17 The Gut–Brain Axis, Cognition and Honey

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Abstract

Honey has been trusted in traditional healing and wellness in most of the civilizations. Modern medicine has accepted wound healing properties of honey in burns and ulcers. There is tremendous evidence regarding antioxidant, antibacterial, anticancer, antimicrobial, and anti-inflammatory properties of honey. There are some experimental—in vitro and in vivo data and a little clinical data demonstrating role of honey in reversing the effects of neurodegenerative disorders and cognitive amelioration. Despite all the proven and assumed goodness, honey has not been able to establish to its full potential as a brain tonic under modern science. A casual search on PubMed and Cochrane databases reveals that there is not enough research on the neuroprotective aspects of honey. However, dissection of key components of the composition of honey has deciphered many compounds which are individually appreciated for their role in improvement of cognition and neurodegenerative disorders. The recent acceptance of gut–brain axis and role of microbiome in the development and modulation of neuronal functions has led to new insights; growing data recognizes honey as a prebiotic. It may be concluded that improvement in cognitive functions is a cumulative effect of the unique chemical composition of honey and it may not be identical for all types of honey. More longitudinal research is required to establish honey as a brain tonic.

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Keywords

Honey · Gut-brain axis · Diet · Cognition · Gut microbiota · Nootropic agent · Prebiotic agent

17.1 Introduction

Honey has been used for therapeutic purposes since time immemorial by popular civilizations in Arab, Egypt, India and Greece. Most of the ancient cultures and philosophies have advocated use of honey for health including Islamic medicine called Tibb-e-Nabwi, Ayurvedic, Unani, etc. Modern medicine has also kept honey on a high pedestal. A large number of in vitro and in vivo studies have proven its antioxidant, antitumor, antimicrobial, anti-inflammatory, antilipidemic, antidiabetic and antiviral properties. There is accumulating evidence in favour of positive cardiovascular, respiratory, nervous and gastrointestinal activities of honey. The recent biomedical literature widely supports its use in wound-dressing and as a healing substance particularly in ulcers and burns. The heterogeneously complex molecular events are still under research and debates play myriad role in neurodegenerative disorders that initiate mild cognitive impairment which may lead to dementia. Uncontrolled dementia is a hallmark of Alzheimer's disease. The current chapter would try to unfurl the potential role of honey in learning and memory besides preventing the trigger leading to mild cognitive decline.

There are various kinds of honey depending on the species of bee, health of the bee, floral source/s, season and geographic location. There are notable differences in colour, flavour, sensory perception and medical response of various kinds of honey. There are three types of honey according to botanical origin (Cianciosi et al. 2018). Honey is classified as floral if it is derived from nectar of a flowering plant; again it can be further distinguished on the basis of its multifloral or monofloral source of nectar. It is classified as honeydew (non-floral) if the bee species obtains nectar by sucking sap of non-flowering plants like acacia. Mixed honey has nectar from both sources, floral and non-floral (Fig. 17.1).

17.2 Nutritional Value of Honey

Honey is a rich source of carbohydrates, proteins, essential minerals, vitamins, enzymes, and organic acids (Figs. 17.2 and 17.3). No two honeys are same; they have different pH and chemical signatures depending on floral source, climate, geographical location and bee species. The botanical origin of honey makes difference in quality of honey depending on the presence of phenolic compounds (phenolic acids and flavonoid) content of the nectar (Cianciosi et al. 2018). There are as many as 600 volatile organic compounds in honey. As a general rule, dark coloured honey is qualitatively better due to its rich phenolic and flavonoid content. The

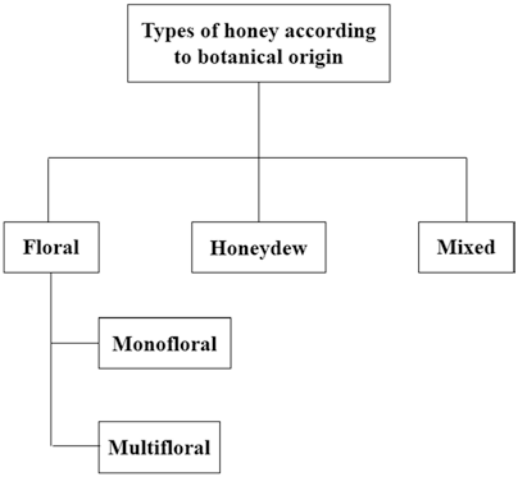

Fig. 17.1 Various types of honey depending on the botanical origin

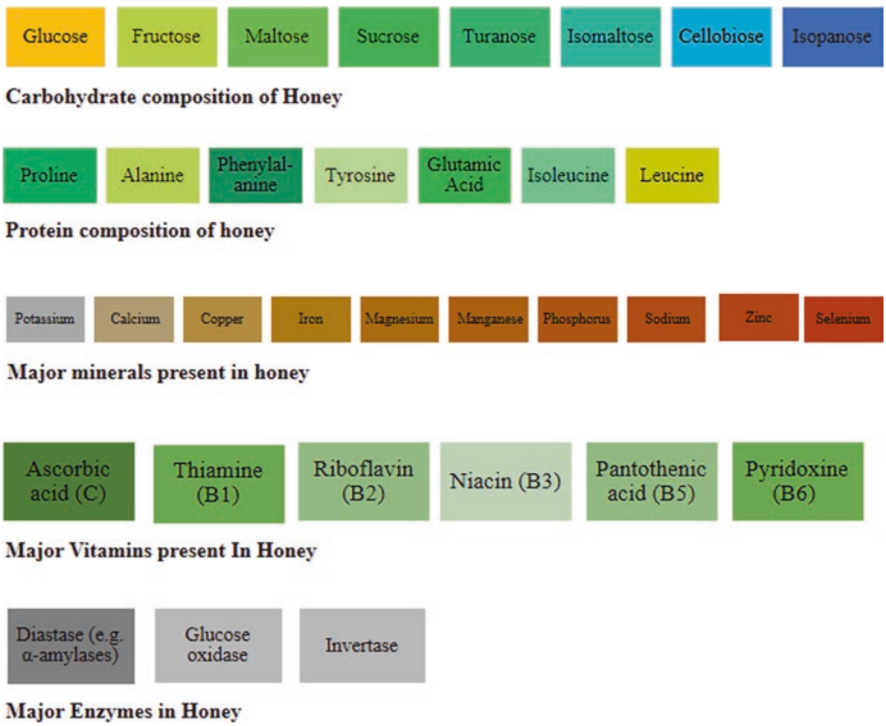

Fig. 17.2 Major carbohydrate, protein, minerals, vitamins and enzymes present in honey

polyphenols present in honey scavenge free radicals. Honey of the same botanical origin may turn out to have different properties depending on season and geography (Castro-Várquez et al. 2010).The volatile compounds contribute to sensory and aromatic properties of honey and just like fingerprints, they are mostly helpful to

Gluconic acid	Pyruvic glyoxylic acid	α-Hydroxyglutaric acid	Aspartic acid	Citric acid
Formic acid	Fumaric acid	Galacturonic acid	Glutamic acid	Butyric acid
Acetogalactur-onic acid	Gluconic acid	Methylmalonic acid	Quinic acid	Shikimic acid
Propionic acid	2-hydroxybutyric acid	Isocitric acid	Lactic acid	Malic acid
Malonic acid		Succinic acid	Tartric acid	Oxalic acid

Fig. 17.3 Major organic acids present in honey

differentiate different honeys. The methods of storage and heating also contribute to some changes in volatile organic compounds composition of honey. Floral markers, along with volatile organic compound analysis, help us in identifying specific honey (Manyi-Loh et al. 2011). Purity of honey has recently been certified using antioxidant activity as biomarker (Dżugan et al. 2018). Standard tests of honey reveal presence of certain microbes. Post-harvest handling of honey and non-hygienic sanitary conditions may lead to contamination of honey with certain yeast and bacteria, which sometimes lead to adverse effects on human health (Snowdon and Cliver 1996).

In a comparative study on various properties of monofloral honey, it was found that the colour parameters of honey had direct correlation with phenoloic content and antioxidant capacity. It was reported that dark coloured honey samples had higher phenolic content levels and antioxidant activity than the light coloured honey samples. High level of magnesium was reported in all samples. Cornflower honey sample had the highest phenolic content (645.85 mg/100 g) while antioxidant activity of cedar honey sample was found at the highest level, thorn honey sample showed the least antioxidant activity (Ozcan and Olmez 2014). In another study, it was found that acacia honey was the most acidic while pineapple honey had least moisture. Both high acidity and low moisture content ensure that the honey can resist microbial activity (Moniruzzaman et al. 2013). Proline (an amino acid) is present in all kinds of honey. The concentration of proline is highest in pineapple honey (Moniruzzaman et al. 2013).

17.3 Some Famous Botanical Types of Honey and Associated *Apis* Species

Apis sp. and Meliponini sp. (*Scaptotrigona* sp. also known as stingless bees) are popularly called as 'lebah kelulut' in Malaysia. The honey of Meliponini sp. has higher moisture content, acidity and low sugars when compared to that of *Apis* sp.

(Chuttong et al. 2016). Manuka honey, a monofloral honey derived from the manuka tree (*Leptospermum scoparium*) found in New Zealand, has greatly attracted the attention of researchers for its biological properties, especially its antimicrobial and antioxidant capacities. Tualang honey is derived from trees of *Koompassia excelsa* found in forests of Malaysia and Thailand by the bee, *Apis dorsata.* Tualang honey, amber in colour has the highest concentration of phenolic compound, flavonoids, DPPH, FRAP and lowest AEAC values making it a very strong honey (Moniruzzaman et al. 2013).

17.4 Dissection of Key Components of Honey (Figs. 17.2 and 17.3) and Their Individual Role in Memory and Neurodegenerative Disorders

The proline content in honey varies between 240 and 848 mg/kg (Moloudian et al. 2018). Amino acid composition of honey should be given more attention than phenolic content as high proline content was found to be more effective in free radical scavenging (Meda et al. 2005). The neuroprotective effect of proline rich polypeptide led to the recovery of monoaminergic system in a model of Alzheimer disease like rat model (Yenkoyan et al. 2018). Amino acid, tyrosine a precursor of dopamine is also a chemical component of honey. Transcranial direct current stimulation of human brain using Tyrosine in healthy humans has led to improvement of working memory (Jongkees et al. 2017).

Selenium, a microelement is also found in honey and neuroprotective effects of selenium are well recorded (Zafar et al. 2003). Zinc and copper homeostasis plays a crucial part in the maintenance of body including nervous system. There is a very narrow range for the functioning of both the metals. Accumulation or lack of these metals may lead to the development of neurodegenerative disorders. Zinc, besides being involved in neuronal glutamate signalling, is a cofactor of more than 250 enzymes and metallothioneins in our body. Supplementation with zinc has shown to enhance memory and was able to reverse age-dependent increase in plasma copper in animal study (Sandusky-Beltran et al. 2017).

Vitamin C, B, iron, zinc, copper, selenium, and a protein rich diet have been shown to be part of the nutrition strategies that improve cognition by optimizing brain function (Martínez García et al. 2018); interestingly, they are all present in honey. Similarly, manganese (Mn) and magnesium (Mg) are also components of honey. The dynamics of magnesium and manganese homeostasis has a narrow range. Besides, their role in learning and memory is also getting deciphered (Hoane 2011; (Pfalzer and Bowman 2017). Calcium and potassium have crucial established roles but data regarding role of their homeostasis in microcircuits of astrocytes in leading to Alzheimer's disease is under study (Osborn et al. 2016).

Butyric acid in honey has shown to be neuroprotective in in vivo studies (Sun et al. 2015; Garcez et al. 2018). Honey is a major source of organic acids particularly butyric acid (Pauliuc et al. 2020). High content of galacturonic acid is present in honey. Recently, glycoproteins derived from Chinese *Panax ginseng*, which was found to be neuroprotective had high content of glucose and galacturonic acid (Luo et al. 2018).

17.5 Effect of Honey on Brain Cells, Astrocytes and Microglia

In cultured astrocytes honey prevented cellular death in a dose-dependent manner (Ali and Kunugi 2019). The pro-inflammatory cytokines TNF-alpha and IL-1Beta were inhibited along with reduced markers for reactive oxygen species (ROS) and reactive nitrogen species when microglial cells were exposed to honey flavonoid markers (Candiracci et al. 2012). In streptozotocin-induced diabetic rats, natural honey prevented neuronal cell death in various areas of hippocampus (Jafari et al. 2014). Tualang honey has shown to improve architecture of brain, reduce brain-derived neurotrophic factors (BDNF) and reduce acetylcholinestrase concentration in homogenate (Othman et al. 2015).

17.6 Effect of Honey on Memory of Ovariectomised Rats and Menopausal Women

Tualang honey led to the enhancement of anti-depressive effects in stressed and ovariectomised rats through increase in BDNF levels through restoration of hypothalamic pituitary axis (Al-Rahbi et al. 2014a, b, c). Tualang honey has anti-anxiolytic effect; it helped ovariectomised rats to overcome stress by reducing free radical stress (Al-Rahbi et al. 2014a, b, c). A study conducted on postmenopausal women demonstrated improvement in their immediate memory when they were given 20 g/day of tualang honey (Othman et al. 2011).

17.7 Effect of Honey on Various Neurological Markers Induced by Chemical as Well as Noise Induced Stress in Animal Models

In a controlled study conducted on Sprague-Dawley rats, long-term replacement of sucrose with honey gave very promising results by decreasing anxiety levels and increasing spatial memory in ageing rats (Chepulis et al. 2009). Honey reversed oxidative stress leading to deficit in cognitive performances induced by exposure to lead acetate by ameliorating oxidative stress markers in experimental rats (Wahab et al. 2016). The tualang honey protected the male Sprague-Dawley rats against kainic acid-induced excitotoxicity which is also a hall mark symptom of major neurodegenerative disorders in pyriform cortex by reducing the free radical marker thiobarbituric acid reactive substances (Sairazi et al. 2017). Tualang honey also protected experimental rats against paraquat (PQ) induced dopaminergic neurotoxicity in midbrain and lungs of rats (Tang et al. 2017). In a study conducted on rats, it was concluded that 200 mg/kg body weight of tualang honey was able to attenuate the effect of noise stress which lead to depressive symptoms in rats (Azman et al. 2015). In the subsequent year, another study on rats concluded that 200 mg/kg body weight of tualang honey when given to rats exposed to noise of 100 dB, 4 h daily for 14 days protected against memory decline through enhancement of neuronal proliferation in the medial prefrontal cortex (mPFC) and hippocampus, decline in brain oxidative stress and/or upregulation of BDNF concentration and cholinergic system (Azman et al. 2016).

17.8 The Gut–Brain Axis, Dietary Habits and Cognition

The accumulating evidence from last two decades finally led to the proposal of brain-gut-microbiota axis (Kowalski and Mulak 2019). The healthy brain is developed as a result of pre- and postnatal molecular signals emerging from the gut. The molecular signals from gut emerge from its microbiome. Human gut microbiome is a collection of around 1000 microbial species distributed across 7000 communities representing various strains of biota Human Microbiome Project Consortium (2012). They range from the dominant bacterial and archeal populations to relatively less dominant viruses, fungi and eukaryotes. Significant studies on evolutionary history demonstrates that helminthes and many eukaryotes were previously part of human gut (Lloyd-Price et al. 2016). The Human Microbiome Project Consortium (2012) project indicates *Firmicutes* and *Bacteriodetes* as dominant groups in human intestine. MetaHit (Qin et al. 2010) and Human Microbiome Project Consortium (2012) have revealed that regular ecological interaction between different microbial communities across the kingdoms leads primarily to healthy gut besides skin, vagina, lungs and brain. There is geographical variation in gut microbiome of human populations. The precipitation of gut microbiome is influenced by early-life stimuli including first and subsequent diet (breast feeding), mode of delivery normal or C-Section (Sharon et al. 2016). The functional profile of microbiota particularly in gut is established early in life. Key neurodevelopmental events coincide with changes in the maternal and neonatal gut microbiome. In adulthood, the microbiome reaches a steady state in terms of bacterial strains, and does not change significantly under stable environmental or health conditions. The high functional diversity of different taxa is an evidence of healthy human body particularly gut. Use of germ-free mice and antibiotic-induced gut dysbiosis are two methods to study gut–brain relationship (Fröhlich et al. 2016).

17.9 Role of Microbiota in Neurodegenerative Disorders

Recent studies have demonstrated that gut microbiota has substantial role in neurogenerative processes like formation of blood–brain barrier, myelination (Hoban et al. 2016), neurogenesis, microglia maturation and animal behaviour (Sharon et al. 2016). There is mounting evidence from both animal (Bonfili et al. 2017) and human studies (Zhuang et al. 2018) that any fluctuation in gut microbiome leads to

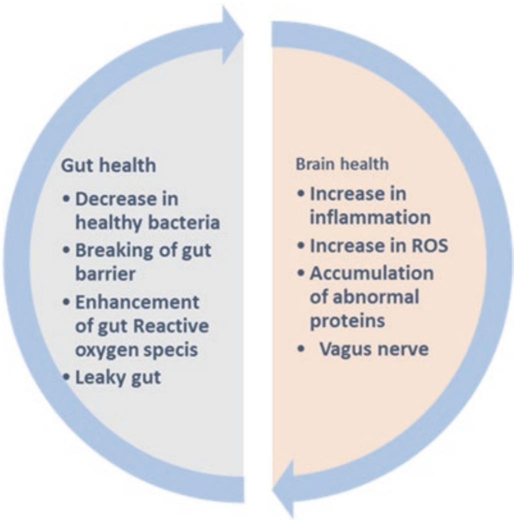

Fig. 17.4 There is direct communication between gut and brain, any alteration in gut microbiota population sends impaired signals to brain which reflects in poor brain health

structural and functional alteration in brain functions. The two way exchange of information between brain and gut has already been accepted by researchers (Zhu et al. 2017) (Fig. 17.4).

17.10 Cognitive Function and Diet

A number of studies have claimed that cognitive function can be improved by diet (Romo-Araiza et al. 2018). Increasing rodent and animal studies claim that the modern diet based on high sugar (Hsu et al. 2015), refined food and high fat (Ledreux et al. 2016) leads to cognitive decline (Chong et al. 2019) accompanied by inflammation of hippocampus (Tsai et al. 2018; Noble et al. 2017). In an animal study on early Alzheimer's stage, researchers were able to reverse the cognitive decline by treatment of mice with probiotics leading to alteration in gut microbiota and their metabolites through restoration of two neuronal proteolytic pathways (Bonfili et al. 2017).

17.11 Probiotics, Prebiotics, Gut Microbiome and Cognition

Pre and probiotics alter intestinal microflora in favour of human mental health (Liu et al. 2015). Recent trends show populations of probiotic microbial strains of genera *Lactobacillus* and *Bifidobacterium* residing in gut are influenced by oligosaccharides of prebiotic food, honey (Mohan et al. 2017). Fluctuation in numbers of healthy microbiota in gut produces reactive oxygen species (Jones et al. 2012), which directly and indirectly enhances free radical stress in brain (Fig. 17.5).

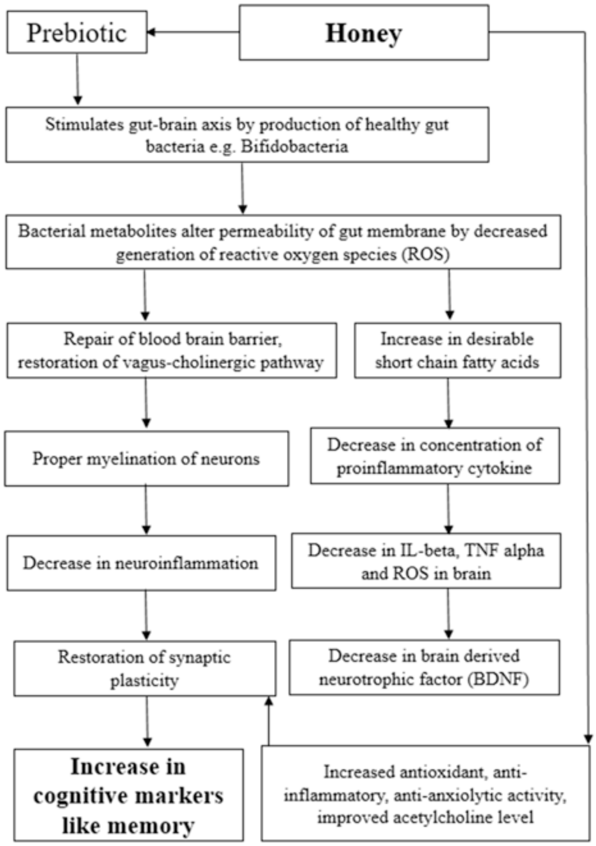

Fig. 17.5 Proposed mechanism for action of honey as a nootropic agent

Age-related neuronal loss, neuronal inflammation, loss of synaptic plasticity and accumulation of free radicals inside brain also contributes to age associated loss of memory. Many studies have suggested supplementation with prebiotics and probiotics to altering gut microbiota as a possible treatment for age-related cognitive impairment (Romo-Araiza and Ibarra 2020). A systematic review using 14 studies concluded that chronic prebiotic interventions lasting more than 28 days led to improvement of verbal episodic memory (Desmedt et al. 2019). Experimental studies on treatment of mice to antibiotics from weaning onwards led to depletion of gut microbiota, coupled with impact on anxiety and cognition (Desbonnet et al. 2015).

17.12 Honey Is a Nootropic Agent

A randomized, controlled, double blind 5 year pilot study conducted in Iraq concluded that one daily teaspoon of honey controlled dementia and cognitive decline (Al-Himyari 2009). It is proposed (Fig. 17.5) that honey stimulates brain through gut–brain axis by altering the bacterial population of favourable species like bifidobacteria. They act by decreasing free radical stress of gut along with release of short chain fatty acids. These events lead to proper myelination of neurons, repair of blood brain barrier, decreased release of inflammatory cytokines IL-beta and TNF-alpha besides decrease in BDNF. All these events restore synaptic plasticity of brain leading to increase in memory. Besides, honey is a source of vitamin C, B, iron zinc, selenium and various microelements, amino acids including proline, flavonoids and other organic acids particularly butyric acid. These constituents individually have well established neuroprotective record. There is tremendous support of honey as a nootropic agent (Azman and Zakaria 2019). The high oligosaccharide content of honey promotes healthy gut microflora (Ali and Hendawy 2018). The presence of 4 hydroxybenzaldehyde in buckwheat honey regulates growth of healthy gut bacteria, bifidobacteria restricts the growth of pathogenic bacteria in gut (Jiang et al. 2020). Additionally, 4-Hydroxybenzaldehyde marker in Buckwheat honey selectively promotes growth of bifidobacteria in the gut promoting health (Jiang et al. 2020). Honey is also a source of acetyl/butyl cholinesterase inhibitors, making therapeutic value of honey high (Baranowska-Wójcik et al. 2020).

17.13 Conclusion

Every year millions of people are losing cognitive functions, starting from mild cognitive impairment which progresses into full-blown dementia or Alzheimer's disease with age. The markers are in favour of honey as a brain tonic. The scientific fraternity should seriously consider candidature of honey as nootropic agent by conducting human trials and improve life of millions of patients and caregivers of Alzheimer's disease.

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