# 9 Recent Advances in the Discovery of Bioactive Components from Natural Honey

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**Abstract**

Honey is one of the most valued natural products introduced to mankind since antiquity. Traditionally, honey is not only used as a food product but also as an alternative remedy for clinical conditions ranging from wound healing to cancer treatment. Honey contains about 200 beneficial bioactive constituents primarily comprising glucose and fructose and it also encompasses some vitamins, amino acids, minerals, and enzymes from fructo-oligosaccharides. Honey is an essential source of phenolic compounds and it is of great interest to see the amount and type of phenolic acids and flavonoids as they are responsible for nutraceutical properties as well as promising pharmacological functions such as antimicrobial, antidiabetic, anticancer, neuroprotective, cardioprotective, and wound healing properties. Additionally, several recent reports have also verified that the phenolic compound profile in honey is closely linked to the botanical and, often, the geographic origin of this food product. In this book chapter, therapeutic effects associated with the bioactive compounds in natural honey have been thoroughly discussed.

**Keywords**

Honey · Therapeutic effects · Phenolic acids · Flavonoids

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## 9.1 Introduction

It is generally accepted that a natural product imparts better health benefits than that of synthetic source. However, this frontier is still open for the debate, and many investigations are going-on on this subject (Topliss et al. 2002). In the recent past, plant-derived natural products have been used at larger scale due to the occurrence of vital components such as vitamins, enzymes, phytochemicals hormones, antioxidants, minerals, and other nutritional components. These substances provide vital nutrients for human use and avert the nutrition-associated diseases and thus help in improving the health of the human beings (Atanasov et al. 2015).

Honey is the most appreciated and valued product of natural origin produced by honeybees (*Apis mellifera* L.). It is an essential food product that has been excruciatingly used for its ethnopharmacological applications. Honey contains nearly 200 beneficial bioactive components majorly comprising fructose and glucose as well as fructo-oligosaccharides (Chow 2002), vitamins, minerals, amino acids, and enzymes (Da Silva et al. 2016). Its constitution varies and depends on the plants on which the bee nourishes. Any natural honey type contains flavonoids (e.g., quercetin, kaempferol, chrysin, galangin, pinocembrin, apigenin, and hesperidin), phenolic acids (such as p-coumaric, caffeic, ferulic acids, and ellagic), antioxidants (SOD: superoxide dismutase, ascorbic acid, GSH: reduced glutathione peptides, tocopherols, CAT: catalase, and Maillard reaction products). These chemotypes induce synergistic antioxidant effect and mostly act in mishmashes (Alvarez-Suarez et al. 2010; Johnston et al. 2005; Turkmen et al. 2006; Rakha et al. 2008; Al-Mamary et al. 2002). Evidence suggests that honey possesses several health-associated effects such as antioxidant (Ahmed and Othman 2013), anti-inflammatory, antimicrobial activity (antibacterial, antifungal, and antiviral) against diverse human pathogens (Khalil et al. 2012) and anticancer activity against different kinds of tumors by targeting diverse molecular pathways that play key role in cell division and antidiabetic activity with the reduction of fructosamine, glucose, and glycosylated hemoglobin concentrations in serum (Estevinho et al. 2008). Honey also exerts protective effects in the lungs against asthma and respiratory infections, in the gastrointestinal tract (Abdulrhman et al. 2008) in the cardiovascular system as well as in the nervous system by preventing the low-density lipoproteins (LDL) oxidation (Ghosh and Playford 2003). Although numerous studies were done on nectar honey types, only a few are accounted for.

This book chapter is a comprehensive update which highlights the recent advances in the discovery of bioactive components from natural honey. Moreover, therapeutic role (Fig. 9.1) of honey in antimicrobial, antidiabetic, anticancer, wound healing, apoptotic, and ophthalmological conditions has been thoroughly discussed.

## 9.2 Composition of Honey

The composition of all natural honey types relies upon the plant species on which the honeybee feeds. Major components of all natural honey types remain same. The average composition of natural honey is summarized in Table 9.1.

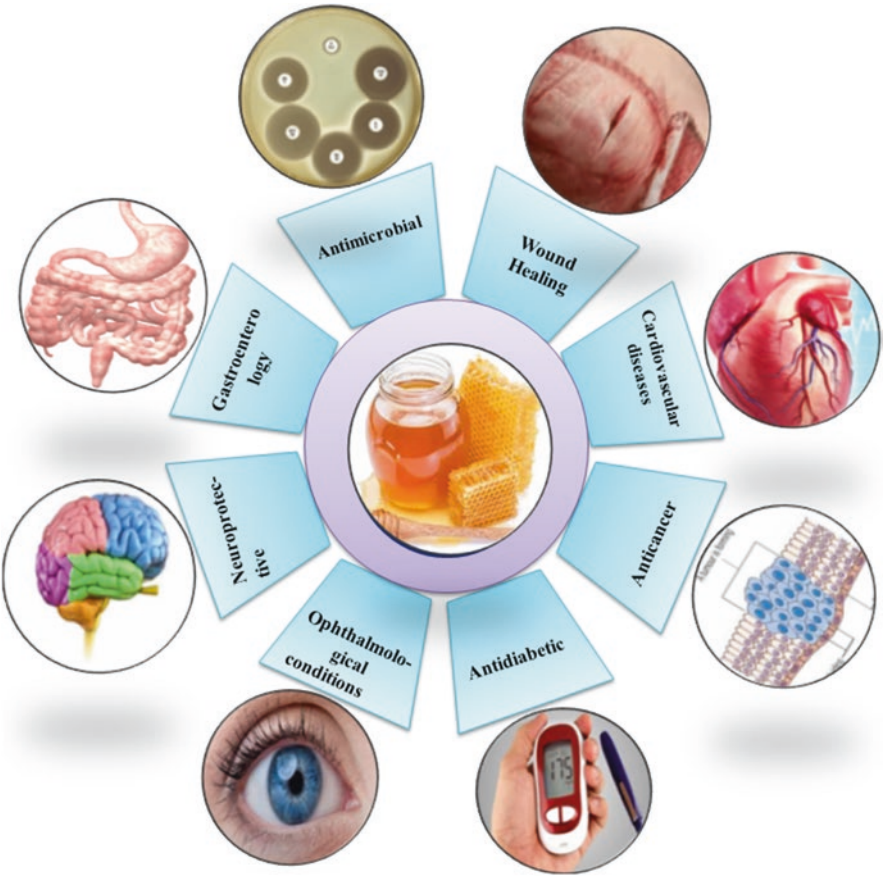



**Fig. 9.1** Therapeutic properties of honey

**Table 9.1** Average composition of honey (Adapted and modified from the references (White et al. 1962; Amy and Carlos 1996))

| Constituents | Average (%) |
|---|---|
| Moisture | 17.2 |
| Glucose | 31.28 |
| Fructose | 38.19 |
| Sucrose | 1.31 |
| Disaccharides, calculated as maltose | 7.31 |
| Higher sugars | 1.5 |
| Lactone as gluconolactone | 0.14 |
| Total acid as gluconic | 0.57 |
| Free acid as gluconic | 0.43 |
| Nitrogen | 0.041 |
| Ash | 0.169 |

## 9.3 Bioactive Compounds in Honey

Honey contains several essential bioactive components such as vitamins (retinol, thiamine, riboflavin, pyridoxal phosphate, ascorbic acid, tocopherol, menadiol, niacin, pantothenic acid), enzymes, fatty acids, and phenolic compounds (octadecanoic acid, hydroxybenzoic acid, cinnamic acid, flavonoids, and ethyl ester) (Bogdanov et al. 2008; Muhammad et al. 2015). Chemoprofile of honey also encompasses pinocembrin, acacetin, apigenin, and acids like ferulic acid and abscisic acid (Marghitas et al. 2010). The amino acid composition of physiological significance is arginine, cysteine, proline, aspartic acid, and glutamic acid (Qamer et al. 2007). The presence of this dynamic compound profile indicates better insightful of the potent biological role of honey in the management of human diseases. The bioactive compounds identified in honey are summarized in Table 9.2.

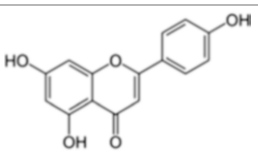
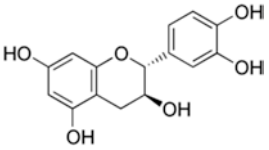
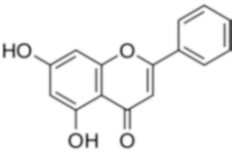
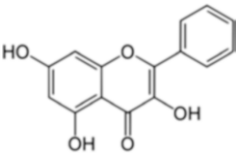
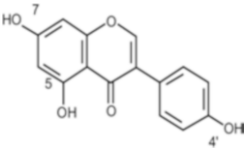
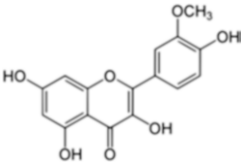
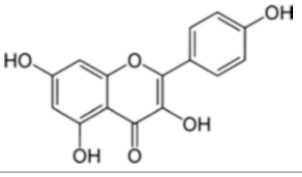
## 9.4 Antibacterial Activity

Antimicrobial activities of honey are majorly credited to the phenolics present in honey, including benzoic acid derivatives, flavonoids, and other volatile compounds (Pita-Calvo and Vázquez 2017). The other main factors that append to antimicrobial activity of honey include the enzymatic oxidation of glucose as well as some of its physical aspects (Beretta et al. 2007; Cushnie and Lamb 2005). Moreover, acidic (low pH) environment, high carbon (C)/nitrogen (N) ratio, high osmotic pressure/low water activity (WA), low protein content, and high level of reducing sugars lead to low redox potential; a viscosity that is limiting the dissolved oxygen content as well as other chemotypes/phytochemicals can contribute to the antimicrobial activity of honey.

Honey has long been exploited as a remedy for the control of microbial infections. It exerts an inhibitory effect against nearly 60 bacterial species that comprise aerobic and anaerobic, Gram-negatives and Gram-positive bacteria (Olaitan et al. 2007). Honey inhibits the growth by manifold (Al-Waili 2004). Previous investigations on antimicrobial activity of honey (Visavadia et al. 2006) indicated its antimicrobial activity against several pathogenic bacteria, including *Salmonella typhimurium*, *Escherichia coli*, *S. aureus, Enterobacter aerogenes* (Lusby et al. 2005; Visavadia et al. 2006). The spectrum of antibacterial effect of honey also encompasses different types of *methicillin-resistant S. aureus* (MRSA), β-*hemolytic streptococci* and vancomycin resistant *Enterococci* (VRE) (Allen et al. 2000; Kingsley 2001). The coagulase negative staphylococci are very akin to *S. aureus* (Cooper et al. 2002; Abhishek et al. 2010) in their sensitivity to honey and more sensitive than Enterococcus species and *Pseudomonas aeruginosa* (Cooper et al. 2002). Recent investigations reported antibacterial activity of against *Aeromonas hydrophilia*, *Salmonella enteric*, and *Klebsiella pneumoniae* (Table 9.3).

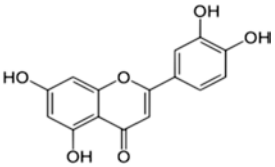
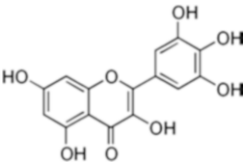
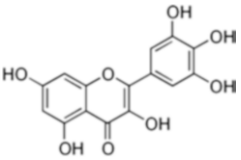
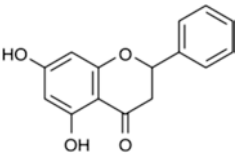
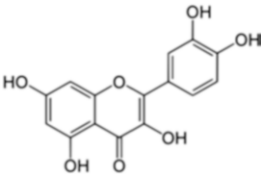
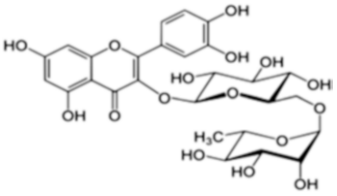
Neat honey exhibits inhibitory effects against fungi, and diluted honey inhibits the production of toxin by these microorganisms (Al-Waili and Haq 2004). Inhibitory activity of honey has also been reported against some yeast. Growth

**Table 9.2** Most common phenolic compounds identified in honey

| | Structure | Significance | Reference |
|---|---|---|---|
| *(a) Flavonoids* | | | |
| Apigenin |  | Inhibits the proinflammatory mediators release, induces anticancer and immunomodulatory effects, protects endothelium-dependent vasorelaxation of the aorta | Jin et al. (2009) |
| Catechin |  | Protects against ischemia-reperfusion-induced nerve cell death | Inanami et al. (1998) |
| Chrysin |  | Controls proliferation of cell by activating p38-MAPK via accumulation of p21Wafi/Cip1 | Weng et al. (2005) |
| Galangin |  | Antitumor activity apoptosis induction, elevates the cytotoxic activity, anticlastogenic effects, inhibits osteoclastic bone destruction as well as osteoclastogenesis | Hossen et al. (2017) |
| Genistein |  | Anti-inflammatory effects via STAT-1 and NF-κB activations | Hämäläinen et al. (2007) |
| Isorhamnetin |  | Inhibits NF-κB activation by inhibiting the ions expression and no production in stimulated macrophages | Hämäläinen et al. (2007) |
| Kaempferol |  | Downregulates the lipid peroxidation and cell division and enhances the susceptibility to apoptosis | Almasaudi et al. (2016) |

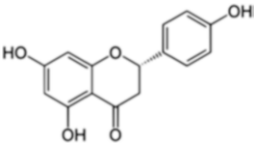
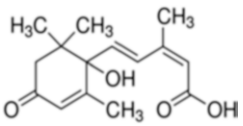
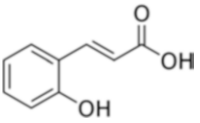
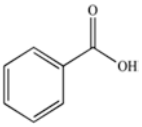
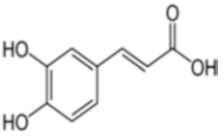
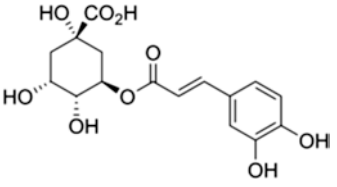
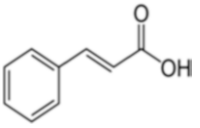
(continued)

**Table 9.2** (continued)

| | Structure | Significance | Reference |
|---|---|---|---|
| Luteolin |  | Antidiabetic effect through several mechanisms to reduce blood sugar levels | Jung et al. (2004), Mcdougall and Stewart (2005) and Rouse et al. (2014) |
| Myricetin |  | Reduces ROS and free radical generation after ischemic injury cell swelling | Gordon and Roedig-Penman (1998) |
| Pinobanksin |  | Antiproliferative effect, inhibits peroxidation of LDL, reduces oxidative stress and antimutagenic effect, improves cognition | Hossen et al. (2017) |
| Pinocembrin |  | Neuroprotective, effects, ameliorates effect against blood–brain barrier injury, prevents atherosclerosis, improvement in memory impairment, induces apoptosis, reduces cardiac arrhythmia infarct size, inhibits inflammatory mediators and ameliorates nephrotoxicity | Hossen et al. (2017) |
| Quercetin |  | Antidiabetic effect via several mechanisms to reduce blood sugar levels | Jung et al. (2004), Mcdougall and Stewart (2005) and Rouse et al. (2014) |
| Rutin |  | Inhibits in vitro platelet aggregation by binding to the A2 receptor of thromboxane | O'malley et al. (1995) |

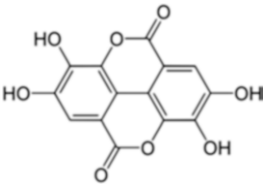
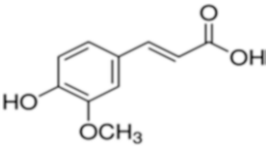
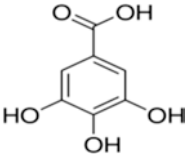
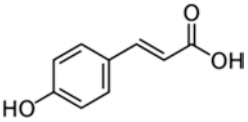
(continued)

**Table 9.2** (continued)

| | Structure | Significance | Reference |
|---|---|---|---|
| Narigenin |  | Alters the fluidity in both outer and inner membrane of hydrophilic and hydrophobic regions | Tsuchiya and Iinuma (2000) |
| *(b) Phenolic acids* | | | |
| 2-*cis*, 4-*trans* Abscisic acid |  | Antidiabetic activity | Uzor et al. (2017) |
| 2-Hydroxycinnamic acid |  | Antibacterial activity against *Mycobacterium tuberculosis* and *M. bovis* with an MIC ranging between 122 and 244 μM | Guzman et al. (2014) |
| Benzoic acid |  | Inhibits the active uptake of some amino and oxo acids in *Escherichia coli and Bacillus subtilis* | Russell and Chopra 1996; Park et al. 2001 |
| Caffeic acid |  | Inhibits the oxidative stress in the rats that were overloaded by iron, reduces the lipid peroxidation, and increases the tocopherol (vitamin E levels) in the plasma | Lafay et al. (2005) |
| Chlorogenic acid |  | Neuroprotective effects by preventing methylmercury-induced apoptosis of PC12 cells | Li et al. (2008) |
| Cinnamic acid |  | Improves the insulin resistance and glucose homeostasis by increasing the glucose uptake, pancreatic β-cell functionality, and reducing the dipeptidyl peptidase-4 and protein glycation | Adisakwattana (2017) |

(continued)

**Table 9.2** (continued)

| | Structure | Significance | Reference |
|---|---|---|---|
| Ellagic acid |  | Anti-inflammatory activity, prevents high fat/ carbohydrate diet-induced metabolic syndrome, induces anticancer effect, prevents kidney toxicity, inhibits protein kinase CK2, ameliorates cisplatin induced injuries to sperm quality, redox system, and the histologic structure of the rat testicles, hepatoprotective, cardioprotective, gastroprotective effects, inhibits the cell proliferation | |
| Ferulic acid |  | Induces glucose uptake by increasing the expression of P13K and GLUT4 transcripts via P13K dependent signaling pathways | Prabhakar and Doble (2009) |
| Gallic acid |  | Protects against the bacterial cytotoxicity, exhibits antimicrobial activity, prevents oxidative stress, induces apoptosis, exhibits cardioprotective, hepatoprotective, and gastroprotective effect, induces antihyperglycemic, anti-lipid peroxidative effects, induces anti-melanogenic, pro-inflammatory activities | Hossen et al. (2017) |
| p-Coumaric acid |  | Cardioprotective role, antioxidant effects on LDL cholesterol oxidation, pesticide detoxification | Hossen et al. (2017) |

(continued)

**Table 9.2** (continued)

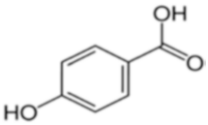
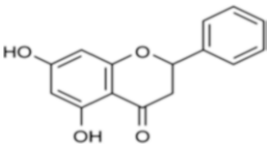
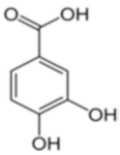
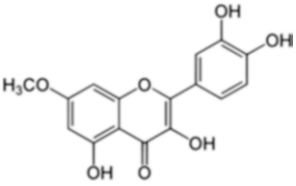
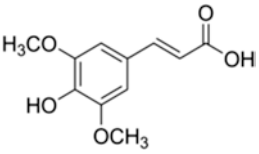
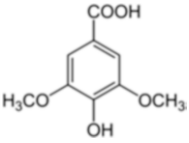
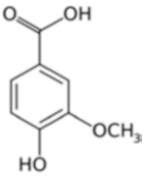
| | Structure | Significance | Reference |
|---|---|---|---|
| p-Hydroxybenzoic acid |  | Antifungal and antimicrobial effects, antiproliferative effects against PC-3 and MCF-7 cells, lowers the expression of adhesion molecules in HAEC | Spilioti et al. (2014) |
| Pinocembrin |  | Antibacterial, antifungal, anticancer, and neuroprotective activities | Rasul et al. (2013) |
| Protocatechuic acid |  | Antioxidant and anti-inflammatory roles, antioxidant and hepatoprotective effects | Rasul et al. (2013) |
| Rhamnetin |  | Anti-inflammatory effect, reduces pro-inflammatory cytokines levels by regulating the c-Jun NH2-terminal kinase 1 and p38 MAPK signaling pathway | Jnawali et al. (2014) |
| Sinapic acid |  | Acetylcholinesterase inhibitor, potential antioxidative agent, and antimutagenic by inhibiting the carcinogenesis and the induction of inflammatory cytokines | Nićiforović and Abramovič (2014) |
| Syringic acid |  | Nephroprotective, hepatoprotective antidiabetes, cardioprotective, anticancer, antimicrobial, antioxidant, anti-inflammatory, and antiendotoxic activities | Srinivasulu et al. (2018) |
| Vanillic acid |  | Exhibits estrogen-like effects in osteoblast-like UMR 106 cells by MAP kinase (MEK/ERK)-mediated ER signaling pathway | Xiao et al. (2014) |

**Table 9.3** Bacteria that are sensitive to honey (Molan 1992, 1997)

| Bacterial strain | Clinical importance | Reference |
|---|---|---|
| *Actinomyces pyogenes* | Endometritis | |
| *Corynebacterium diphtheriae* | Diphtheria | Molan (1992) |
| *Escherichia coli* | Urinary tract infection, diarrhea, septicemia, wound infections | Chauhan et al. (2010) |
| *Bacillus anthracis* | Anthrax | Molan (1997) |
| *Haemophilus influenzae* | meningitis, ear infections, sinusitis, respiratory infections | Molan (1997) |
| *K. pneumoniae* | Pneumonia | Molan (1997) |
| *Helicobacter pylori* | Chronic gastritis, peptic ulcer, gastric malignancies | Molan (1997) |
| *Mycobacterium tuberculosis* | Tuberculosis | Molan (1992) |
| *Proteus sp.* | Septicemia, urinary infections, wound infection | Molan (1997) |
| *Salmonella sp: Salmonella typhi, Salmonella typhimurium Salmonella cholerae-suis* | Typhoid, enteric fever | Mulu et al. (2004), Chauhan et al. (2010), and Molan (1992) |
| *Nocardia asteroids, Microsp. Canis, M.. gypseum* | Mastitis | Molan (1992) |
| *Shigella sp.* | Dysentery | Molan (1997) |
| *Serratia marcescens* | Wound infections, septicemia | Molan (1997) |
| *Pseudomonas aeruginosa* | Wound infection, urinary tract infections, diabetic foot ulcer | Chauhan et al. (2010) |
| *Streptococcus faecalis* | Urinary tract infections | Molan (1992) |
| *Streptococcus mutans* | Dental carries | Molan (1992) |
| *Staphylococcus aureus* | Community acquired and nosocomial infection | Molan (1992) |
| *Streptococcus pneumoniae* | Meningitis, sinusitis, ear infections, pneumonia | Molan (1997) |
| *Streptococcus pyogenes* | Ear infections, impetigo, rheumatic fever, puerperal fever, scarlet fever, wound infections, sore throat | Molan (1997) |
| *Trichophyton rubrum, T. tonsurans, T. mentagrophytes* var., *Epiderm floccosum* | Tinea | Molan (1997) |
| *Vibrio choleriae* | Cholera | Molan (1992) |
| *Aeromonas schubertii* | Burn, wound infection | Hassanein et al. (2010) |
| *Stenotrophomonas maltophilia* | Pneumonia, urinary tract infection, blood stream infection, nosocomial infection | Tan et al. (2009) |

inhibitory effects of honey has also been against other species of Aspergillus, Penicillium, and against all the common dermatophytes (Brady et al. 1997; Sampath Kumar et al. 2010). *Candida albicans* (causative agent of Candidiasis) also exhibits some sensitivity to honey (Obaseiki-Ebor and Afonya 1984; Bansal et al. 2005).

Surface mycoses such as ringworm and athletes foot cutaneous have also been reported to exhibit sensitivity to honey. This sensitivity is attributed to the inhibition of fungal and bacterial growth (Bansal et al. 2005). Additionally, topical application of honey has been shown to be effective in treating the seborrheic dermatitis and dandruff (Al-Waili 2005; Bansal et al. 2005)

## 9.5 Wound Healing

The use of honey in wound dressing dates back to ancient times. Its effectiveness in wound healing in the modern science has become available only recently. The treatment effects of honey for both acute wounds and superficial partial thickness burns are almost equal or a little better than conventional treatments (Yaghoobi and Kazerouni 2013). The wound dressing capacity of honey is due to the combinatorial effects that act in synergism to accelerate the process of wound healing. Wound healing capacity of honey is the widely studied and most effective application of honey (Medhi et al. 2008). In World War I, the Russians used honey to stop wound infection and to expedite wound healing. Honey combined with cod liver oil was used by Germans to treat burns, boils, fistulas, and ulcers (Bansal et al. 2005). All wound types including skin abrasion, bed sores/decubitus ulcers, septic wounds, abscess, burns, amputation, chill blains, surgical wound, abdominal wound (burst), nipples cracking, fistulas, diabetic, cervical, leprosy, traumatic, malignant, varicose, sickle cell ulcers, wounds of abdominal wall, and perineum have been indicated to be responding to honey treatment. Honey therapy as wound dressing leads to the initiation of healing process and removal of the infection. Honey has sanitization action on wounds, stimulates tissue regeneration, and reduces inflammation.

Treatment of cutaneous wounds in rabbits with honey was found to reduce edema (swelling), lower the inflammation, lessen the necrosis, attenuate the epithelialization, and improve wound contraction. On histological examination, honey has also been demonstrated to accelerate wound healing on cutaneous wounds in murine model (Bashkaran et al. 2011).

The application of honey (dressings soaked with natural honey) in diabetic wounds as topical wound dressings resulted in excellent treatment effects. Application of honey improved the diabetic wound and the rate of leg or foot amputations which in turn enhanced the life quality and productivity (Makhdoom et al. 2009).

In a double-blind randomized controlled clinical trial, healing time with honey dressing was found to be equivalent to hydrogel dressings in the abrasions or minor lacerations patients (Ingle et al. 2006). Similar effects in average healing times were observed with honey, paraffin gauze, or iodoform gauze in the studies of randomized, double-blind controlled clinical trial (McIntosh and Thomson 2006) and a randomized single-blind controlled clinical trial, respectively. A meta-analysis of these minor acute wounds indicated no statistically significant difference in mean time to healing between honey and conventional dressing (Marshall et al. 2005).

## 9.6 Cardiovascular Disease

The promising role of honey in the treatment of cardiovascular diseases is attributed to the presence of polyphenols (Habauzit and Morand 2012) such as quercetin, kaempferol, and caffeic acid phenethyl ester (CAPE). Polyphenols are the valuable natural products in honey for managing the blood pressure (Sánchez-Moreno et al. 2006). Quercetin lowers the risk of stroke and coronary heart disease (Zahedi et al. 2013). Kaempferol prevents the accumulation of the low-density lipoprotein (LDL) cholesterol that poses the great risk for cardiac diseases. The role of polyphenols in the prevention of the cardiovascular diseases is mainly due to oxidization of LDL cholesterol, scheming the vasodilatation of heart vessels and reversing platelet clotting in the blood circulation. Honey repressed blood coagulation through each of the three coagulation cascades including extrinsic, intrinsic, and the common cascade and thus reducing the fibrinogen levels. Owing to these excellent features, honey is believed to counteract the process of formation of atherosclerotic plaques that are associated with the development of cardiac disorders. Thus, the atherosclerosis that contributes to arterial hardening and narrow down of the lumen of the vessel are effectively neutralized (Kas'ianenko et al. 2010).

## 9.7 Anticancer Activity

Recent studies provide the strong evidences that honey induces anticancer effects through several mechanisms such as modification of the immune responses, apoptosis, anti-mutagenic, anti-proliferative, and anti-inflammatory pathways (Eddy et al. 2008). Honey has also been reported to inhibit the cell division, induce the apoptosis, modulate the cell cycle progression, and induce the mitochondrial membrane depolarization in several types of cancer cells including cervical cancer cells, adenocarcinoma epithelial cells (Pichichero et al. 2010), skin cancer cells (melanoma), (Erejuwa et al. 2014), and endometrial cancer cells (Yaacob et al. 2013; Tsiapara et al. 2009).

The potential of honey as an ameliorating agent has been indicated in all stages including prevention, progression, and treatment of the disease. Most of the investigations have been documented in in vitro, and they have been performed out on several types of cell lines and numerous types of honey. Several studies have also been performed out in animal models (mice/rats) with induced or transplanted tumor (Miguel et al. 2017). Honey operates at different stages of cancer including the initiation, cell multiplication, and disease progression. The mechanism of anticancer effects of honey includes induction of apoptosis (physiological form of cell death), arrest of cell cycle, oxidative stress reduction, the lowering of inflammation, the induction of mitochondrial outer membrane permeabilization (MOMP), and angiogenesis inhibition (Orsolic et al. 2003).

Honey has been found to induce apoptosis in cancer cells through mitochondrial membrane depolarization (Fauzi et al. 2011). Honey has been reported to elevate poly-ADP-ribose polymerase (PARP) cleavage and caspase 3 activation in colon

cancer cell lines of humans owing to its high content of amino acid (tryptophan) and phenolic compounds (Jaganathan and Mandal 2009). Additionally, honey induces cell death in colon cancer cell lines by modulating the expression levels of pro- and anti-apoptotic proteins (Jaganathan and Mandal 2010). Honey elevates the expression of p53, proapoptotic protein Bax, and caspase and decreases the expression of anti-apoptotic protein Bcl-2 (Jaganathan and Mandal 2010). Honey attenuates the generation of ROS leading to p53 activation which in turn fine tune the expression of pro- and anti-apoptotic proteins like Bax and Bcl-2 (Jaganathan and Mandal 2010).

## 9.8 Honey and Diabetes

Diabetes is a metabolic disease with multifactorial and diverse causes. Diabetes mellitus, a chronic disorder, is one of the leading diseases in the modern world, and >285 million people were estimated to have the disorder in 2010. It is estimated that 438 million people will develop diabetes mellitus by the year 2030 globally (Shaw et al. 2010). Diabetes prevalence is either hereditary or can develop any time during life.

It has been indicated in numerous studies that use of honey results in decrease in the blood sugar levels in partial insulin deficiency diabetic rats in which diabetes was induced by simultaneous administration of streptozocin (STZ)-nicotinamide. Rats treated with honey for about 1 month showed a significant reduction of fetal bovine serum (FBS) level compared to the control (untreated) diabetic rats that is credited to a remarkable improvement in serum insulin level. Additionally, treatment with honey considerably increased catalase (antioxidative enzyme) expression as indicated in the immunohistochemical analysis, which lowered the oxidative stress in the pancreas and promoted the healing of the pancreatic tissue (Aziz et al. 2017). L-Phenylalanine amino acid present in honey have been indicated for stimulating the insulin release from pancreas which improves the glucose tolerance in diabetic rats (Aziz et al. 2017).

It has been investigated that a 3-month ingestion of honey in type 1 diabetic patients induced a significant reduction in fasting blood glucose, serum triglycerides (TGs), total cholesterol (TC), LDL, and a significant rise in fasting C-peptide and 2-h postprandial C-peptide. Additionally, a prolonged ingestion of honey triggered considerable reductions in fasting serum glucose, 2-h postprandial serum glucose, serum TGs, and HbA1C (Abdulrhman et al. 2013). These findings indicated that long-term ingestion of honey has improved the metabolic imbalances of type 1 diabetes mellitus.

## 9.9 Nervous System

Honey plays a key role in the neuroprotection owing to the presence of polyphenols. Honey prevents the generation of ROS, which are toxic to the central nervous system. Polyphenols in honey neutralize various neurological pathologies involved in

the process of aging. Additionally, polyphenols in honey prevent the accumulation of misfolded proteins, such as β-amyloid plaques, that have central role in some age-related neurological pathologies (Syarifah-Noratiqah et al. 2018).

It has been investigated that administration of honey to kainic acid (KA)-induced neurodegeneration in the cortex of male Sprague–Dawley rats resulted in the decrease in the neurodegeneration in the rat cerebral cortex, and this property is attributed to its antioxidant property of honey (Sairazi et al. 2017). Additionally, The neuroprotective effects of honey owing to its antioxidant rich potential were also examined in cultured astrocytes. These cells were exposed to honey at the different doses (0.1%, 0.3%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 3%, and 5% [*v*/*v*]) for 24 h followed by hydrogen peroxide ($H_2O_2$) at the concentration of 100 μmol/L for 3 h. Cell viability was analyzed with MTT assay. Honey treatment prevented the cell death in a dose–response manner compared with $H_2O_2$-treated cells. Honey at the dose of 1% had the most significant effect (Ali and Kunugi 2019). The neuroprotective effects of honey flavonoid extract (HFE) on the production of pro-inflammatory mediators in lipopolysaccharide-activated N13 microglia cells were examined. The findings from this study indicated that the HFE considerably inhibited the release of TNF-α and IL-1β (pro-inflammatory cytokines). The expression of iNOS and the production of ROS were also considerably inhibited. In this study, it was indicated that HFE is a potent inhibitor of microglial cell activation and thus a potential neuropreventive–therapeutic substance involving neuroinflammation (Candiracci et al. 2012).

Earlier study indicated that pretreatment with honey to Sprague–Dawley rats that were exposed to hypoxia-induced memory deficits reduced the neuronal damage in hippocampus of rats and improved the memory of the rats (Abdulmajeed et al. 2016).

On in vivo use, administration of different honey samples to mice induced the behavioral effects including central inhibitory effects, antinociceptive, anxiolytic, as well as antidepressant effects. Additionally, significant hypnotic and partial protection of picrotoxin-induced convulsions was also observed. These findings provide crystal clear indications that honey can be used as nutraceutical agents (Akanmu et al. 2011). In another study, preemptive administration of honey (Tualang honey) at the dose of 1.2 and 2.4 g/kg body weight reduced the pain responses in male Sprague–Dawley rats (Aziz et al. 2014).

## 9.10 Ophthalmological Conditions

Ophthalmology is one of the most promising areas of application of honey. Ample source of investigation provides the strong evidences that honey can be successfully used in the management of different ophthalmological conditions. In vitro corneal fibroblast cell lines isolated from New Zealand white rabbits have indicated that honey promoted wound healing by improving the healing process, maintaining corneal crystallin and retaining the production of type I collagen as well as by decreasing the scar development risks through reduction of myofibroblasts transformation which may be a potent natural adjunct for corneal wound treatment (Yusof et al.

2019). In another study of contact lens-induced corneal ulcer, complementary treatment with honey was explored, and it was indicated that honey is an effective antimicrobial agent for corneal ulcers treatment. Additionally, honey exerts promising antibiofilm and anti-inflammatory effects and thus becomes an attractive ophthalmologic agent (Majtanova et al. 2015). Other studies in which ophthalmological use has been explored include dry eye syndrome (Albietz and Lenton 2006; Jankauskiene et al. 2007), bullous keratopathy (Sethi and Rai 2005), and opacities of the cornea after herpetic keratitis (Mozherenkov and Prokofjeva 1991).

Honey has been found to exhibit antiangiogenic and anti-inflammatory properties on corneal abrasions and endotoxin-induced keratitis in Lewis rats in which keratitis was induced by topical application of *P. aeruginosa* endotoxin to scarified corneas (Uwaydat et al. 2011).

The effectiveness and safety of topical honey eye drops was evaluated in the clinical trial in the patients with diagnosed vernal keratoconjunctivitis (VKC). Honey drop in VKC patients resulted in the significant increase in eye pressure and decrease in redness as well as limbal papillae (Salehi et al. 2014).

## 9.11 Gastroenterology

Protective effects of honey on the gastrointestinal tract have been established in several studies. Rats fed with honey demonstrated a modulation in the lactic acid bacteria in the intestines possibly indicating the role of honey in modulating the gut microbiota (Shamala et al. 2000). The antimicrobial activity of different types of honey against *H. pylori* isolated from patient stomach with gastric diseases has been determined. The antimicrobial potential of honey against *H. pylori* was evaluated by minimum inhibitory/minimum bactericidal concentration. *H. Pylori* has indicated to be susceptible to honey with a median level of antimicrobial activity due to the presence of $H_2O_2$ (20%) concentration (McGovern et al. 1999).

All the honey samples tested in the study indicated a high antibacterial activity with obvious therapeutic potential (Manisha and Shyamapada 2011). Furthermore, honey also acted against gastric ulcers in indomethacin and alcohol-induced rat models (Ali 1995; Gharzouli et al. 2002). Honey inhibits the production of prostaglandin and stimulates the sensory nerves in the stomach that respond to capsaicin (Ali 1995). This accounts for the antioxidant properties of honey. The effects of natural honey on absolute ethanol-induced gastric lesions were also studied in rats. Honey demonstrated the healing properties in acetylsalicylic acid–induced gastric ulcer in rats. The healing properties demonstrated by the honey were equivalent to the cimetidine (used for the treatment and prevention of certain types of stomach ulcer) (Bukhari et al. 2011).

Honey ingestion has been found to resolve the gastroenteritis and diarrhea quickly (Haffejee and Moosa 1985; Bansal et al. 2005). Ingestion of honey at the dosage of 5.0% (v/v) decreased the length of diarrhea associated with bacterial gastroenteritis when compared to sugar solution in replacement fluid concentration. However, No change was observed in viral gastroenteritis. The addition of honey to

rehyderation fluids resulted in increase in K and $H_2O$ uptake with no increasing in sodium uptake (Bansal et al. 2005). Pretreatment with honey at the dose of 2 g/kg body weight ameliorated indomethacin-induced gastric lesions, myeloperoxidase activity and microvascular permeability of the stomach in the rats that were administered (orally) honey (Nasutia et al. 2006).

## 9.12 Concluding Remarks

This chapter summarizes the recent update on the identification of bioactive components from natural. Use of honey as a valued natural product as well as traditional medicine has been appreciated from the time immoral. Its effectiveness in the modern medicine for the treatment of human diseases has become available only recently. The major effects of honey include its antibacterial activity against a wide spectrum of bacteria, fungi, and yeast. Additionally, the role of honey in the treatment of diabetes, wound healing, eye care, neuroprotection, and gastroenterology has been well established in several studies and has been thoroughly discussed. The diverse pharmacological property of honey is due to its constituents such as phenolics, peptides, vitamins, enzymes, organic acids, and Maillard reaction products which plays an vital role in its useful effects for the management of human diseases.

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