Honey: A Powerful Natural Antioxidant and Its Possible Mechanism of Action

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Abstract

Honey, a supersaturated concentrated solution with complex constituents, has been used as therapeutic agent since ancient times. Natural products have been used as a substitute for various conventional treatments and drug discoveries. Different in vivo and in vitro studies have shown properties of honey including antioxidant, antibacterial, anti-inflammatory, anti-cancerous, and much more. Therapeutic properties of honey greatly depend on its constituent composition

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which may vary based on various factors like species of bee, environmental conditions, type of flower, and processing methods. Oxidative stress due to cellular metabolism and other physio-biochemical activities of the body demand the necessity of antioxidants in diet which can be fulfilled by honey. Antioxidant and other biological properties of honey are greatly determined by the polyphenol composition. This chapter comprises honey composition, type, antioxidant properties, and antioxidant mechanism of honey according to different research studies.

Keywords

Apitherapy · Antioxidant · Polyphenols · Reactive oxygen species (ROS) · Oxidative stress

Abbreviations

CAT	Catalase
COX-2	Cyclooxygenase-2
CZE	Capillary zone electrophoresis
DPPH	1, 1-Diphenyl-2-picrylhydrazyl
FRAP	Ferric reducing antioxidant power
GPx	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
HPLC	High-performance liquid chromatography
IL-6	Interleukin-6
LDL	Low-density lipoprotein
MEKC	Micellar electro-kinetic chromatography
MMP9	Matrix metallopeptidase 9
MRSA	Methicillin-resistant *Staphylococcus aureus*
ORAC	Oxygen radical absorbance capacity
PGE2	Prostaglandin E2
SOD	Super oxide dismutase
TLR	Toll-like receptor
TNF	Tumor necrosis factor
UPLC	Ultra-performance liquid chromatography
VREF	Vancomycin-resistant *Enterococcus faecium*

2.1 Introduction

Natural products being rich source of compounds are intended for various drug discoveries. Practical substitute by products from nature to lessen the escalating rebuke of diseases and their inevitable aftermath has clinched the consideration

toward honey and has led toward an alternate medicine branch called apitherapy (Aggarwal and Shishodia 2006; Othman 2012). Honey remained the foundation of pharmacy from ancient period since classic civilization (Greeks and Romans) and of Middle Age Arab people. Honey as a balanced diet and folk medicine since ancient times from the history of human race has been used as a remedy in various fields like medicine, cosmetics, a preserving substance (Wieckiewicz et al. 2013), and its therapeutic value is even intensely specified in Qur'an (Eteraf-Oskouei and Najafi 2013). Honey being one of the ancient traditional medicine by *Apis mellifera* (*A. mellifera*) has various medicinal properties like antioxidant, antibacterial, hepatoprotective, hypoglycemic, reproductive, and antihypertensive, thus significantly used in human ailments. Meanwhile production of free radicals by various disease conditions especially in chronic cases cause potential damage at molecular level and further aggravate the conditions; incorporation of honey as an antioxidant in the diet neutralizes these free radicals either directly or indirectly and lessen the harm by these reactive species without having any adverse effects. Usage of present-day antibiotics has abandoned the use of honey, but in recent studies, several investigations are being carried out regarding the bioactive properties of honey and bee products against numerous diseases (Carter et al. 2016). Currently, honey with standardized antibacterial activity levels are present, the finest identified honey from *Leptospermum scoparium* (*L. scoparium*) is recognized to inhibit about 60 diverse species of microorganisms including gram-positives, gram-negatives, aerobes, and anaerobes (Babacan and Rand 2017). Honey has a water activity of 0.56–0.62 and 3.9 pH value (Escuredo et al. 2014). The main objective of this chapter is to understand and evaluate the properties of honey with the main focus on antioxidant properties and the possible mechanism of antioxidant action. This chapter also highlights the role of honey in ameliorating various disease conditions, antioxidant effects on GIT, pancreas, inflammation, reproductive organs, and other chronic and degenerative diseases. Honey either alone or in combination with conventional therapy acts as a novel antioxidant in regulation of various conditions associated with oxidative stress. The study regarding the therapeutic role of honey is still under different phases and may be used as a main antioxidant in near future.

2.2 Composition of Honey

Composition and properties like color, aroma, flavor, and antioxidant nature of honey greatly depend on

1. Honeybee species
2. Flowers
3. Geographical regions
4. Weather and climate
5. Processing and storage (Tornuk et al. 2013; Alvarez-Saurez et al. 2009)

Table 2.1 General composition of honey

Component	Value/100 g
Total carbohydrates	82.4 g
Fructose	38.5 g
Glucose	31.28 g
Moisture content	17.1 g
Maltose	7.31 g
Sucrose	1.31 g
Total acid as gluconic	0.57 g
Fiber	0.2 g
Amino acids/proteins	0.3 g
Ca	6.00 mg
Ash	0.169 g
P	4.00 mg
K	52 mg
Mg	2.00 mg
Fe	0.42 mg
Zn	0.22 mg
N	0.041 g
Cu	1–100 μg/g
Vitamin B2	0.038 mg
Vitamin B3	0.21 mg
Vitamin B5	0.068 mg
Vitamin B6	0.024 mg
Vitamin B9	2 μg
Vitamin C	0.5 mg
Miscellaneous groups	Bogdanov et al. (2008) and Gheldof et al. (2002)

Honey is a concentrated aqueous solution with >95% of its dry weight constituted by sugars followed by water (Sato and Miyata 2000). Of the sugars chiefly present are fructose and glucose (Gheldof et al. 2002) which determine its nutritional and physical features. Honey is a complex mixture whose constituents are mentioned in Table 2.1. Honey constituting less than 18% water can be stored without the risk of fermentation. Alcohols, aldehydes, ketones, acids, terpenes, and esters are the main volatile compounds present in honey (Molan 2002; Zhou et al. 2002). Organic acid predominantly in honey is gluconic acid and originates largely from glucose and water in the presence of glucose oxidase enzyme (Bastos and Alves 2003) and a minor amount from genus Gluconobacter bacteria (French et al. 2005). Another group of compounds contributing to the anti-oxidant capacity of honey and responsible for its geographical properties are the polyphenols (Davis 2005). Classifications of 501 polyphenols into six different classes and 31 subclasses have been done by "phenol explorer," as flavonoids, phenolic acids, nonphenolic metabolites, lignans, stilbenes, and other polyphenols (Tomás-Barberán et al. 2001).

2.2.1 Types of Honey

Variety of honey can be determined on the basis of time of nectar existence and the accessibility of individual nectar flows. Currently, beekeepers use melissopalynological method based on the microscopic quantitative identification of plant pollens present in the honey; it is the only laboratory method providing certainty about the variety of honey. On the basis of different characteristics, honey can be divided into various classes as given below in Fig. 2.1.

2.3 Antioxidants in Human Health

Antioxidants are the molecules that have the capability to accept or donate electrons in order to neutralize free radicals produced by various biological processes. Consequences of biological processes cause generation of free radicals called reactive oxygen, reactive sulfur, and reactive nitrogen species (ROS, RSS, RNS) such as hydroxyl radical (·OH), superoxide anion (O_2•), hydrogen peroxide (H_2O_2), nitric oxide (NO), and further other types like singlet oxygen, hypochlorous acid, and peroxynitrite (Vajragupta et al. 2004) with hydroxyl radical (.OH) being the

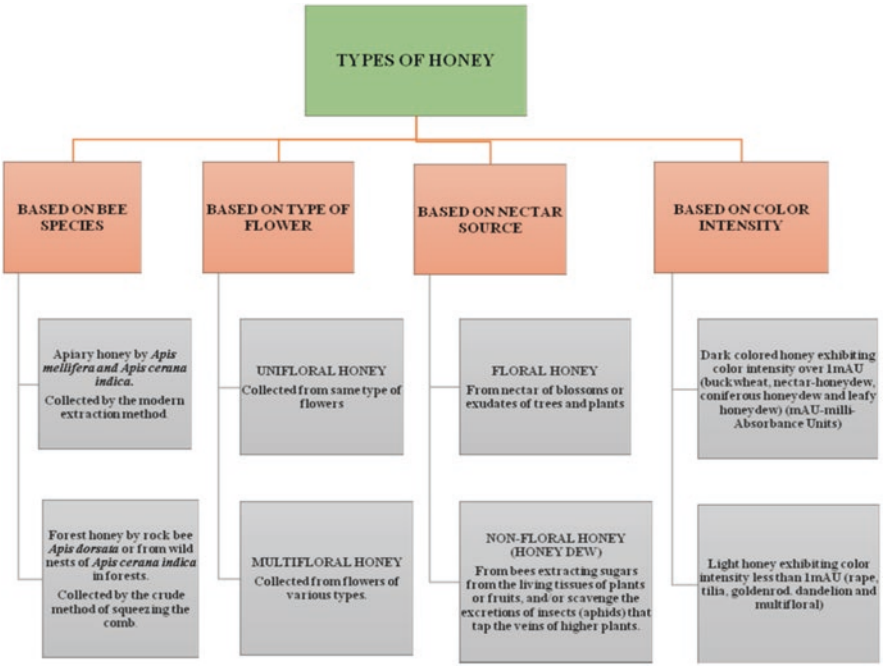

Fig. 2.1 Types of honey based on different features (Subrahmanyam 2007). Honey can be classified into different types based on different features, viz. bee species, type of flower, nectar source, and color intensity

Table 2.2 Different polyphenols present in honey

Phenolic acids	Flavonoids
4-Dimethylaminobenzoic acid	Apigenin
p-Coumaric acid	Pinocembrin
Caffeic acid	Genistein
Vallinic acid	Chrysin
Gallic acid	Tricetin
Chlorogenic acid	Luteolin
Syringic acid	Quercetin

strongest. Oxidative stress is the resultant stress that arise due to free radicals attacking on nucleic acids, unsaturated fats, and amino acid which play an important role in pathogenesis of various diseases like inflammatory diseases, cancer, Alzheimer's disease, aging, diabetes, cardiovascular diseases, and various other diseases (Giles and Jacob 2002; Geier et al. 2009). Our body has established an antioxidant defence system to tackle the oxidative damage brought by ROS which include chelation of metals, enzymatic activities, scavenging free radicals, oxidation shielding agents like catalase (CAT), peroxidase, superoxide dismutase (SOD), polyphenols, and vitamin E and C (Nagai et al. 2001). All these defences act to deactivate these radicals. Honey acts as a dietary antioxidant with polyphenols chiefly accountable for its strong antioxidant action (Hussein et al. 2011), and this characteristic of honey significantly reduces several acute and chronic disorders. The neutralization of free radicals by antioxidant molecules can occur either by directly reacting with them or they may become less active free radicals and less dangerous than those they have neutralized, though dietary intake of antioxidants maintains satisfactory antioxidant status in the body. According to a research, honey at the rate of 1.2 g/kg enhances the activity of beta-carotene, glutathione reductase, vitamin C, and uric acid as antioxidants (Tomás-Barberán et al. 2001). Polyphenol constituents of honey are potential biochemical markers as they are phytochemicals, i.e., plant-based molecules with antioxidant properties. Flavonoids and phenolic acids are the polyphenols accountable for antioxidant properties of honey and are cited in Table 2.2 (Davis 2005).

2.3.1 Mechanism of Antioxidant Effect

Flavonoids present in honey have been demonstrated as very effective scavengers of reactive oxygen (ROS) and reactive nitrogen species (RNS) (like peroxyl, alkyl peroxide, hydroxyl, superoxide radicals, nitric oxide, and peroxynitrite) to counter the oxidative damage induced by these molecules (Snow and Harris 2004). Flavonoid structure is attributed with three chemical features, presence of a 2, 3 double bond in the C-ring, B-ring having ortho-dihydroxy structure (Sekher Pannala et al. 2001; Burda and Oleszek 2001) and presence of a 4-oxo function (Heim et al. 2002). On the B-ring, hydroxyl groups donate an electron and hydrogen to stabilize peroxynitrite and peroxyl and hydroxyl radicals making comparatively stable

flavonoid radicals. On the B-ring occurrence of catechol leads to oxidation of flavonoid (Van Acker et al. 1996a) facilitating electron delocalization (Arora et al. 1998) and forms relatively stable ortho-semiquinone radical (Mora et al. 1990). Presence of a free 3OH in some flavonoids impart them a heterocyclic character which allow conjugation of aromatic rings between them, although activity of flavonoids does not need closed C-ring itself (Matthiesen et al. 1997). Ebselen, a known RNS scavenger, is reported to be tenfold less potent than flavonoids with 3-OH and 3′,4′-catechol against peroxynitrite radical (Heim et al. 2002). Oxidative damage brought about by metal and nonmetal is regulated partially by free 3-OH substituent on quercetin (Heim et al. 2002; Arora et al. 1998), which enhances the stability of this flavonoid radical, in contrast its stability decreases on substitution by a methyl or glycosyl group at 3-OH position (Burda and Oleszek 2001). Conjugation between 4-oxo function and unsaturated 2–3 bond offers a characteristic feature among the structural classes of general flavonoids, and the lack of one or both of these features results in the reduction of antioxidant capacity (AOC). Presence of more number of hydroxyl groups leads to increased free radical scavenging capacity of flavanols than flavones (Lien et al. 1999). Honey avoids RBC oxidative damage most probably due to its integration into cell membrane and capability to enter and reach cytosol. Antioxidants protect key cell components from damage by neutralizing the free radicals. Antioxidants that occur naturally in the body or are consumed through the diet may block damage to cells. Various other constituents of honey responsible for reducing the oxidative stress are mentioned in Table 2.3.

2.3.2 Honey as Antioxidant from In Vitro Studies

The antioxidant properties contributed by honey can be assessed by the method of antiradical activity through different assays like ORAC, FRAP, and DPPH scavenging assay (Davis 2005; Hussein et al. 2011; Tomasin and Gomes-Marcondes 2011). Individual honey polyphenol contents in honey can be analyzed by HPLC

Table 2.3 Antioxidant mechanism of various constituents present in honey

Constituent	Mechanism of action to control the oxidative damage
Quercetin	Antiradical activity by scavenging, chelation of ion inhibition of lipid peroxidation inhibition of xanthine oxidase (Sekher et al. 2001; Burda and Oleszek 2001)
Caffeic acid	Reduction in lipid peroxidation, increase in plasma levels of vitamin E
Caffeic acid phenethyl ester (CAPE)	Free radical scavenging
Kaempferol in hippocampal cell line HT-22 of mouse	Hindering ROS generation (Heim et al. 2002) Blocks oxidative stress during apoptosis induced by low potassium in granule cells (van Acker et al. 1996b)
Apigenin	Lessens oxidative damage, prevents NO-induced vasorelaxation of aorta in male Sprague–Dawley rats (Arora et al. 1998)

with its modified form UPLC having advantage of more resolution, speed, and sensitivity over HPLC (Hussein et al. 2011). Another new technique, alternative method to analyze phytochemicals is called capillary electrophoresis (CE), done by two different types of methods: MEKC and CZE are gaining popularity (Hussein et al. 2011). Honey obtained from *Marchalina hellenica* (Turkish red pine honey) has been reported to scavenge DPPH due to its antiradical action (Kassim et al. 2010). Honey obtained from *Trigona carbonaria* (Australian stingless bees) show good antioxidant properties (Akbulut et al. 2009), similarly good antioxidant and antiradical activities in tualang honey of Malaysia by *Apis dorsata* the giant Asian bees and American buckwheat honey have been reported (Oddo et al. 2008; Mohamed et al. 2009). Pine honey from Greece showed antioxidant effect on human serum lipoproteins and LDL; similarly oxidative stress caused by cumen hydroperoxide (CuOOH) causing damage to membrane and intracellular levels was reversed by antioxidant and antiradical effect of honey by inhibiting the progression of oxidative cascade, free radical species, and increasing the cell longevity as compared to control cells. A protective effect shown by pre-incubated cells with honey when exposed to CuOOH stress showed little oxidative damage, increased GSH levels, fewer morphological changes, and an increase in cell survivability compared to control cells. The outcome of these studies showed antioxidant and anti-inflammatory role of honey on endothelial cells (Makedou et al. 2012).

2.3.3 Honey as Antioxidant from In Vivo Studies

Honey as an in vivo antioxidant has been studied with respect of its effects on various body parts to ameliorate oxidative stress as mentioned.

2.3.3.1 Effect of Honey on GIT

Besides antioxidant action, gastroprotective effect of honey in ethanol-, aspirin-, indomethacin-, or ammonia-administered rodents is reported (Beretta et al. 2007). The gastroprotective effect of honey studied by Kim revealed that gastric injury and duodenal ulcers induced by *Helicobacter pylori* is due to oxidative stress, and honey inhibits its growth (Gharzouli et al. 2002; Kim 2005). GIT in diseased conditions is prone to oxidative stress, disturbing fluidity of brush border membrane (BBM) (Bhor and Sivakami 2003). Honey having gastroprotective action improves glycemic control in diabetic rats stimulating the hypoglycemic drug bioavailability through alteration of intestinal oxidative state (Erejuwa et al. 2011a), and co-administration of honey with antibiotic (sulfasalazine) reduced oxidative damage, colonic inflammation, and mucosal malondialdehyde (MDA) level in ulcerative colitis induced by trinitrobenzosulfonic acid (TNBS) in rat model (Ali et al. 1991; Medhi et al. 2008).

2.3.3.2 Effect of Honey on Liver

The abnormalities in diabetes mellitus usually seen are increased susceptibility of liver to oxidative stress and elevated levels of serum aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase (Bilsel et al. 2002; Leeds et al. 2009). Studies showed that pine honey restored the activities of hepatic CAT, GPx, and SOD in the liver of young and middle-aged rats (Gumieniczek 2005) and reduced hepatic damage in trichlorfon-administered male BALB/c mice, hepato protective effect in sheep administered carbon tetrachloride (CCl4) (Yao et al. 2011), STZ-induced diabetic rats and in common bile duct obstruction of rats (Erejuwa et al. 2012). Supplementation of honey-restored hepatic glutathione levels ameliorated the mononuclear cellular infiltration induced by NEM and congestion in liver (Erguder et al. 2008).

2.3.3.3 Effect of Honey on Diabetes Mellitus and Pancreas

Fall of glycemic control in diabetes mellitus is seen as β-cells of pancreas are susceptible to oxidative stress leading to reduction in the efficiency of insulin secretion by pancreas an outcome of oxidative stress (Korkmaz and Kolankaya 2009; Poitout and Robertson 2002). Honey improves total antioxidant status (TAS), glutathione reductase (GR), CAT, glutathione S-transferase (GST), and GPx enzyme activities (Evans et al. 2003). It also reduced the levels of lipid per-oxidation and restored SOD activity. On kidney, its antioxidant effect reduced the thickening of glomerular basement membrane and mesangial matrix expansion in the honey-treated diabetic rats. Combination of honey with hypoglycemic agents like glibenclamide and metformin distinctly protected the pancreas and kidney against oxidative damage and restored antioxidant enzymes much better than any of these agents when given alone (Grankvist et al. 1981).

2.3.3.4 Effect of Honey on Plasma/Serum

Elevated levels of plasma glucose are responsible for oxidative stress by generating ROS. Supplementation of honey reduced hyperglycemia in Sprague–Dawley rats with streptozotocin-induced diabetes (Evans et al. 2003; Erejuwa et al. 2010) rats with diabetes induced by alloxan (Erejuwa et al. 2009), Wistar–Kyoto rats with streptozotocin-induced diabetes (Fasanmade and Alabi 2008). Formation of advanced glycation end products (AGEs) on reaction of glucose (carbonyl group) and protein (amino group) results in the formation of a stable compound called fructosamine, a glycosylated protein formed as a consequence of diabetes (Erejuwa et al. 2011b), and consumption of honey reduces formation of fructosamine due to its antioxidant properties. A study on Nigella grains and honey against carcinogenesis and oxidative stress induced by methylnitrosourea showed that combination of *Nigella sativa* and honey stopped the increase in MDA and NO levels and exerted 100% protection against the effects of methylnitrosourea (Selvaraj et al. 2006). The antioxidant activity of honey in plasma is also revealed by an increase in the activity of GPx and NO in rats with alloxan-induced diabetes (Mabrouk et al. 2002).

2.3.3.5 Effect of Honey on Reproductive Organs

Cigarette smoking leading to cigarette smoke-induced testicular damage by causing apoptosis and damage in the testis in response to oxidative stress (Hassan and Bayoumi 2010; Rajpurkar et al. 2002). Honey brings higher Leydig cell count, larger diameter and epithelial height of seminiferous tubules and reduction in the percentage of tubules holding germ cell loss result in the amelioration of testicular damage (Mohamed et al. 2011). Honey caused an increase in epididymal sperm count and improvement in testicular marker enzyme activity owing to reduction in lactate dehydrogenase and elevation in sorbitol dehydrogenase a study in rats conducted by Abdul-Ghani and colleagues (Mohamed et al. 2011). Another study on ovariectomized female rats also suggested advantageous effects of honey on reproductive organs of female (Abdul-Ghani et al. 2008) (Fig. 2.2).

2.3.4 Advantages of Honey as an Antioxidant

Different antioxidants with valuable effects have been documented in various disease models (rodents as well as humans) (Köhler et al. 2011; Shargorodsky et al. 2010; Rodrigo et al. 2008). However, shortcomings of these antioxidants or vitamins have been reported due to their complex mechanism by acting as

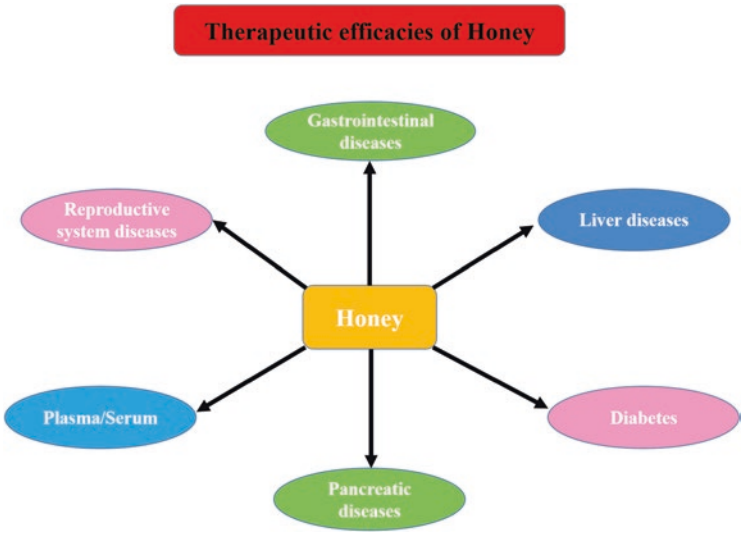

Fig. 2.2 Various pathways regulating antioxidant mechanism of honey. Honey acts as potent antioxidant and can be used in different diseases. The antioxidant property of honey is by elevation of total anti-oxidant defense of the body, donation of hydrogen, free radical sequestration, chelation of metallic ions, and acts as substrate for radicals

pro-oxidants that need antioxidants for their activation (Bowry et al. 1992). Vitamins C and E considered as first-choice antioxidants when used in trials had a disadvantage of undefined dose selection and with supplementation of large doses of α-tocopherol in the diet, and they interfere with the plasma bioavailability of γ-tocopherol (Handelman et al. 1985) or may increase tumor formation (Mitchel and McCann 1993). α-Tocopherol is less effective as inhibitor of nitrogen dioxide-mediated nitrosation than γ-tocopherol (Cooney et al. 1993). Study on smokers supplemented with β-carotene is reported to exaggerate cancer risk (Heinonen and Albanes 1994). Beneficial effects of honey over other vitamins are that honey is devoid of pro-oxidant properties, comprises several bioactive constituents which may produce synergistic antioxidant effects, and does not require regeneration into active form (Köhler et al. 2011; Rodrigo et al. 2008), and honey can scavenge both free radicals like OONO−, O2•− and non-free radicals like NO (Estevinho et al. 2008; Bilsel et al. 2002), upregulates intracellular transcription factor Nrf2 moderately, and is capable of reducing inflammation by inhibiting the production of NO and prostaglandin E (2) (Kassim et al. 2011; Bilsel et al. 2002). In view of the few above-mentioned advantages, honey might be more advantageous in preventing complications of various acute and chronic coursed diseases (Fig. 2.3).

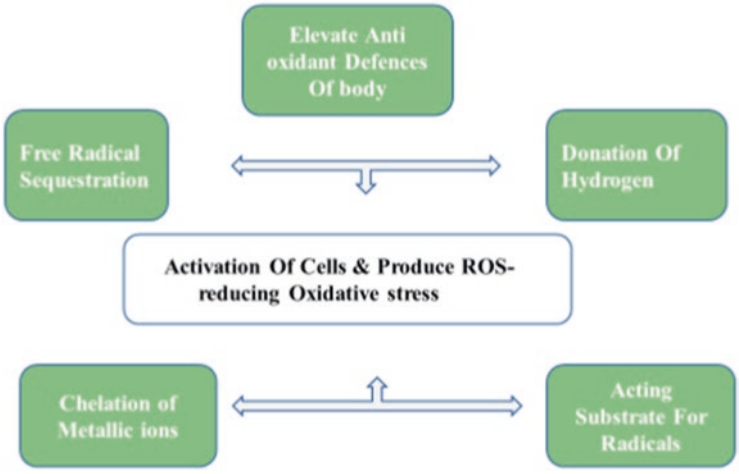

Fig. 2.3 Various anti-inflammatory pathways through which honey acts (Swartz 2005; Larocca et al. 1995). Honey inhibits release of various cells like macrophages, neutrophils, monocytes which have anti-inflammatory effects. It also increases the production of H_2O_2 which also accounts for anti-inflammatory effects. It is known to decrease the levels of IL-6, PGE2, COX-2, etc., which acts as proinflammatory molecules and inhibits expression of MMP9

2.4 Other Biological Activities of Honey

In addition to the antioxidant activity, honey also exhibits some other beneficial health roles as follows.

2.4.1 Antimicrobial Activity

Various constituents present in honey like H_2O_2, methylglyoxal, NO-metabolites, flavonoids, defensins, and phenolic acids along with certain other properties of honey like high osmolarity and acidity make it an effective antibacterial against various bacteria like MRSA, VREF, and ciprofloxacin-resistant *Pseudomonas aeruginosa* (Ishige et al. 2001; Samhan-Arias et al. 2004; Kwakman and Zaat 2012). Antibody production, lymphocytic and phagocytic activities may also increase by using honey (Alvarez-Suarez et al. 2010). Level of H_2O_2 produced determines the antibacterial action of honey due to increased activity of two enzymes, i.e., catalase and glucose oxidase. Respective levels of these two enzymes determine the level of H_2O_2 in the honey (Weston 2000). In the presence of enzyme catalase, hydrogen peroxide produces oxygen and water and shows inverse relationship between hydrogen peroxide and catalase activity which is used to assess the "inhibine number" of honey. Therapeutic effects of honey are very important especially in immunocompromised individuals, effective against a range of microbes including both pathogenic and non-pathogenic micro-organisms (Zaghloul et al. 2001). Honey can act as bacteriostatic agent or bactericidal depending upon the concentration used. Hydrogen peroxide can destroy microbes by the generation of strong free radicals on decomposition, but catalase enzyme or heat can easily destroy its activity. Catalase has no effect on antibacterial action of manuka honey (from New Zealand) and jelly bush (from Australia); both are examples of non-peroxide honey (Snow and Harris 2004: Weston 2000). Flavonoids and cinnamic and benzoic acid are the constituents of nonperoxide honey (Weston 2000) due to which they show more stable and persistent antibacterial action (Alvarez-Saurez et al. 2009). Upon reaction of hydrogen peroxide with benzoic acids, more stable and more powerful peroxyacids exhibiting antimicrobial properties are formed. Manuka honey has the highest level of non-peroxide activity (Cushnie and Lamb 2005). Infections caused by *E. coli* and *S. aureus* can be prevented by manuka honey (Lusby et al. 2005).

2.4.2 Beneficial Role of Honey on Immune System

In cell culture, honey has shown immunostimulatory effect by activating T- and B-immune cells. Besides showing potent antibacterial activity, honey also helps in clearing infection by activating immune system. It stimulates multiplication and activation of neutrophils (Tonks et al. 2003). It also stimulates monocytes where from cytokines (IL-1, IL-6 and TNF-alpha) are released, which further activates immune system thus clearing the infection. An active component in manuka honey has been found to

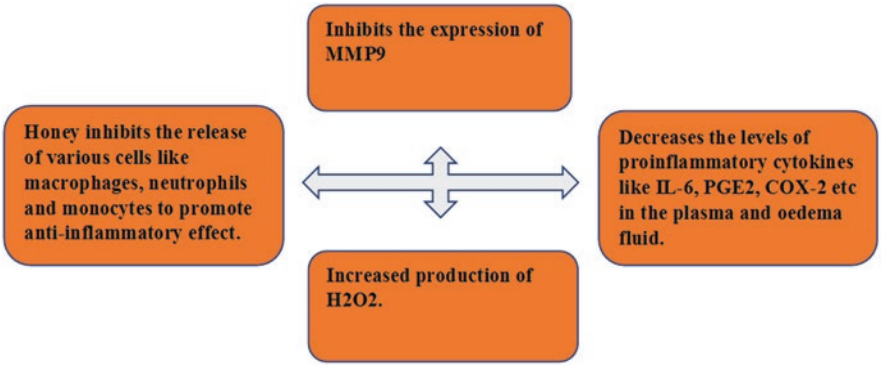

Fig. 2.4 Overall therapeutic efficacy of honey: Honey is known to have therapeutic efficacy in different disorders. It has been known to prevent disorders related to GIT, liver, reproductive system, diabetes, pancreas, plasma, and serum. This efficacy could be attributed to different mechanisms discussed in the chapter

stimulate the release of TNF from macrophages by the activation of TLR (Tonks et al. 2007). Respiratory burst in macrophages requires supply of glucose that produce hydrogen peroxide to destroy the bacteria (Molan 2001), and such substrates of glycolysis in the macrophages for energy production to perform its action in injured tissue with low oxygen supply and exudates are provided by honey. Honey has suitable pH at which macrophages show enhanced phagocytic activity (Molan 2001) (Fig. 2.4).

2.4.3 Honey in Wound Healing

Honey from different sources has been used for a broad spectrum of wounds (Al-Waili 2004). Presently a blend of jelly bush and manuka honey (Medihoney) is first certified and medically licensed for wound care in many European countries (Molan and Betts 2004; Molan 2006). It stimulates regrowth of tissues, angiogenesis, and fibroblast growth to produce collagen fibers and replace connective tissue. Honey facilitates formation of new skin by stimulating the regrowth of epithelial cells over healed wounds, prevents scar and keloid formation, and eliminates the necessity of skin grafting (Rozaini et al. 2004). Honey facilitates autolytic debridement due to its high osmotic pressure, it takes lymph from deeper tissue and immerses the wound bed constantly, and protease activity of lymph is responsible for debriding activity (Molan and Rhodes 2015).

2.4.4 Apoptotic Activity of Honey

Honey because of its apoptotic activity is considered as natural substance with anticancer property. Apoptosis inducers are the chemicals used in the treatment of cancer, as uncontrolled cellular proliferation and inadequate apoptotic turnover

occur in cancer (Rozaini et al. 2004; Boukraa and Niar 2007). Honey is responsible for apoptosis through depolarization of mitochondrial membrane (Boukraa and Niar 2007) by changing the expression of pro- and anti-apoptotic proteins in neoplastic cells. Honey having more phenolic constituents increases cleavage of poly(ADP-ribose) polymerase (PARP) and caspase-3 activation in the human colon neoplastic cells (Earnshaw 1995). It causes upregulation of proapoptotic proteins (Bax, caspase-3, p53) and downregulation of Bcl2 anti-apoptotic factor (Earnshaw 1995). Manuka honey through intravenous injection exhibits its apoptotic effect through the involvement of caspase-9 which then causes caspase-3 activation, PARP activation, DNA fragmentation, and inexpression of Bcl2 factor in neoplastic cell lines (Tomasin and Gomes-Marcondes 2011). Cancerous tissue of Wistar rats on oral administration of honey showed increased expression of pro-apoptotic protein (Bax) and reduced expression of anti-apoptotic protein Bcl-2 (Park et al. 2005). Presence of Quercetin in honey reduces transcriptional activity and signaling of β-catenin/Tcf in cell lines of SW480 (Gulati et al. 2006), and inhibition of the PI3K-Akt/PKB by Quercetin present in honey also exhibits an anticancer effect.

2.5 Conclusion

Changing lifestyle and food habits have exposed humans to various stress conditions leading to the enhanced incidence of different diseases like hypertension, cancer, atherosclerosis, and diabetes mellitus resulted in decreased lifespan of humans and increased mortality. Oxidative stress having vital role in pathogenesis of these diseases demands the incorporation of dietary antioxidants beneficial for bringing down such conditions to a low level. But the antioxidants to be selected should be effective without any harmful effects. Honey being a natural product have plentiful benefits which in combination with conventional therapy can produce synergistic effects to ameliorate the oxidative stress in different body parts and produce positive effects in the management of several disease conditions suggesting that honey can be used both as nutrient and as medicine.

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