structures. Therefore, narrowing of airways occurs causing difficulty in breathing (Fahy et al. 2000). The long-term therapy of asthma by conventional drugs can be accompanied by several side effects such as osteopenia, ocular hypertension, marked decrease in growth rate, and oral thrush (Fanta 2009). These serious side effects encouraged seeking for more safe alternatives. The antioxidant and anti-inflammatory properties of honey reported by several studies suggest its medical value in controlling asthmatic attacks. Honey is mostly administered by oral route to produce its therapeutic effects, but the case is different in case of asthma. It was expected that inhalation of aerosolized honey will be more effective

than ingested honey in relieving asthma because the amount of honey that reaches the altered airways will be much more in case of inhalation which will accelerate the curing process (Rhman 2007). Kamaruzaman et al. reported that 25 and 50% of honey aerosol inhibited goblet cells excessive proliferation. Therefore, mucous secretion was much reduced. Decrease in inflammatory cell response was observed as well. These two major effects of honey suggest its clinical importance in both improving symptoms in asthmatic patients and prevention of asthmatic attacks (Kamaruzaman et al. 2014).

14.5 Honey as Antidiabetic Agent

The most common chronic metabolic disorder that largely affects general human health and his quality in performance is diabetes mellitus (DM). This disease features uncontrolled high blood glucose level which then causes multiple symptoms starting simply with excessive urination, severe thirst, dehydration, and body weight loss. With time, these symptoms develop serious conditions such as retinopathy, kidney failure, nerve cells damage, diabetic foot infections (DFIs) that usually ends with limb amputation, dyslipidemia, and cardiovascular diseases (Bobiș et al. 2018). Diabetes mellitus is classified into two types that differ primarily in their etiology, onset of clinical manifestations and even therapeutic strategies. Type-I DM is characterized by low or non-insulin secretion by the beta pancreatic cells due to its autoimmune destruction. Inherited genes are behind this type of diabetes combined with some environmental factors that accelerate its emersion. Type II DM found to be associated with overweight and obese individuals who have improper lifestyle and diet control. In this type, the beta pancreatic cells are still able to secrete insulin to which body cells become resistant. The hyperglycemia is the characteristic sign that both types of diabetic patients share (Kokil et al. 2010).

Honey has a wide variety of nutritional and nonnutritional compounds that contribute to its different biological activities. Honey as a natural product has been used for long time as a sweetening agent. Several studies have demonstrated the hypoglycemic effect of honey upon oral administration by either laboratory animals or human which might suggest its use as an antidiabetic agent beside the conventional drug therapy (Kokil et al. 2010).

The monosaccharides, fructose and glucose, constitute about 80% of honey in total. Glucose in honey was found to promote fructose absorption (Kokil et al. 2010). Previous studies had reported the lowering effect of fructose on blood glucose level (Erejuwa et al. 2012). Slowing gastric emptying rate caused by fructose with subsequent decrease in food intake explain in part its hypoglycemic effect (Gregory et al. 1989). Besides, the prolonged contact time between fructose and intestinal receptors might adversely affect intestinal absorption of macronutrients such as carbohydrates which then improves satiety sensation (Anderson and Woodend 2003). In addition, fructose catalyzes glucokinase enzyme that help glucose uptake and its storage as glycogen in the liver (Van Schaftingen and Vandercammen 1989).

Another possible explanation for the hypoglycemic effect of honey was supposed by Abdulrahman et al. who attributed the increase in C-peptide serum level to the increased insulin secretion caused by oral administration of honey (Abdulrhman et al. 2013). The elevated insulin level results from the hydrogen peroxide stimulatory effect (evolved upon mixing of honey along with water) on beta pancreatic cells to secrete more insulin (Al-Waili 2003).

The high glucose uptake by adipose tissue causes massive production of reactive oxygen species (ROS) resulting in oxidative stress. This condition strongly stimulates development of diabetes especially type II where disruption of insulin signaling pathway makes body cells resistant to insulin. The antioxidant compounds in honey act through its free radical scavenging ability to clear the oxidative stress of the pancreas as well as the other body tissues (Kim et al. 2006). Moreover, honey acts as a protective antioxidant against lipid peroxidation and altered lipid metabolism in type II DM (Rahimi et al. 2005). Polyphenols present in honey are suggested to decrease hyperglycemia and improve lipid metabolism in diabetic patients through different pathways. The alpha amylase and alpha glucosidase enzymes are basically involved in carbohydrate hydrolysis. The inhibitory effect exerted by some polyphenolic compounds (i.e., quercetin, myricetin, and luteolin) on these enzymes beside its antioxidant activity will then reduce blood glucose level (Tadera et al. 2006; Hussain et al. 2012). The increase in peripheral glucose uptake is another way for controlling blood glucose level by the polyphenols in honey (Lee et al. 2012). Moreover, in type II DM patients, polyphenols present in honey such as luteolin proved to induce adipokines production, and thus preventing insulin resistance (Ding et al. 2010).

The level of adiponectin, a hormone found to regulate fat and glucose metabolism, is elevated upon ingestion of honey. This hormone caused marked amelioration in blood glucose level and lipid metabolism as well (Hemmati et al. 2015). In addition, Aziz et al. attributed the hypoglycemic activity of stingless bee honey to the high expression of catalase enzyme that acts as antioxidant in addition to the L-phenylalanine that stimulates insulin release (Aziz et al. 2017).

Honey is rich in highly valuable compounds that act together to exert its beneficial health effects. Reviewing different explanations for the antidiabetic effect of honey strengthens the scientists' recommendations for using honey as an adjuvant in the control of diabetes and its associated deteriorative effects.

14.6 Honey and Testosterone Hormone

Testosterone is the prime male sex hormone secreted mainly by Leydig cells in the testes and in part by the adrenal gland. This hormone controls both maturity of male sex organs and secondary sexual characters. Testosterone also, contributes in major to sperm production and sexual desire. The importance of this hormone is not limited to sexual life improvement and reproduction in male only but also it extends to normal body health e.g., body muscle mass, bone density, and generalized physical state of the body (Kloner et al. 2016). At the age of 40, testosterone level starts to

decrease. Several diseases (such as cardiovascular diseases, osteoporosis, infertility, obesity, type II diabetes mellitus, and sarcopenia) were found to be associated with low testosterone level in serum (Petering and Brooks 2017).

For scientists, improving testosterone level is a major concern. Several studies targeted the effect of different food stuffs on serum testosterone level (Banihani 2018). Most of these studies were conducted on male animal populations (either associated or not with chemically induced reproduction toxicities) with different dosing range of various types of bee's honeys. The duration of the experiments done in this issue varied from 2 to 12 weeks (Banihani 2019). Studies that emphasized the role of bee's honey in elevation of testosterone level suggested different possible mechanisms. These mechanisms can be summarized as follows:

1. Honey increases the level of luteinizing hormone which in turn increases the serum testosterone level.
2. Honey participates in maintenance of healthy testicular tissues which increases their ability to produce testosterone.
3. As the oxidative stress state in the testes negatively affects testosterone production by Leydig cells, the antioxidant activity of honey promotes the following:

   (a) The antioxidant compounds in honey (either phenolic or non-phenolic) help removal of the harmful free radicals and then retrieve the Leydig cell ability to produce testosterone normally (Banihani 2019).
   (b) The antioxidant flavonoid chrysin in bee's honey increases the activity of antioxidant enzymes such as catalase and superoxide dismutase (Ciftci et al. 2012), inhibits aromatase enzyme (this enzyme stimulates testosterone conversion into estradiol (Oliveira et al. 2012), and augments StAR gene expression that encodes StAR protein, a protein involved in cholesterol transport through mitochondrial membrane for subsequent cleavage into pregnenolone in Leydig cells (Jana et al. 2008).
   (c) Quercetin, in addition to phenolic compounds present in honey (e.g., caffeic acid, rosmarinic acid, and ellagic acid) augment testosterone production in reproduction toxicity resulted from exposure to certain chemicals (Banihani 2019).

In conclusion, most researches that investigated serum testosterone level in relation to bee's honey intake revealed that there is a positive effect for oral administration of honey on elevation of serum testosterone and no harmful effects were detected in any of those studies.

14.7 Honey and Cancer

Cancer is considered one of the major causes of death all over the world (Jemal et al. 2011). Following the western life habits, ageing, awareness campaigns through different media that teach people about syptoms of cancer, amelioration in detection

techniques play important role in the noticeable increment in number of recorded cancer diseased population (Kanavos 2006). It was found that types of cancers that are largely affected by prevalence of certain infectious agents predominate in developing countries, while those affected by food habits and lifestyle are more dominant in developed countries (Othman 2012). Developing cancer means genetic modifications start to occur leading to irreversible damage (Pitot 1993). Secondly, high proliferation rate of mutated cells ending with a benign mass. In the third stage, the cancerous cells extend to the distant tissues (Tubiana 1998).

Treatment of cancer undergoes several procedures according to type of cancer and its stage. Radiotherapy, surgical removal of cancerous mass, and chemotherapy are the main therapeutic strategies employed to control the disease. Besides being somewhat expensive and have limited availability in some areas, chemotherapeutic drugs used in cancer managements are known for its serious side effects that largely affect the general health of patients and its normal life practices (Chidambaram et al. 2011). These facts encourage seeking for alternative therapeutic agents that are safe, low in cost, and readily available. Honey satisfies all these criteria which favor its use as adjuvant therapy in cancer (Mendel 2004). Many studies had reported the efficacy of honey as anticancer against several types of human cancer cells. Figure 14.2 demonstrates factors stimulating cancer occurrence and possible previously explained mechanisms for the activity of honey as anticancer.

14.8 Honey as Oral Curing Agent

Oral health provides a key sign for the overall body health. Wide spectrum of oral diseases commonly occurs including dental plaque, gingivitis, malodor, alveolar osteitis, and cancer. Several studies advice the use of honey along with the basic oral medications to accelerate patient cure from different oral ailments (Seymour 2007).

Dental plaque is highly prevalent and usually associated with dental caries and other periodontal diseases. Mechanical removal is the most successful method employed to get rid of plaque and retrieve the healthy gingiva (Gupta et al. 2014). Anti-plaque agents are used along with mechanical removal techniques to support complete removal (Kayalvizhi et al. 2014). Manuka honey was reported as antibiofilm agent that decreases colonization by bacteria and dental plaque formation (Nayak et al. 2010).

In root canal inflammation, dentists find that the first measure is to debride necrotic tissue and clear microbial inhabitants. Honey as a root canal irrigant was less potent than sodium hypochlorite but more compatible with tissues (Sundaram et al. 2016).

Mucositis is an aching inflammation in mucous layer of the oral cavity. This inflammation can arise from radiotherapy or chemotherapy directed to cancerous cells. Honey was found to decrease radiation-based mucositis (Rao et al. 2017). Alveolar osteitis is an oral disease appears 2–3 days post tooth extraction. Severe pain and disintegrated blood clot are characteristic signs for alveolar osteitis. Reduction in pain, malodor, and edema was notified by Singh et al. in patients

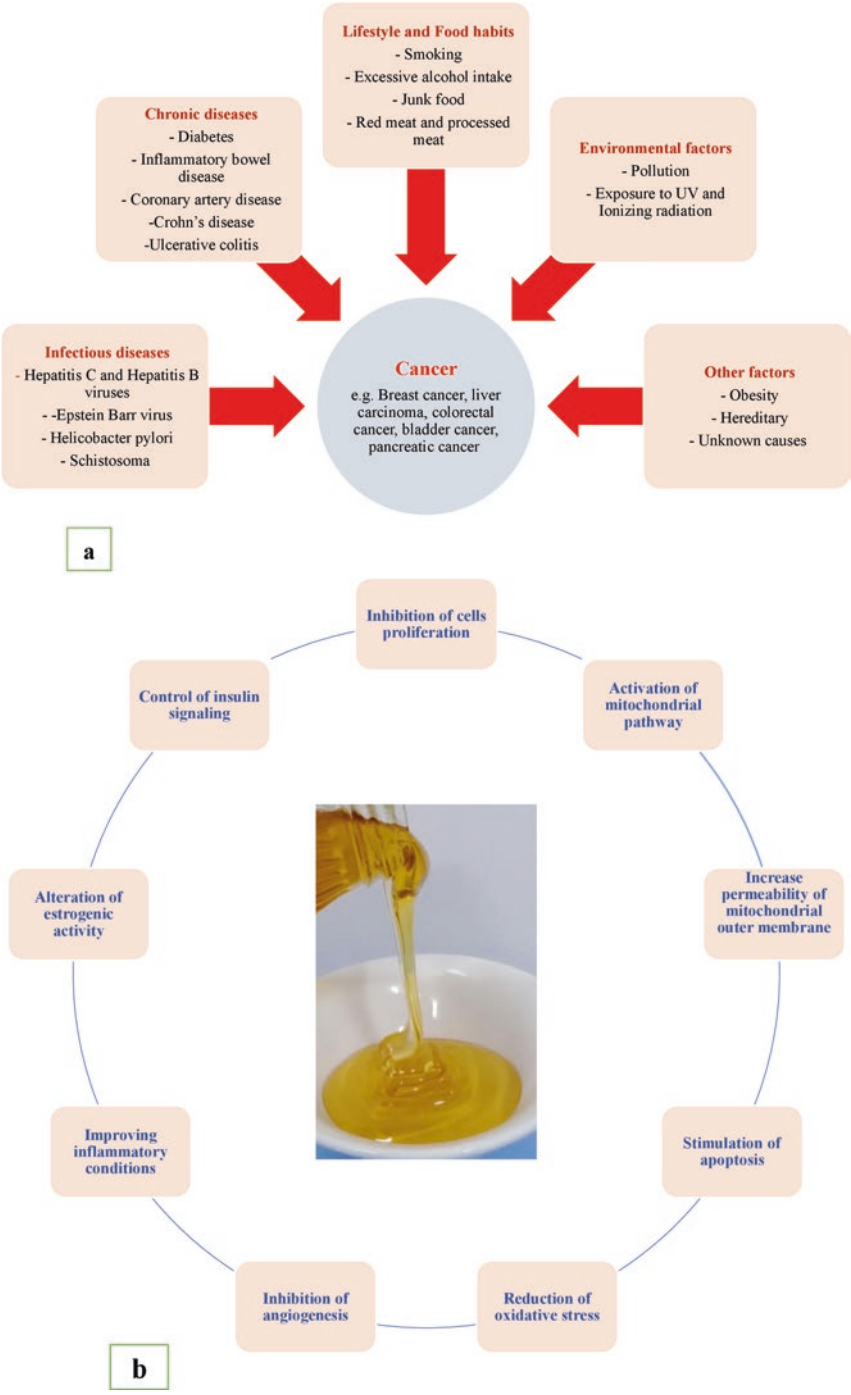

Fig. 14.2 Schematic diagram of (**a**) some causes of cancer and (**b**) mechanisms exerted by honey to combat cancer

receiving honey as adjuvant therapy for alveolar osteitis (Singh et al. 2014). Moreover, honey was beneficial in oral ulcers, stomatitis and halitosis supported by its antibacterial and anti-inflammatory properties (Pasupuleti et al. 2017).

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