Positive Influence of Honey on Human Health

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Abstract

Use of honey is advocated by the people of all religions, traditions, and cultural beliefs, and it is one of the most valued natural products owing to its nutritional and medicinal properties. Honey is known to be the rich in sugars, phenolic compounds, free organic acids, and enzymes. It also contains lipids, amino acids, trace elements, vitamins, and few toxic compounds. It has been known to exert neuroprotective, cardioprotective, gastroprotective, antidiabetic, antioxidant, antimicrobial, anticancer, and anti-inflammatory activities. This chapter focusses on the positive influence of honey on human health and the mechanisms involved in the same. It also sheds light on the chemical composition and the ongoing clinical trials on honey.

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12.1 Introduction

Honey is a natural product formed by honeybees (*Apis mellifera*; Family: Apidae) from nectars of the flowers and offer huge benefits to human beings because of nutritional and medicinal values (Samarghandian et al. 2017; Subramanian et al. 2007). Approximately 1.20 million tons per annum of honey is produced globally and its major producers are Argentina, China, Mexico, Ukraine and the United States (Meo et al. 2017).

Use of honey has been advocated by all religious and cultural beliefs and all traditions due to its nutritional and medicinal values and has been accepted by all civilization and generations whether ancient and modern. A whole chapter named Surah al-Nahl which means a chapter of the honey bee is mentioned in Holy Qur'an, which contains a verse And your Lord inspired the bee(s), saying: "Take your habitations in the mountains and in the trees and in what they erect. Then, eat of all fruits, and follow the ways of your Lord made easy (for you)". There comes forth from their bellies, a drink of varying colour wherein is healing for men. Verily, in this is indeed a sign for people who think". The final Prophet Muhammad (S.A.W) emphasized the utilization of honey because of its restorative, therapeutic and healing property. Use of honey has also been advocated in books of Exodus, Judges, Mathew and Proverbs in the Bible (Ajibola et al. 2012).

Consumption of honey is also popular with ancient civilization such as Greeks, Chinese, Egyptians, Romans, Mayans and Babylonians (Samarghandian et al. 2017). Honey bee colony exhibits a perennial life cycle. Honey bees are divided into three categories viz., Queens, Drones (mates the new queens) and workers. The queens are responsible for producing egg and lay it in the comb's cells. Within 3–4 days, the eggs give off larvae. Worker bees fed these larvae after which the larva pupates by crossing several stages of development in the cells (Ediriweera and Premarathna 2012). The Worker bees collect nectar from the flower by inserting their long hollow tube (formed from labium and maxillae) to into the flowers. After extracting the nectar they pass it into the honey sac or crop through their oesophagus. The nectar which mainly contains sucrose is converted into invert sugar by the enzyme invertase present in the saliva of the worker bee (Khemchand et al. 2015). In the hive, the bee ingests the nectar and regurgitate it several rounds until the nectar is partly digested. The bees continue to carry this performance until the product of the desired quality is obtained. The honeycomb is remained unsealed until 80% of water present in honey is evaporated by a strong draft created by the wings of the bees inside the hive. The dried form of honey thus obtained is sealed inside the cells of the honeycomb (Ediriweera and Premarathna 2012).

Honey is plentiful in carbohydrate and contains other components such as polyphenols, organic acids, proteins, amino acids, minerals, vitamins and over 500 enzymes.

These components impart medicinal property to honey such as antioxidant, anti-inflammatory and antimicrobial potential. There are approximately 320 different range of honey, the composition of which depends upon plant variety from which the nectar is obtained and the environment in which the plants mature (Hills et al. 2019).

This chapter gives insights into the health benefits associated with the consumption of honey and brief about the composition and clinical trials of the honey.

12.2 Composition of Honey

Honey has been identified to possess 181 different substances and some of these are exclusive to honey only (Przybylowski and Wilczynska 2001). Honey contains approximately 8% of sugar which is dissolved in 17–20% of water. The composition of honey is dependent upon factors such as air, water and soil, the geographical region from which it is collected, type of flowers visited by bees and environmental condition where the plants grow and mature (Hack-Gil et al. 1988). The nutritional and medicinal value of honey is attributed to both major and minor components present in it**.** The ideal density of honey is 1.52 g/mL at 15 °C, Optically, it is laevorotatory due to the presence of high fructose content. The caloric value of honey on an average is 3500 calories/kg (Czipa et al. 2019). The common range of specific gravity is 1.3648–1.4101 g/mL (Gairola et al. 2013). The viscosity of honey ranges from 10 to 30 poises (James et al. 2009).

There are various factors which regulate the colour, taste, aroma and chemical composition of honey. The colour of the honey varies based on its nectar source, season, duration between the collection of nectar and harvesting of honey, production and storage. Dark honey is known to be rich in minerals. Reactions such as Maillard reaction, caramelization or tannates and polyphenols make the honey to appear darker. Darker honey tends to have strong flavour compared to pale honey. The physiochemical properties of honey are related to the quality of storage, texture, granulation, flavour and its medicinal and nutritional properties and are important for the industry (Przybylowski and Wilczynska 2001). Different chemical constituents present in honey are mentioned in Table 12.1.

12.3 Health Benefits of Honey

Apitherapy is defined as the use of honey derived products and other bee products for medicinal purposes (Ab Wahab et al. 2018).

12.3.1 Neuroprotective Effect

Honey has also been reported to prevent cognitive impairment and dementia due to its antioxidant and brain's cholinergic system enhancing properties. It has been hypothesized that Tualang honey could remove ROS and regress oxidative stress that was caused during noise-induced stress. In ovariectomized stressed rat, Tualang

Table 12.1 Chemical constituents of honey

S. No	Constituents		Name	References
1	Sugars	Monosaccharides	Glucose, fructose	Da Silva et al. (2016)
		Disaccharides	Sucrose, maltose, turanose, isomaltose, maltulose, trehalose, nigerose, kojibiose, maltotriose, melezitose	
		Oligosaccharides	Maltotriose, melezitoze, erlose, theanderose, panose, isomaltosyltetraose, 1-ketose, centose, isopanose, isomaltosyl glucose, isomaltosyltriose, isomaltosyltaose	Afroz et al. (2016)
2	Phenolic compounds	Flavonoids	Hesperetin, pinocembrin, naringenin, chrysin, apigenin, luteolin, tricetin, galangin, kaempferol, quercitin, isorhamnetin, myricetin, pinobanksin	Santos-Buelga and González-Paramás (2017)
		Phenolic acids	4-hydroxybenzoic acid, protocatechuic acid, gallic acid, vanillic acid, syringic acid, cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid, phenylacetic acid, mendelic acid, homogentisic acid, phenylpropanoic acid, rosmarinic acid	
3	Free organic acids		Gluconic acid, acetic acid, butyric acid, citric acid, formic acid, malic acid,, oxalic acid, succinic acid, lactic acid fumaric acid, pyroglutamic acid, maleic acid, α- ketoglutaric acid	Afroz et al. (2016)
4	Enzymes		Diastase, amylase, invertase, sucrase, sucrose hydrolase, saccharase, glucose oxidase, catalase, acid phosphatase, protease, esterase, β-glucosidase	White Jr. (1978)
5	Lipids		Glycerides, sterols, phospholipids, palmitic acid, oleic acid, lauric acid, miristic acid, stearic acid, linoleic acid	Machado De-Melo et al. (2017)
6	Amino acids		Proline, phenylalanine, tyrosine, lysine, arginine, glutamic acid, histidine, valine , methionine, cysteine, valine, a-alanine, tyrosine	Hermosín et al. (2003)
7	Trace elements		Aluminium, arsen, barium, boron, bromine cadmium, chlorine, cobalt, flouride, iodide lead, lithium, molybdenum, nickel, rubidium silicium, strontium, sulfur, vanadium, zirkonium	Bogdanov et al. (2016)
8	Amino acids		Proline, phenylalanine, tyrosine, lysine, arginine, glutamic acid, histidine, valine methionine, cysteine, valine, a-alanine, tyrosine	Hermosín et al. (2003)
9	Vitamins		Phyllochinon, thiamin, riboflavin, pyridoxin, niacin, panthothenic acid, ascorbic acid	Bogdanov et al. (2008)
10	Toxic compounds		Grayanotoxins, polycyclic aromatic hydrocarbons (PAHs), polyhydroxylated cyclic hydrocarbons (diterpenoids)	Machado De-Melo et al. (2017)

honey improved memory performance. In a study, stress was induced in the rats using noise. Following the exposure of noise, it was demonstrated that the stressed rats contained a less number of neurons in hippocampus and medial prefrontal cortex region compared to a non-stressed rat which resulted in short- and long-term decrease in memory in stressed rats compared to nonstressed rat. Administration of Tualang honey imparted neuroprotection; the histopathological study revealed an enhanced number of neuron in hippocampal and medial prefrontal cortex region and short- and long-term memory was also improved in the stressed rats (Azman et al. 2018).

Astrocytes, the neuroglia which forms a part of the blood–brain barrier (BBB) are one of the main locations that express genes responsible for neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Neuroinflammation and oxidative stress lead to the dramatic transformation of astrocytes called "reactive astrocytes" which is characterized by alterations in morphological and functional aspects that degrade biomolecules such as DNA leading to the occurrence of neuropsychiatric disorders. In a study, the antioxidant potential of honey was examined in astrocytes cell culture. Astrocytes from the cortex of pups of Wistar rats were reseeded in 96-well microplate at a density of 1.8 × 104 cells/well with complete Dulbecco's Modified Eagle Medium (DMEM) containing 10% foetal bovine serum (FBS) as a medium. The cell was treated with various concentrations of honey (from 0.1 to 5% v/v) for 24 h which was followed by H_2O_2 (100 μmol/L) treatment for 3 h followed by MTT assay. The result of the study demonstrated that H_2O_2 treatment resulted in substantial cell death due to oxidative stress. Whereas with honey, the cell viability was preserved compared to H_2O_2-treated cells, and the most significant effect of honey was observed at 1% concentration. The investigator concluded that honey exerts a protective effect on Astrocytes (Ali and Kunugi 2019).

Neuroprotective effect of Tualang honey was investigated against kainic acid (KA)-induced neurodegeneration and oxidative stress in rats. KA administration is known to induce excitotoxicity and develop well-characterized seizures due to its ability to cause severe oxidative stress. Pretreatment with Tualang honey was able to reduce neuronal degeneration in the piriform cortex following KA administration, attenuated decreased of total antioxidant level, and increased thiobarbituric acid reactive substances level in cerebral cortex however it was not able to prevent KA-induced seizures (Mohd Sairazi et al. 2017).

All these above studies demonstrate the neuroprotective effect of honey which is attributed to the mechanism mentioned below.

12.3.1.1 Mechanism

1. Honey is reported to contain choline and acetylcholine which enhances the brain cholinergic system enhancing property.
2. It imparts neuroprotection due to its antioxidant potential.
3. The neuroprotective potential of Tualang honey was attributed to its high flavonoids content, enzymes such as peroxidase, catalase and glucose oxidase and non-enzymatic antioxidants such as ascorbic acid, α-tocopherol, carotenoids (Azman et al. 2018).

4. Gallic acid, caffeic acid present in Tualang honey has been demonstrated to lessen the seizure behaviour, decreased oxidative stress and apoptosis and prevent memory impairment (Sairazi et al. 2017).
5. Tualang honey has also been shown to enhance brain-derived neurotrophic factor (BDNF) and *acetylcholine* (ACh) levels, and decrease *acetylcholinesterase* (AChE) in the brain homogenates (Othman et al. 2015).

12.3.2 Respiratory Infections

Respiratory tract infection has a high prevalence, especially in children. Various microorganisms such as *H. influenza*, *S. aureus*, *P. aeruginosa*, *K. pneumonia*, and *S. pyogenes* are responsible for respiratory infections such as influenza, pneumonia, nosocomial infection, pneumonia in debilitated individual and pharyngitis (El-Kased 2016). *P. aeruginosa* is known to disturb the homeostasis of the upper and lower respiratory tract. *P. aeruginosa* utilizes its flagella, pili, lipopolysaccharides, lipoproteins and type III secretion system to interact with host cell resulting in epithelial damage by recruiting immune cells subsets (Curran et al. 2018). In a study, Macuna honey lowered *P. aeruginosa* viability in an ex vivo infection model and was believed to serve as potential therapeutics for upper respiratory tract infections especially in resistance is observed against other antimicrobials (Roberts et al. 2019). Theoretically, drugs such as diphenhydramine and histamine or other cold medicines are effective in relieving runny nose and cough. However, the evidence has proved it another way, that is, only to relieve rhinorrhoea and not cough and if taken in large doses these could pose a potential threat to child's health. Honey on contrary serves a safer alternative for treating distressing cough in children however it is restricted for infants less than 1 year of age (Chan 2014).

On oral administration, honey first acts on the upper respiratory tract topically followed by its action on lower respiratory tract followed by its absorption in the systemic circulation. In a study, a simulated sugar solution mimicking the property of honey (the high sugar content and low water content) was prepared and it showed an amazing antimicrobial effect. The antimicrobial potential of honey and simulated sugar were checked. Honey at 75% of its concentration and simulated sugar at 100% of its concentration inhibited all the tested bacterial isolates (El-Kased 2016).

A darker variety of honey named buckwheat honey which is higher in phenolic content is demonstrated to relieve nocturnal cough and improve sleep quality in children and parents. The relief by honey was found to be superior then dextromethorphan (Paul et al. 2007). Effects of aerosolised honey were studied against OVA-induced injury in the rabbit airway to find whether honey alleviates asthma-related histopathological changes. The results revealed that honey 25 and 50% significantly decreased the epithelial and mucosal thickening in Asthma which is one of asthma's characterized changes. Aerolised honey also inhibited hyperplasia of goblet cells and eliminated the mucus overproduction and hence, it proved to be useful in decreasing histopathological changes in asthma and prevention of allergen-induced asthma. It can also provide symptomatic relief in asthma (Kamaruzaman et al. 2014).

12.3.2.1 Mechanism

1. The antimicrobial action of honey against pathogen causing respiratory tract infection was attributed to its high sugar content which exerts the high osmotic pressure in both crude honey and simulated sugar solution. The study also revealed that apart from high osmotic pressure other components may also be responsible for antimicrobial effects because honey at limited dilution showed better antimicrobial activity. Presence of enzyme glucose oxidase was counted as one of the reasons for honey's antimicrobial effects as it releases hydrogen peroxide on dilution which is a potent antimicrobial compound (El-Kased 2016).
2. World Health Organization has postulated that the benefit of honey in cough is attributed to its demulcent effect. There is also a hypothesis that sweet substances such as honey relief dry/unproductive cough by its demulcent effect on pharynx and larynx which is attributed to reflex salivation and enhancing the secretion of airway mucus. And, their beneficial effect in productive cough is attributed to the improvement of mucociliary clearance in airways. It has been also suggested that the interaction between opioid responsive sensory fibre which are stimulated following the consumption of sweet substances and gustatory nerves via a central nervous system may be responsible for antitussive action of honey (Paul et al. 2007).

12.3.3 Cardioprotective Effect

Intake of honey has been shown to improve the cardiovascular diseases in the patients as well as healthy people at risk. Several studies affirmed that consumption of honey is associated with the positive impact on metabolic and cardiovascular health as revealed by recording some health profiles. The cardioprotective effect of honey was confirmed by another study; in which experimental rats were fed with a diet supplemented with natural honey or sugar (golden syrup, GS) for 84 days and compared their metabolic response in metabolic syndrome (MetS). The rat with GS administration had a significantly increased level of glucose and triglycerides and caused hyperinsulinemia, hepatomegaly, hypercholesterolemia, fatty liver and visceral adiposity and the rat with NH administration did not display the above-mentioned risk factors (Ajibola et al. 2012).

In a study, a reduction in systolic blood pressure was noted after 3 weeks of consumption of Malaysian Tualang honey in streptozotocin-induced diabetic spontaneously hypertensive rats. This effect was attributed to the reduction of oxidative stress in the kidney. Similarly, in another study, after 60 and 120 min of honey inhalation, a significant reduction in systolic and diastolic blood pressure was noted in the hypertensive patient. Honey also increases the NO level, which is also responsible for mitigating hypertension. C-reactive protein (CRP) is an important biomarker of cardiovascular disease risk and its levels increase in various deteriorating cardiovascular conditions. Honey, on oral administration, can reduce CRP (Al-Waili et al. 2013).

The postmenopausal state is highly correlated with the prevalence of cardiovascular disease and hence in a pilot study systolic blood pressure (SBP) was measured in postmenopausal women in two groups, one receiving Tualang honey and other

receiving HRT and the result demonstrated that group receiving Tualang honey reduced systolic blood pressure significantly compared to the one receiving HRT (Ab Wahab et al. 2018). However, obtained from the Black Sea coast of Turkey contained acetylandromedol, occasionally was reported to cause atrioventricular block (AVB), arterial hypotension and bradycardia but none of the fatalities was reported.

In a report, "Mad" honey which is utilized to treat gastric pains, hypertension and bowel disorders (as alternative medicine), may increase the change of atrioventricular block (AVB) when consumed in about "one teaspoonful". The toxicity is attributed to grayanotoxin present in it (Ozhan et al. 2004).

In isoproterenol-induced myocardial infarction in Wistar rats, pretreatment with honey restored the reduced levels of enzymes such as glutathione peroxidase, superoxide dismutase, and glutathione reductase including creatine kinase-MB, aspartate transaminase, lactate dehydrogenase and alanine transaminase. In another model of myocardial infarction, administration of honey improved cardiac troponin I, total cholesterol, triglyceride and lipid peroxidation (LPO) products (Ahmed et al. 2018).

In a study, the effects of natural honey were evaluated in ischemia/ reperfusion (I/R) induced wounds in isolated rat heart. The result of the study confirmed the consumption of honey for 45 days produce significant anti-infarction and anti-arrhythmic activity and serve preconditioning agent in such condition. In another study, pretreatment of stressed rat for 1 h with natural honey (5 g/kg), before adrenaline (100 μg/kg) administration preserve them from epinephrine-induced vasomotor dysfunction and cardiac disorder. The researchers clinched that this protective effect of honey was due to nitric oxide release from endothelium (Ahmad et al. 2017).

12.3.3.1 Mechanism

1. Honey has been shown to benefit cardiovascular disease via several mechanisms such as ameliorating endothelial function and coronary dilatation, platelet aggregation inhibition, reduction of inflammatory responses, reduction of oxidative stress (Ab Wahab et al. 2018).
2. Some flavonoids present in honey are known to increase the bioavailability of nitric oxide, a very well-known mediator for vasodilatation. For instance, rutin enhances eNOS gene expression and its activity and promotes the production of NO. Similarly, catechin and quercetin in honey exert a negative effect on aortic atherosclerotic lesion development (Ahmed et al. 2018).
3. Lowering of total cholesterol, low-density lipoprotein (LDL)-cholesterol, TGs, glucose level, C-reactive protein and increase of high-density lipoprotein (HDL) cholesterol in blood was noted (Ajibola et al. 2012).
4. Free radicles and reactive oxygen species (ROS) remains the key reason in the pathogenesis of the cardiovascular disease (Vallianou et al. 2014).
5. Honey is enriched with various natural antioxidants such as flavonoids, polyphenols (like caffeic acid, acacetin, quercetin, phenethyl ester (CAPE), galangin, and kaempferol), Vitamin C, and monophenolics and is reported to exert cardioprotective effect (Khalil and Sulaiman 2010; Samarghandian et al. 2017). And hence, can lower the levels of free radicals and reactive oxygen species (ROS) to exert cardioprotective effects.

12.3.4 Antidiabetic Effect

Diabetes mellitus is a complicated metabolic condition which is characterized by elevated glucose levels which occur due to deficiency of insulin or nonfunctional insulin. It is also characterized by abnormal lipoprotein and carbohydrate metabolism. Honey has known to display antidiabetic effects from preclinical to clinical studies and it has been referred to as a potential antidiabetic agent by researchers.

Inhalation of honey (60% w/v) was found to reduce glucose levels in type 2 diabetes mellitus. The most important component of honey which is known to exert antidiabetic effect is fructose. Fructose controls blood glucose level by regulating the insulin response system. It follows protein- and energy-mediated diffusion and taken up by the receptor GLUT5 and/or GLUT2. Both glucose and fructose increases the expression of GLUT2 mRNA. However, fructose increases the expression of GLUT5 mRNA specifically facilitating its fast absorption (Ahmed et al. 2018).

Natural honey has demonstrated to reduce the fasting blood glucose in obese by 4.2%. It is also reported to significantly improve the metabolism of glucose in type 2 diabetes. The glucose-lowering effect of the honey is contributed to fructose, antioxidant, oligosaccharides and trace elements present in it. However, there are some studies which demonstrate that consumption of Tualang honey for 4 months significantly increased fasting blood glucose levels compared to their baseline levels. Increase in the level of HbA1c after 8 weeks consumption of honey supplement was also noted. Therefore, cautious usage of honey is recommended in diabetic individuals (Ab Wahab et al. 2018).

It was found in a study that oral consumption of honey at various doses for 4 weeks increased body weight, total antioxidant status, activities of catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, and superoxide dismutase activity in diabetic rats, significantly. Tualang honey reduced elevated malondialdehyde level and re-establish superoxide dismutase and catalase activities in streptozotocin-induced diabetic rats. The hypoglycaemic effect of honey was attributed to its antioxidant property on the pancreas. Combination of Glibenclamide or Metformin with honey improved glycaemic control in the streptozotocin-induced diabetic rat (Ahmed et al. 2018).

Natural honey has been considered as non-injurious and curative agent in diabetes in the folklore. Presently, it is used as a sweetening agent in eastern/Unani herbal antidiabetic preparations (Akhtar and Khan 1989).

12.3.4.1 Mechanism

1. The most important component of honey which is known to exert antidiabetic effect is fructose (Ahmed et al. 2018). Honey contains 21–43% of fructose and the ratio of fructose to glucose is from 0.4 to 1.6 or higher. Compared to glucose and sucrose which have glycaemic index of 100 and 60, respectively, the glycaemic index of fructose is 19. Fructose display blood-glucose-lowering effect via several mechanisms such as reduction of intestinal absorption rate, gastric emptying time prolongation, and reduction of food intake (Bobiş et al. 2018).

Fructose plays a pivotal role in glucose uptake by the liver and storage of glucose as glycogen by stimulating glucokinase in hepatocytes. Fructose control blood glucose level by regulating the insulin response system. It interacts with GLUT5 and/or GLUT2 receptor via protein and energy mediated diffusion. Both glucose and fructose increases the expression of GLUT2 mRNA. However, fructose specifically increases the expression of GLUT5 mRNA, facilitating its fast absorption.

2. Honey also modulates the insulin signalling pathway. PI3K/Akt is a key component in insulin signalling which is known for cell growth and survival. In a study, the effect of the honey extract on Akt-activated insulin signalling pathway in pancreatic cells under hyperglycaemic condition was explored. Insulin resistance progression was described by enhanced levels of MAPK, NF-κB, and insulin receptor substrate 1 (IRS-1) serine phosphorylation and reduced Akt expression and insulin content. The results of the study revealed that pretreatment of honey along with quercetin improved insulin content and resistance. Alternatively, expression of Akt was increased and that of IRS-1 serine phosphorylation, NF-κB, and MAPK was decreased following honey treatment (Ahmed et al. 2018).
3. Glucose present in honey along with fructose promotes the absorption of fructose and enhances its delivery to liver thereby promoting its hepatic action. Honey also protects pancreas, an important organ in diabetes against oxidative stress.
4. Administration of fructose alone or with sucrose is demonstrated to ameliorate homeostasis of glucose and response of insulin when compared to the rats receiving glucose. Enzymatic cleavage of proinsulin to insulin is accompanied by co-secretion of C-peptide by the pancreatic cell and, is considered as a good insulin secretion marker. Honey raises the preprandial C-peptide levels compared to sucrose and glucose in non-diabetic individuals. This suggests the direct stimulatory effect of honey on the healthy pancreas beta cells.
5. As it is well known that diabetic wounds are slower to heal compared to typical wounds. Honey was used since folklore for healing various kinds of wounds. Recently, honey is reported to be used in diabetic wound management. The mechanism involved is: when honey is diluted with water or body fluid it forms hypochlorite anions and hydroxyl radical at the wound site. Moreover, the antioxidants of honey reduce the ROS and inflammation, fight against microorganism around the wound enhancing the healing process. Honey also contains nitric oxide metabolite which again ameliorates the healing process. In a study effect of manuka honey was studied in wound healing and result demonstrated that manuka honey has a healing effect on wound due to its antioxidant capacity and cell proliferation promoting property (Bobiş et al. 2018).
6. After several up and down in one of the clinical trial conducted, “honey as a sole treatment to type 2 diabetes” the investigator concluded that honey benefits the macrovascular complications of DM in a patient under the trail. The mechanism for the same includes a reduction in weight, reduction in blood pressure in hypertensive patients, preservation of Apo A-1 and attenuation of postprandial hyperglycaemia. The investigator also revealed that honey might heal the pancreatic

insult and ameliorate insulin resistance. However, two patient in the same study developed microvascular complication like enhanced peripheral neuropathy, development of the diabetic foot, non-proliferative retinopathy and cataract. Contrary to this, a patient who already had peripheral neuropathy did not show progress in this condition (Abdulrhman 2016).

12.3.5 Antioxidant Effect

Free radicals and reactive oxygen species generated during various metabolic process exhibits the tendency to interact with the lipid and protein composition of the cell membranes, DNA and enzymes. Thanks to antioxidants which seize free radicals before any damage caused. Honey is a rich source of antioxidant. Darker the honey more is its antioxidant value (Samarghandian et al. 2017). Oxidative stress contributes to the pathogenesis of various diseases and disorders such as Cancer, mutagenesis, ageing, atherosclerosis and many degenerative lingering diseases. Natural defence system present in the cells consists of catalase, superoxide dismutase, peroxidase, vitamin C, tocopherol and polyphenols. The antioxidant property of Honey is attributed to its flavonoids and phenolic acids, carotenes, organic acids, sugars, amino acids, protein, Maillard reaction products. Honey (1.2 g/kg) has demonstrated to increase the activity of other antioxidants such as ascorbic acid, glutathione reductase, beta carotene in healthy individuals (Ahmed et al. 2018).

Honey is rich in several phenolics (viz, ferulic acids, p-coumarin, caffeic acids, ellagic acids,) flavonoids (viz., quercetin, kaempferol, apigenin, pinocembrin, hesperetin, chrysin and galangin), vitamin C & E, superoxide dismutase and catalase. These antioxidants synergize with each other to exert its antioxidant effect. The antioxidant activity of honey is strongly correlated with its total phenolics content and its colour. Darker is the colour of honey, more is its phenolic content, consequently more phenolic content means more antioxidant potential (Vallianou et al. 2014).

In vitro and in vivo studies have demonstrated the antioxidant potential of honey. For instance, in an in vitro study free radical scavenging property of honey was demonstrated against (1,1-diphenyl-2-picrylhydrazyl, peroxyl radicals, 2,2′-azinobis [3-ethylbenzothiazoline-6-sulphonic acid] and nitric oxide. Honey also reduced ferric cations, form metal ion chelates, inhibit lipid peroxidation and β-carotene bleaching (Miguel et al. 2017).

12.3.5.1 Mechanism

1. The proposed mechanism of honey's antioxidant activity include sequestration of free radical, chelation of metallic ion, donation of hydrogen, superoxide radical action and flavonoids substrate action for hydroxyl group (Ahmed et al. 2018).
2. The in vivo antioxidant study of honey revealed that it stimulates antioxidant defence system such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione *S*-transferase, tissues of rat and mice.

3. Honey also contains gluconic, malic, and citric acids which exhibit antioxidant property, as these chelates metal ions and enhancing the antioxidant potential of flavonoids (Miguel et al. 2017).

12.3.6 Antimicrobial Effects

Recently investigators have reported antimicrobial property of the honey. Many researchers have found that natural honey possesses broad-spectrum antibacterial potential against oral and food spoilage bacteria. Plenty of honey is sold nowadays with systemized antibacterial potential. For instance, honey obtained from *Leptospermum scoparium* has reported possessing an inhibitory effect on approximately 60 species of aerobic, anaerobic, gram-positive and gram-negative bacteria. Tualang honey is effective against the various wound and enteric bacteria.

Back to 2100–2000 BC, honey was mentioned as a drug and ointment. Aristotle (384–322 BC) described pale honey as being "good as a salve for sore eyes and wounds". Manuka honey exhibit inhibitory potential against pathogenic bacteria such as *Staphylococcus aureus* (*S. aureus*) and *Helicobacter pylori* (*H. pylori*) *Escherichia coli* (*E. coli*), *Enterobacter aerogenes*, *Salmonella typhimurium. Breakthrough in this regard is the potential of honey against* methicillin-resistant *S. aureus* (MRSA), β-*haemolytic streptococci* and vancomycin-resistant *Enterococci* (VRE), coagulase-negative *staphylococci* (Mandal and Mandal 2011).

In a study antibacterial activity of honey was checked against MRSA isolates from wound infection using disk diffusion technique. The result of the study demonstrated that honey in the range of 18.75–37.5% v/v completely inhibited the growth of MRSA. Although, not all honey displays the same degree of antibacterial potential (Mama et al. 2019). Honey has also been demonstrated to have antiviral activity. In a study antiviral activity of honey, royal jelly and acyclovir were checked against herpes simplex virus-1 via Vero cells cultured in the Dulbecco's Modified Eagle's Medium (DMEM) along with 10% foetal bovine serum (FBS). The result of the study revealed that honey at 500 μg/mL concentration displayed an inhibitory effect against HSV-1(Hashemipour et al. 2014). Honey has also been demonstrated to be active against the rubella virus and at 5% of honey concentration complete inhibition of rubella virus was achieved (Ghapanchi et al. 2011). Manuka honey and clover honey demonstrated to be active against varicella-zoster virus (Shahzad and Cohrs 2012).

Honey is also known for its antifungal activity. It is active against *Rhodotorula* sp. *C. albicans, Candida glabrata*, and *Candida dubliniensis*, *Candida parapsilosis, Candida tropicalis, Candida kefyr, Candida glabrata*, and *Candida dubliniensis* (Moussa et al. 2012). In a study, hydrogen peroxide type honey was demonstrated to exhibit greater antifungal effects against dermatophyte fungi. Prophylactic use of honey is recommended to prevent some serious infection. For instance, the effectiveness of honey when placed around the catheters was same as mupiron or povidone-iodine in checking exit site infection. Honey could also be used for treating vaginal candidiasis when incorporated into pessary (Irish & Dee 2006). *Agastache*

honey was found to be the most effective honey against *T. mentagrophytes* and *T. rubrum*, closely followed by Tea tree honey, with Manuka honey showing some activity. The antifungal activity of honey was due to production of H_2O_2, the presence of volatile and phenolic compound (Anand et al. 2019).

12.3.6.1 Mechanism

1. The antibacterial property of honey is due to its capacity to liberate hydrogen peroxide, moisture drawing capacity from the environment, hence causing dehydration of bacteria, high osmolarity due to the high content of sugar, acidity (pH 3.2 and 4.5) and presence of non-peroxide components such as methylglyoxal (MGO).
2. The most important mechanism of antibacterial activity is the liberation of hydrogen peroxide due to dilution of honey hence activating enzymes such as glucose oxidase which carry oxidation of glucose to gluconic acid and H_2O_2.
3. On the other hand "non-peroxide honey" is honey which preserves its antimicrobial potential even in the presence of catalase (which normally decreases the antibacterial activity of honey). The constituents responsible for the non-peroxide honey's antibacterial are methyl syringate and methylglyoxal especially in manuka honey derived from the manuka tree (*L. scoparium*) (Mandal and Mandal 2011).
4. The antiviral effect of honey might be due to the existence of glucose oxidase which generates gluconic acid and hydrogen peroxide (Ghapanchi et al. 2011).
5. The antifungal potential of honey is attributed to the production of H_2O_2, the presence of volatile and phenolic compound (Anand et al. 2019).

12.4 Anticancer Activity

Studies demonstrating the anticancer potential of honey cover cell and tissue culture, preclinical to clinical trials. Honey contains flavonoids, phenolic acids, sugars, enzymes, amino acids, protein and miscellaneous compounds. The polyphenols and phenolic compounds present in honey have been demonstrated to possess antileukemic potential against various leukemic cell lines. The anticancer potential of honey has been studied extensively and has been reported against various cancers cell lines such as breast, colorectal, endometrial, prostate, renal and oral cancers. Additional benefits of honey are that it supplements the antitumour activity of drugs such as cyclophosphamide and fluorouracil.

In a study, the treatment with Tualang honey reduced the tumour incidence and delayed the tumour initiation (Ahmed and Othman 2017). Malaysian jungle Tualang honey was proved to be potential anticancer agents against human breast, cervical, oral and osteosarcoma cancer cell lines (Othman 2012a, b).

Patients with breast cancer display abnormal and poor blood parameters. It was demonstrated that values of blood parameter of the rats treated with TH were nearer to that of normal rats. TH has been proved to potentiate the haematological

parameters such as RBCs, Hb, PCV, eosinophils, lymphocytes and platelet compared to negative control rats which had reduced value of RBC, Hb, PCV, lymphocytes and platelets (Ahmed and Othman 2017).

Manuka honey was demonstrated to possess an inhibitory effect on cellular proliferation in human breast cancer MCF-7, murine melanoma B16.F1, and mouse colon carcinoma CT26 cell lines in time and dose-dependent manner. Similarly, thyme honey has been proved to have an inhibitory effect on proliferation in breast, endometrial and prostate cancer cell lines. Gelam and nenas honey also displayed antiproliferative effect against colon cancer cell lines (Porcza et al. 2016).

The cytotoxic effect of Tualang honey against breast cancer cell lines was proved by enhanced leakage of lactate dehydrogenase (LDH) from the cell membranes. The investigator found that the cytotoxic effect of TH was limited to breast cancer cell lines and not to the normal breast cell line, which is a pivotal characteristic of the good chemotherapeutic agent.

Honey having greater phenolic content employed a higher antitumor effect (Erejuwa et al. 2014). However, the beneficial effect of honey against cancer draw sceptics as it also contains sugars such as glucose, fructose, sucrose and maltose which itself are carcinogenic (Othman 2012a, b).

12.4.1 Mechanism Involved

1. *Induction of apoptosis*: Cancer cells are characterized by uncontrolled proliferation of cells and inadequate apoptotic mechanism. Two apoptotic mechanisms are followed by cell: (1) the caspase 8 or death-receptor pathway, (2) caspase 9 or mitochondrial pathway. Manuka honey induces caspase 9 which in succession cause activation of executor protein caspase 3. It also induces DNA fragmentation, PARP activation and decreased Bcl-2 expression. All these effects ultimately induce apoptosis on the cancer cells.

   In human colon cancer cell lines, honey enhances the level of caspase 3 activation and *poly (ADP-ribose) polymerase (PARP)* cleavage, upregulates and modulates pro and antiapoptotic protein expression, this effect of honey was due to its high phenolic and tryptophan content. Honey upregulates caspase 3, p53, and proapoptotic protein Bax expression and downregulates antiapoptotic protein Bcl2 expression (Ahmed and Othman 2013).

   Rats in TH treated group also displayed to normalize E2 (increased level of which is associated with risk of breast cancer in postmenopausal women) and Apaf-1 and caspase-9 (decreased level of which is associated with higher chances of cancer) compared with the rats in negative control group indicating TH acts as a natural estrogen-lowering agent (Ahmed and Othman 2017). The inhibitory effect of manuka honey on cellular proliferation was attributed to caspase-9-dependant apoptotic pathway activation (Porcza et al. 2016).
2. *Mitochondrial membrane depolarization*: Honey depolarizes mitochondrial membrane which leads to induction of apoptosis (Ahmed and Othman 2013). TH treated tumour hindered expression of Bcl-xL (overexpression of which is associated with metastasis in a breast cancer patient). The mechanism involves

blockade of mitochondrial swelling and membrane hyperpolarization hence inducing cellular proliferation and apoptosis (Ahmed and Othman 2017). Other mechanisms such as activation of the mitochondrial intrinsic pathway during which several proteins such as cytochrome c are released leading to cell death. Honey is also known to reduce the mitochondrial membrane potential which leads to mitochondrial membrane hyperpolarization ultimately causing leakage of intermembrane space proteins into the cytosol and ultimately cell death (Erejuwa et al. 2014).

3. *Cell cycle arrest*: Tumour cells are characterized by aberrant proliferation and hence, are a pivotal target for conventional and novel chemotherapeutics. DNA alterations initiate cell growth arrest at G0/G1 and G2/M phases or apoptosis. Inhibition of cell cycle in S and M phases are the target of many chemotherapeutic drugs. Honey treatment on the bladder (T24, 253 J, RT4, and MBT-2), colon and human melanoma cancerous (A375) cell lines arrested cell growth in the G0/G1 phase (Porcza et al. 2016). The honey treatment causes substantial arrest of the cell cycle in the sub-G1 phase in bladder cancer cell lines. The ability of honey to arrest is attributed to the presence of the several flavonoids and phenolic compounds present in it. Chrysin, quercetin and kaempferol are some of the flavonoids and phenolic compound present in honey in large quantities which arrest the cell cycle in G0/G1, G1 and G2/M in various cancer cell lines (Erejuwa et al. 2014).

   Tumorigenesis has also been linked to dysregulation and/or overexpression of cell cycle growth factors such as cyclin-dependent kinases (CDK) and cyclin D1. Ki-67, the nuclear protein which is expressed during G1, S, G2, and mitosis of the cell cycle, is a novel marker to investigate the "growth fraction" of cell proliferation. Honey has been proved to arrest the cell cycle. Honey when administered with *Aloe vera* solution markedly decreased Ki67-LI expression in tumour cells of rats. Honey has been reported to block the cell cycle in many cancerous cell lines via downregulation of various cellular pathway through kinases, ornithine decarboxylase and tyrosine cyclooxygenase (Ahmed and Othman 2013).
4. *Miscellaneous*: Antitumour activity of jungle honey is attributed to the chemotactic induction for neutrophils and generation of reactive oxygen species. Honey acts via several mechanisms such as stimulating the release of TNF-alpha (tumour necrosis factor-alpha), inducing apoptosis, inhibiting lipoprotein oxidation and causing cell cycle arrest (Othman 2012a, b).

   The proliferative effect of honey may also be attributed to its capacity to generate hydrogen peroxide, hence liberate radicals. Apoptosis induction by honey is also caused by depletion of intracellular non-protein thiols (Erejuwa et al. 2014).

12.4.2 Gastroprotective Effect

In the Greek, Chinese, Romans and Egyptian honey is used for treating stomach-related diseases and wounds. It has the efficacy to impart cytoprotection of the stomach. There are dozens of studies which highlight the gastroprotective effects of honey against ulcer. In a study, the antiulcer effect of honey, turmeric and honey

turmeric combination were seen. The honey treated group at 2125 mg/kg dose showed the healing percentage of 49.10% which was as significant as the group treated with Omeprazole. However, the same effect was not observed with the high dose of 4250 mg/kg BW. Honey also reduced the loss of body weight compared to nontreated rats.

In a study, the effect of honey (monofloral and polyfloral) and honey-like solution (a mixture of glucose-fructose-sucrose-maltose) on gastroprotection against ethanol, indomethacin, or ASA-HCL gastric ulcers were evaluated. Both honey and honey-like solution prevented lesions formation of the gastric mucosa. In another study, it was found that after treatment with honey for 2 weeks, 66% of the animals showed recovery from gastric ulcers and extension of treatment for 6 weeks showed that 83.4% of animals had no lesions on gastric mucosa against NSAIDS-induced gastric ulcers (Fazalda et al. 2018).

Similarly, in one more study, the antiulcer effect of honey was evaluated against aspirin (200 mg/kg BW). On the histopathological study of gastric mucosa in the aspirin-treated group presented necrosis and desquamation of lamina epithelium of gastric mucosa and necrosis of lamina propria whereas in honey-treated group apparent normal gastric mucosa reduction in gastric juice volume and increase in pH was noted (Header et al. 2016).

In vitro growth of Helicobacter pylori (H. pylori) which is one of the main etiology of ulcers is inhibited by honey (Bukhari et al. 2011). Unifloral manuka honey has been demonstrated to have significant gastroprotective activity against ethanol-induced stomach ulcer (Almasaudi et al. 2016).

12.4.2.1 Mechanism

1. Honey contains high levels of flavonoids which are believed to prevent the gastric ulcers formation through its antioxidant and anti-secretary mechanisms.
2. The gastroprotective effect of honey may also be attributed to the fact that the pH of honey is 3.88 which plays a role in increasing the pH of the gastric juice (Fazalda et al. 2018).
3. The osmotic effect of honey cause dilution of the necrotizing agent in lumen, delay the gastric emptying, release nitric oxide and non-protein sulfhydryls. Hyperosmolarity of honey also increases prostacyclin synthesis in antral and fundic mucosa of the rat (Gharzouli et al. 2002).
4. Gastroprotective effect of manuka honey was attributed to increased glycoprotein production, preservation of gastric mucosal GSH, decreased lipid peroxidation product MDA and increased formation of nitric oxide (Almasaudi et al. 2016).
5. Gastroprotective effect of manuka honey was attributed to increased glycoprotein production, preservation of gastric mucosal GSH, decreased lipid peroxidation product MDA and increased formation of nitric oxide. It also increased the antioxidant capacity of GPx and superoxide dismutase. Manuka honey inhibits proinflammatory cytokines such as TNF-α (important modulator of apoptotic cell death in gastric mucosa), IL-1β, and IL-6 (Almasaudi et al. 2016).

12.4.3 Anti-inflammatory Property

Honey promotes wound healing process via modulating inflammatory response by the dual effect. It prevents the extended inflammatory response by suppressing the production and growth of inflammatory cells at the wound and it warrants occurrence of normal healing by stimulating the production of proinflammatory cytokines. Nuclear factor-kappa beta (NF-KB), a transcription factor is a chief inflammatory marker. It amplifies the inflammatory response by activation proinflammatory cytokines such as interleukin (IL)-6, IL-8, and tumour necrosis factor-α (TNF-α) which further activates an important mediator of inflammation, nitric oxide. Flavonoids in honey inhibit NF-KB activation and nitric oxide production.

New Zealand honey, particularly Manuka and Kanuka honey have been suggested to have significant anti-inflammatory potential. These act by reducing the production of neutrophil superoxide. Manuka honey has also been associated with the decreased inflammatory response in ulcerative colitis due to its antioxidant activity (Tomblin et al. 2014). Gelam and manuka honey has been demonstrated to have anti-inflammatory potential. Anti-inflammatory effect of Acacia honey was confirmed against LPS-stimulated RAW264.7 cells (Kim et al. 2018).

12.4.3.1 Mechanism

1. Chrysin, quercetin and galangin, flavonoids found in honey was demonstrated to suppress the activity of inducible nitric oxide synthase (iNOs) and cyclooxygenase-2 (COX-2), enzymes which are responsible for producing inflammatory mediators (Ahmed et al. 2018).
2. Manuka honey has been demonstrated to activate IL-10, IL-1, IL-6 (an anti-inflammatory cytokine), TNF-α and IL-1β (proinflammatory cytokines) via toll-like receptors (TLR) and growth factors PDGF and TGF-β. Manuka honey was also able to scavenge superoxide anion and inhibit ROS production due to its phenolic content (Tsang et al. 2015).
3. Manuka honey has also been demonstrated to reduce superoxide production, oedema and leukocyte infiltration in a mice model. Anti-inflammatory effect of Manuka honey was attributed to modulation of the TLR1/TLR2 signalling pathway (Tsang et al. 2015).
4. It has also been said that higher phenolic content display increased anti-inflammatory effect (Ruiz et al. 2017; Hadagali and Chua 2014).
5. Acacia honey works by interfering with NF-κB and MAPK/ATF2 signalling pathways resulting in inhibition of potent proinflammatory mediators such as iNOS, NO, IL-6, IL-1β TNF-α, and MCP-1 (Kim et al. 2018).
6. Inhibition of matrix metalloproteinase-9 (MMP) (Hadagali and Chua 2014).
7. Inhibition of leukocyte infiltration (Hadagali and Chua 2014).

12.5 Clinical Trials on Honey

Trails are being conducted to take honey from bench to bedside for treating some of the serious disease and disorders. Table 12.2 summarizes ongoing clinical trials on honey.

Table 12.2 Clinical trials on honey

S. No	Honey type	Condition	Title of the trial	Clinical trial number/ID	Study phase	Recruitment status
1	Manuka honey	Wound healing	Honey Dressings for Local Wound Care of Split Thickness Skin Graft and Free Tissue Transfer Donor Sites: A Prospective, Randomized, Controlled Trial	NCT02259491	Phase 4	Terminated
2	Honey and hydrogel product	Diabetic foot	The Healing Effects of Honey and Hydrogel Products on The Diabetic Foot	NCT03816618	Early phase 1	Not yet recruiting
3	Raw honey	Poor quality sleep	Honey to Improve Sleep Quality: A Feasibility Study	NCT03567395	Not applicable	Completed
4	Ziziphus honey	Idiopathic dilated cardiomyopathy	Honey Supplementation in Children With Idiopathic Dilated Cardiomyopathy: A Randomized Controlled Study	NCT02987322	Phase 2 Phase 3	Completed
5	Dietary supplement	Type 1 diabetes mellitus	Metabolic Effects of Honey in Type 1 Diabetes Mellitus: a Cross Over Randomized Controlled Pilot Study	NCT01554566	Phase 2	Completed
6	Manuka honey	Dysphagia, lung cancer, pain, eosinophilia	Manuka Honey in Preventing Esophagitis-Related Pain in Patients Receiving Chemotherapy and Radiation Therapy For Lung Cancer	NCT01262560	Phase 2	Completed
7	Manuka honey	Radiotherapy-induced mucositis, head, and neck cancer	A Randomized Placebo-Controlled Trial of Manuka Honey for Oral Mucositis Due to Radiation Therapy for Cancer	NCT00615420	Phase 3	Completed
8	Dietary supplement: honey	Hepatitis A	The Effects of Honey, as a Dietary Supplement in Children With Hepatitis A	NCT02300792	Phase 2	Completed
9	Honey (Madu Nusantara)	Laveration of face, arm, and leg, wound injuries	Comparison of Honey and Povidone-Iodine in Wound Healing on Acute Laceration Wounds: A Randomized Controlled Trial Study	NCT03641053	Phase 3	Completed

	Natural honey	Cough, acute upper respiratory tract infection	A Randomized, Double-Blind Study to Evaluate the Efficacy and Tolerability of a Cough Syrup Containing Specific Plant Extracts (Poliflav M.A.) and Honey Versus Placebo in Cough Due to Upper Respiratory Tract Infection	NCT03218696	Not applicable	Not yet recruiting
10	Natural honey	Cough	Efficacy & Tolerability of a Specific Plantain, Thyme and Honey Cough Syrup vs Placebo in Child Cough Due to Common Cold	NCT02486835	Not applicable	Completed
11	Natural honey	Inflammatory indices in sedentary subjects	Effect of High Intensity Interval Training and Honey Consumption on Some Inflammatory Indices in Sedentary Subjects	UMIN000039156		Completed
12	Manuka and leptospermum honey	Bed sores, pressure ulcer, pressure sore, critically III children	Use of Honey Versus Standard Treatment for Pressure Ulcers in Critically Ill Children- A Randomized Controlled Trial	NCT03391310	Not applicable	Completed

12.6 Conclusion

This chapter deals mainly with health benefits associated with the consumption of honey and the possible mechanism through which the benefits are exerted. The chapter also briefs about chemical constituents and ongoing clinical trials of the honey. Honey is known to influence almost all the body system positively. The common mechanism through which honey positively regulates the various systems of the body is its antioxidant potential attributed to its high phenolic content. Considering the above-mentioned review, consumption of honey thus can improve the overall health of an individual.

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