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REVIEW ARTICLE

# Honey on Brain Health: Benefit or Forfeit?

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## *ABSTRAK*

*Kemerosotan kesihatan otak merupakan suatu wabak di seluruh dunia. Penyakit Alzheimer dan demensia lain adalah antara penyakit yang tertinggi kos untuk dirawat, dengan perbelanjaan penjagaan langsung melebihi mereka yang menghidap kanser dan penyakit jantung. Pengambilan terlalu banyak dan terlalu kerap produk makanan terproses telah menyumbang kepada peningkatan kemerosotan kesihatan pada usia yang muda. Madu telah diketahui di seluruh dunia sejak sekian lama merupakan salah satu produk asli dan semulajadi untuk digunapakai sebagai makanan kesihatan terutamanya disebabkan oleh kandungan antioksidan dan fenoliknya. Beberapa dekad kebelakangan ini, banyak kajian telah dilakukan untuk memahami proses biologi gangguan kerosakan terhadap sel otak dan cara untuk menghentikan atau melambatkan proses berkenaan menggunakan produk semulajadi. Madu telah menunjukkan potensi besar yang mampu mengurangkan atau melambatkan gangguan kemerosotan saraf ini. Berdasarkan kajian terbaru penggunakan madu dan kesannya ke atas anatomi dan fisiologi otak, menunjukkan bahawa madu mempunyai potensi untuk menghentikan atau merawat gangguan kemerosotan kesihatan otak.*

*Kata kunci: antioksidan, madu, penyakit degenerasi*

## ABSTRACT

Brain health deterioration is a worldwide health epidemic. Alzheimer's disease and other dementias are among the most expensive diseases to treat, with direct care expenses exceeding those for cancer and heart disease. The consumption of overly processed food products over the time has contributed to the increasing number of health deterioration at an earlier age. Honey has been known worldwide through history to be one of the purest, and popular natural product to be consumed as a health booster notably due to its antioxidant and phenolic contents. In the recent decade, many studies were perfomed to understand the biological process of

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cellular insult to the brain and ways to halt or slow down the process using natural products. Honey was shown in some of these studies as having the potential that may reduce or slow down these neural degenerations. Based on recent studies conducted on the use of honey and its effects on the brain physiologically, and anatomically, the results showed that honey holds potential in halting or even treating brain health deteriorations.

Keywords: antioxidant, degenerative disease, honey

## INTRODUCTION

Honey is a nature fast food that has been used since the earliest of times. It is a sticky and viscous fluid produced by bees and other insects from nectar collected from flowers, and used as a food. History has recorded the use of honey as far as the stone age, some 8,000 years ago (Eteraf-Oskouei & Najafi 2013). Honey is classified based on the source flower where the nectar is derived from, and the type of bees and insects that collect them.

Besides consumed as food, the use of honey in traditional medicine has also been widely acknowledged (Saba et al. 2013). However, its role in modern medicine has yet to gain any notable recognition due to lack of scientific merit. Due to the exquisite properties of honey it is considered to be a functional food (Viuda-Martos et al. 2008) by contributing to the maintenance of health and wellbeing. Besides being a functional and nutritive food, it has been used for wound dressings since ancient times (Allen et al. 1991) and topical antibacterial agents for superficial wounds such as ulcers and bed sores (Blomfield 1973; Mossel 1980). Honey was shown to have antimicrobial, antiviral, antioxidant, and anti-inflammatory and anticancer properties, in both *in vitro* and *in vivo* studies (Estevinho et al. 2008; Oddo et al. 2008; Boorn et al. 2010; Fauzi et al. 2011; Owoyele et al. 2011). Uses of honey for its medicinal benefits are progressive and is continued in the present-day medicine (Matthews & Binnington 2016). It has been reported to be effective in the treatment of gastrointestinal disorders (Haffejee & Moosa 1985; Ladas et al. 1995), wounds and burns healing (Yaghoobi et al. 2013), cataracts (Patricia 2002) and also corneal alkaline injury (Bashkaran et al. 2011).

Honey has been reported to possess at least 200 substances (White 1978) which mostly constitute complex sugars where fructose and glucose are its main contributor (Gheldof et al. 2002). In addition, it is also composed of a wide range of minor constituents such as protein in the form of enzymes and amino acids, organic acids, carotenoids, vitamins, minerals, and aromatic substances (da Silva et al. 2016). Honey is an excellent source of antioxidant. These includes phenolic acid and flavonoids, glucose oxidase and catalase enzymes, ascorbic acids,

Table 1: Effects of honey supplementation on human cognitive function

| Subject | Treatment | Findings | Reference |
|---|---|---|---|
| Cognitive intact control (n=2290) Mild cognitive impaired patients (n=603) | 1 daily tablespoon of honey, and placebo treated control for 5 years | 489 subject developed dementia (394 received placebo; 95 received honey) | Al-Himyari 2009 |
| Postmenopausal women (n=102) | Tualang honey (20 mg/d), oestrogen plus progestin therapy and untreated control for 16 weeks | Improve verbal learning and memory performance in honey-treated participants comparable with oestrogen and progestin therapy | Othman et al. 2011 |
| Postmenopausal women (n=36) | Tualang honey sachets (20g) daily for 16 weeks | Improvement in Auditory Verbal Learning Test | Shafin et al. 2014 |
| Major neurocognitive disorder patients (n=60) | 2 capsules containing 500 mg of sedge, 30mg of saffron extract, and a teaspoon of Astragalus honey for 3 months | Improvement of cognitive and depression score. | Akouchekian et al. 2018 |
| Depressed elderly individuals (n=30) | 1 serving of Talbinah for 7 weeks | Significant decrease on depression, stress, and mood disturbances scores | Badrasawi et al. 2013 |

carotenoids, organic acids, proteins and α-tocopherol (Ferreres et al. 1993). Phenolic compounds such as aromatic acids and flavonoids can be found in honey has increasingly gaining attention because of their benefits in contributing to human health (Gómez-Caravaca et al. 2006).

Within the last decade, studies used regional honey to investigate effects on learning and memory (Al-Himyari 2009; Chepulis et al. 2009; Al-Rahbi et al. 2014a), stress and anxiety-like behavioural in postmenopausal women (Al-Rahbi et al. 2014b), depressive-like behaviour and reduce cognitive function secondary to noise stress induced exposure (Azman et al. 2015), kainic acid-induced oxidative stress and neurodegeneration (Sairazi et al. 2017). This review provides the efficacy of different kind of honey on brain. Further studies are required to clarify the molecular mechanism by which honey affects neuronal and brain health.

## Beneficial Effects of Honey on Brain

Learning and memory are subcomponents of the cognitive functions. In simple terms, learning is the acquisition of skill or knowledge while memory is the expression of what have been acquired (Brem et al. 2013). There are numerous studies looking at the effects of phytochemicals or natural herbs on learning and memory. However, there is scarcity of literature on the effect of honey on this part of the cognitive function, especially in human (Table 1). Among the first to study the effect of honey on the cognition is a report by Al-Himyari (2009). In this double-blind study, a mixed total of 2893 cognitively intact and mild cognitive impaired participants were given either

Table 2: Effects of honey supplementation on cognitive function in animal models

| Animal model | Treatment | Findings | Reference |
|---|---|---|---|
| Ovariectomized rats exposed to social instability stress | Oral feeding of Tualang honey (0.2 g/kg body weight) for 18 days | Improved short-term and long-term memory. Enhanced hippocampal neuronal proliferation | Al-Rahbi et al. 2014 |
| Rats exposed to loud noise stress | Oral feeding of Tualang honey (0.2 g/kg body weight) for 35 days | Relieved depressive-like behaviour and improved memory functions caused by loud noise stress. Significantly increased climbing and swimming times. Significantly decreased immobility times. | Azman et al. 2015 |
| Rats exposed to Pb-induced neurotoxicity | Oral feeding of honey (1 mL/kg body weight) for 28 days | Improved memory function (decreased latency period and increased in time spent in target quadrant). Increased brain SOD, glutathione S-transferase (GST) and GSH activities. No significant effect on MDA level. | |
| Normal mice | Oral feeding of 2000 mg/kg stingless bee honey for 7 and 35 days | 7 days treatment improve spatial working memory. 35 days treatment increased spatial reference memory. Significant up-regulation of BDNF and Itpr1. | |
| Normal rats | Oral feeding of Tualang honey (1 mL/100g body weight with 70% honey) for 12 weeks. | Improved working memory and reference memory component. Increased number of pyramidal neurons. | Kamarulzaidi et al. 2016 |

honey or placebo for 5 years and assessed for dementia every 6 months. Result showed a staggering 28% of the participant that receives placebo developed dementia compared to only 6% of participants that received honey. The author postulated the antioxidant properties of honey which enhances the brain's cholinergic system and circulation. Another clinical study reported that 16-weeks clinical intervention trial with Tualang honey as an alternative therapy to oestrogen and progestin was able to improve verbal learning and memory performance in postmenopausal women which were comparable with the improvement observed in women receiving oestrogen and progestin therapy (Othman et al. 2011). This is further supported by a similar study that examines the correlations between Tualang honey supplementation and oxidative status in post-menopausal women. In this study, participants showed higher score in their Auditory Verbal Learning Test after receiving four months of Tualang honey supplementation compared to pre-intervention (Shafin et al. 2014). In a

randomised double-blind clinical trial involving 60 major neurocognitive disorder patients, supplementation of a combination of sedge, saffron and Astragalus honey for 8 weeks showed improvement of cognitive and depression score (Akouchekian et al. 2018).

Besides learning and memory, honey showed promising results in combating psychiatric illness. In a study by Badrasawi et al., a 3-week randomised clinical trial was conducted to determine the effect of Talbinah on mood and depression among an elderly group that was institutionalised with depression. Talbinah is a barley porridge, cooked with milk and honey and long regarded in the middle east as a healthy nutritious food. Results showed a significant decrease in Geriatric Depression Scale, Depression Anxiety Stress Scales, and Profile of Mood States that were used to determine the mood, depression, stress, and anxiety levels in the treated group compared to control (Badrasawi et al. 2013). Although Talbinah is not purely honey per se, its content in this food might play a role in exerting its effects against depression.

The lack of human studies on the effect of honey on the brain was compromised with increasing number of pre-clinical studies seen lately (Table 2). Such example can be found in the study by Al-Rahbi et al. (2014a) which looks on the effects of Tualang honey on hippocampal morphology and memory performance. They reported that Tualang honey improved both short-term and long-term memory and enhanced the neuronal proliferation of hippocampal cells as compared to that of untreated stressed ovariectomized rats. Another study looked at sub chronic exposure to noise induces stress-like behaviour and decrease cognitive functions which was attenuated by Tualang honey supplementation (Azman et al. 2015).

Supplementation of honey to normal animals was also widely studied. Supplementation of 2000mg/kg stingless bee honey to mice for 7 and 35 days showed improved memory consolidation, spatial working memory and spatial reference memory. The dose given was equivalent to a human dose of 162 mg/kg (Mustafa et al. 2019). Similarly, supplementation of Tualang honey (1 mL/100g body weight with 70% honey) to normal rats for 12 weeks improved working memory and reference memory components, as well as increased the number of pyramidal neurons in the hippocampus (Kamarulzaidi et al. 2016).

## Effect of Honey on Brain: Possible Mechanism

Oxidative stress is an imbalance between the production of free radicals known as reactive oxygen species (ROS) or reactive nitrogen species and its removal from the body (Wang & Michaelis 2010). Free radical contains a free or unpaired electron causing it to be in a highly reactive state. This unstable state causes damage to the biological system. Most of the free radicals that cause damage in the biological system are oxygen radicals and ROS resulting from aerobic

metabolism (Devi & Satpati 2017). Our brain is highly susceptible to oxidative damage due to its high oxygen demand other factors such as low antioxidant enzymes, highly vascularised with high amount of polyunsaturated fatty acids in the neuronal membranes makes it more likely to undergo rapid increased oxidative damage. The neurons are also particularly vulnerable to cumulative oxidative changes because they are non-dividing permanent cells that survive for since birth (Arshad et al. 2018). Oxidative stress has been the centre of most researches questioning the level of anatomical or functional damage of the pathological brain. Results have mostly led to an increase of the free radicals causing this imbalanced condition. Honey have shown to attenuate with damage resulting from oxidative stress (Sairazi et al. 2017; Ranneh et al. 2019; Azman et al. 2018; Abdulmajeed et al. 2016).

Honey contains remarkably high antioxidant activity by which they possesses high phenolic contents (Al-Mamary et al. 2002; Aljadi & Kamaruddin 2004; Gül & Pehlivan 2018; Gheldof et al. 2002; Kishore et al. 2011), high flavonoids content (Blasa et al. 2006), notably radical scavenging activities showed by effectively supressing lipophilic cumoxyl and cumoperoxyl radicals, prevention of cell damage, total inhibition of cell membrane oxidation, of intracellular ROS production and retrieval of intracellular glutathione (GSH) (Beretta et al. 2007; Brudzynski & Miotto 2011; Gül & Pehlivan 2018; Kishore et al. 2011), specific scavenging activity for superoxide anion radicals (Inoue et al. 2005), rich in amino acids which has highest correlation with antioxidant capacity such as aspartate, glutamate, glycine, threonine and glutamine (Pérez et al. 2007), as well as choline and acetylcholine (Heitkamp & Busch-Stockfisch 1986) substance that is important for brain function and act as neurotransmitter (Al-Rahbi et al. 2014a).

Consumption of antioxidant substances lessen oxidative damage (Carney et al. 1991; Kolosova et al. 2006), improve cognitive performance in animals (Carney et al. 1991; Cotman et al. 2002; Ikeda-Douglas et al. 2004; Guilherme dos Santos et al. 2005). In addition, it slows down deterioration in memory and learning middle- and older-age humans (Carney et al. 1991; Fukui et al. 2001; Pietá Dias et al. 2007; Jama et al. 1996; Duffy et al. 2008; Wengreen et al. 2007). A study by Azman and colleagues have recently shown that Tualang honey is able to show the decrease of brain oxidation indices and an increase of antioxidant enzyme activity in noise stress induced rats. The study started off with supplementing the honey at 200mg/kg daily for 14 days, subsequently giving a daily exposure of noise at 100dB(A) for 14 days. Besides a positive result in short and long term memory evaluation using the object recognition test, brain oxidation indices of protein carbonyl (PCO) and plasma malondialdehyde (MDA) also gave out promising results. While the rats not supplemented with honey had significantly elevated PCO and MDA levels, aged rats supplemented with the honey showed significant lower levels

of both of the indices. Brain antioxidant enzyme activities were also measured, namely superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase from brain homogenates. They found that these parameters showed a significant increase in the young rats treated with honey (Azman et al. 2018).

Other than that, antioxidants may play a role in anxiety as demonstrated by their ability to reduce anxiety-like behaviour in mice (Barros et al. 2006) and rats (Kolosova et al. 2006; Pereira et al. 2005; Hasenöhrl et al. 1996). It is possible that the antioxidant content of the honey may have contributed to improve spatial memory as suggested by Chepulis et al. (2009), and this suggestion were supported by some studies that antioxidant intake has been correlated with improved memory scores (Perkins et al. 1999; Raghavendra & Kulkarni 2001; Farr et al. 2003) when ingested at levels similar to those using cordyceps mushroom extracts together with anthocyanin from purple sweet potatoes (Cho et al. 2003).

Another recent study tested the neuroprotective effects of honey against lead (Pb)-induced neurotoxicity (Abdulmajeed et al. 2016). All rats were given 0.2% Pb in drinking water and amongst them were groups given honey (1 mL/kg and 1.5 mL/kg separately). The rats were then tested with an open field and Morris water test and post sacrifice, their brains were harvested and tested for MDA and antioxidant activities specifically catalase, SOD and GSH. Results of this study further grounds the fact that honey could reduce oxidative stress. While both the tests for open field and Morris water showed results of positive neuroprotection effects of the honey, its MDA results showed no significant change between the groups. The results of antioxidant activities (catalase, SOD and GSH) however coincides with the results from the study by Azman et al., 2018 showing a significant increase in honey treated animals with the rats given 1.5 mL/kg honey better results compared to the lower dosed honey (Azman et al. 2018; Abdulmajeed et al. 2016). In another study, stinglees bee honey significantly increases lymphoblastic cell viability by more than 150%. This might be due to the high total phenolic content, total flavonoid content and ferric reducing antioxidant potential which present in this type of honey (Hazirah et al. 2019). The antioxidant constituent in honey might also contribute to the cytoprotective effect in another study which involve cancer cells. Gelam honey was found to reduce lipid peroxidation but not protein oxidation in human lung cancer cells which are subjected to oxidative stress (Goon et al. 2017). With this, we might be able to suspect that even though honey might increase the antioxidant activities, its possible role in mitigating lipid peroxidases and reducing the production of ROS might defer depending on the type of insult or stress exposed to the subject of study.

## Adverse Effect of Honey on Brain

Honey is harmless when taken in a moderate amount but still possesses a

potential risk if taken in excess like any other food. There is no reported adverse effect of honey except when it was contaminated. Risk of infant botulism has been reported before (Fenicia et al. 1993) due to presence of spores of *Clostridia botulinum* where honey is identified to be a natural reservoir for it. There is also theoretical risk of rise in blood glucose levels in person with impaired fasting glucose or diabetics when consuming honey in large amount. Diabetes has been known to impair the brain to a certain degree through insulin resistance, vascular endothelial damage, oxidative stress and chronic low-grade inflammation (Arshad et al. 2018). A latest systemic review suggested otherwise where honey is actually beneficial as it decreases the fasting serum glucose, increases the sting C-peptide and 2-h postprandial C-peptide (Meo et al. 2017). However, the authors cautioned that larger sample sized, multi-center clinical controlled studies are required to reach a better understanding on the mechanisms and conclusions.

## CONCLUSION

To conclude, honey has shown to have the potential beneficial effects on the brain. However, more preclinical and clinical studies are required to fill the questionable gaps in term of the frequency, dose and groups of people that are able to benefit from honey consumption.

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