Neurological Effects of Tualang Honey

Subjects: Nutrition & Dietetics

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Tualang honey exerted neurological effects namely nootropic, antinociceptive, stress-relieving, anti-depressant, and anxiolytic. These effects are attributed to its antioxidant and anti-inflammatory properties.

Keywords: Tualang honey ; antioxidants ; nootropics ; antinociceptive ; antidepression ; anxiolytics

1. Introduction

Malaysian honey is classified according to the bee species, or the floral sources of the honey [1]. There are two main types of bee species, namely Apis (A. dorsata , A. mellifera and A. cerana) (stinging bee) or Meliponine (stingless bee; locally known as Kelulut) [2]. According to floral sources, honey is further classified into monofloral (Acacia honey, Gelam honey, Pineapple honey, Leaf honey, Durian honey, Melaleuca honey, Coconut honey, Starfruit honey and Wax apple honey) or polyfloral honey (Tualang honey, Kelulut honey). An example of extra-floral honey is Rubber honey [3].

Tualang honey is a wild polyfloral honey produced by Apis dorsata . Tualang honey has a dark brown appearance, a pH of 3.6–4.0 with a specific gravity of 1.34 [4]. It is slightly more acidic than other local Malaysian honey, such as Kelulut and Gelam [5], but its low pH is similar to Manuka honey [6]. The sugar composition of Tualang honey is mainly composed of monosaccharides, such as fructose (41.73%) and glucose (47.13%), and disaccharides, such as sucrose (1.02%) and maltose (4.49%) [7]. Several types of phenolic acids (gallic, coumaric, syringic, caffeic, cinnamic, benzoic, chlorogenic, salicylic and ferulic acid) and flavonoids (catechin, quercetin, kaempferol, luteolin, hesperetin, apigenin, 3,7,4′-trihydroxyflavone, naringenin, chrysin, fisetin, vitexin, isoorientin, xanthohumol pinobanksin-3-o-propionate and pinobanksin-3-o-butyratengenin) have been identified in Tualang honey [8][9][10]. Tualang honey contains some common phenolic compounds as found in other honey (**Figure 1**) [11].

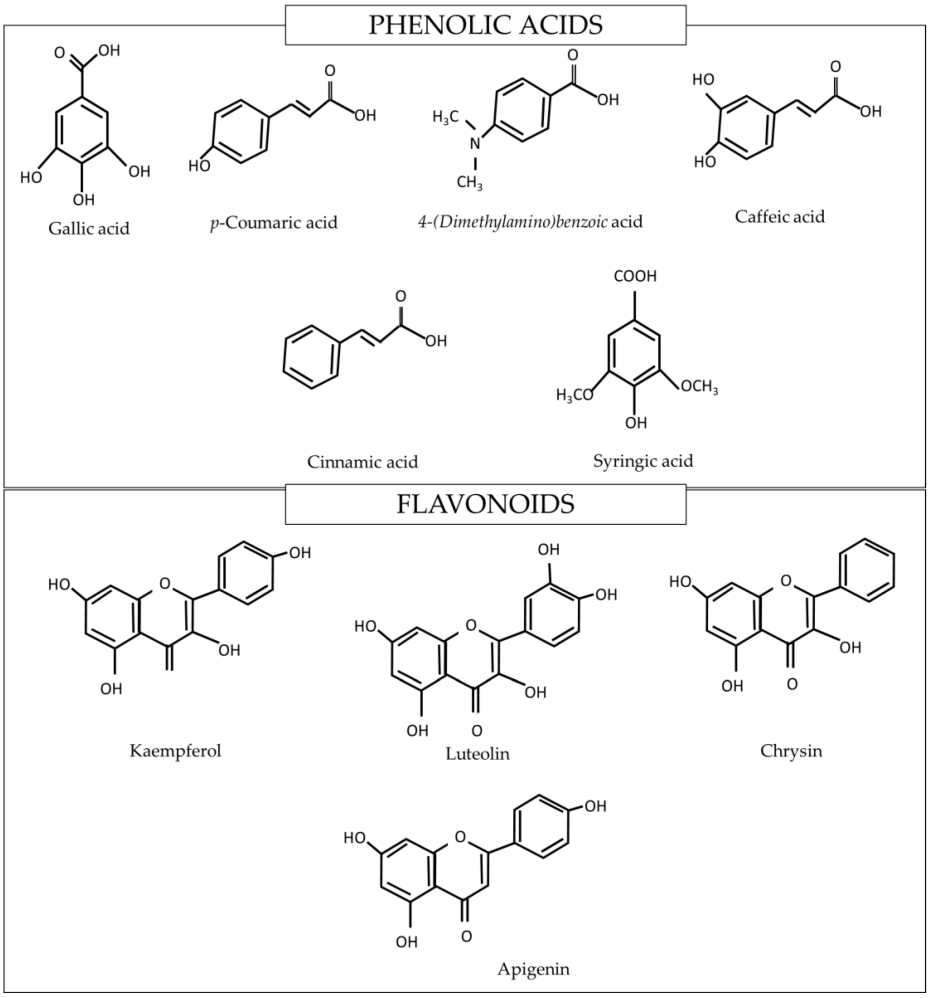

Figure 1. Some of the phenolic compounds found in Tualang honey [11].

Tualang honey's properties are comparable to other types of honey (**Table 1**). Interestingly, Tualang honey contains more phenolic acids and flavonoids compared to Manuka and other local Malaysian honey [12] and is also more effective against some of gram-negative bacteria [13].

Table 1. Summary of the physiochemical characteristics of Tualang honey versus Manuka honey [12].

Physiochemical Properties	Tualang Honey	Manuka Honey
Appearance	**Dark brown**	**Light to dark brown**
Specific gravity	**1.34**	**1.39**
pH	**3.6–4.0**	**3.2–4.2**
Moisture content	**23.30%**	**18.70%**
Total reducing sugars	**67.50%**	**76.00%**
Fructose	**29.60%**	**40.00%**
Glucose	**30.00%**	**36.20%**
Sucrose	**0.60%**	**2.80%**
Maltose	**7.90%**	**1.20%**
Potassium	**0.51%**	**1.00%**
Calcium	**0.18%**	**1.00%**
Magnesium	**0.11%**	**1.00%**
Sodium	**0.26%**	**0.0008%**
Carbon	**41.58%**	**-**
Oxygen	**57.67%**	**-**

Honey has been used in traditional medicine since 2100 BC [14]. The Mayans, Babylonians, Romans, Egyptians, Chinese, and Greeks all consumed honey for its nutritional and therapeutic characteristics [15]. Most health advantages ascribed to honey have been anecdotal, based on observations and generalisations with little scientific backing. However, in the last decade, there has been a revived interest in researching honey's possible health advantages. Moreover, honey has antioxidant, antibacterial, anti-cancer, anti-inflammatory, antidepressant, anxiolytic, and anti-stress properties [16]. Previous reviews on Tualang honey showed comparative differences in medicinal properties [13], potential anti-cancer properties [17], and physicochemical properties [18]. Although the potential roles of honey and honeybee products in neurological actions [19] as well as in learning and memory have been reviewed [20], other potential neurological effects, particularly of Tualang honey, remain to be comprehensively reviewed. This article highlights the current literature on the medicinal effects of Tualang honey with a special focus on its neurological effects based on the mechanisms identified. The possible underlying mechanisms of its effects and its future applications are also discussed.

2. A Decade of Neurological Research

2.1. Nootropic Effects of Tualang Honey

A summary of the nootropic effects of Tualang honey in animals and humans is presented in **Table 2**.

Table 2. Summary of nootropic effects of Tualang honey on humans and animal models.

Study Model	Subject	Dose, Method of Administration and Duration of Tualang Honey Supplementation	Findings	Reference
Humans	Postmenopausal women (n = 102)	20 g/day, oral, 16 weeks	Improved verbal learning and immediate memory performance in honey-treated participants comparable with oestrogen and progestin therapy	[21][22][23]
	Schizophrenia patients (n = 80)	20 g/day, oral, 8 weeks	Improvement in total learning score across domains in immediate memory using MVAVLT in honey-treated schizophrenic patients	[24]
Animal models	Ovariectomised Sprague Dawley Rats (n = 10 per group)	200 mg/kg/bwt, oral, 18 days	Improved short term and long-term memory in Tualang honey-treated comparable to oestrogen-treated in ovariectomised rats exposed to social instability stress	[25]
	Young and aged male Sprague Dawley Rats (n = 12 per group)	200 mg/kg/bwt, oral, 28–35 days	Improved short- and long-term memory function in aged rats exposed to loud noise stress treated with Tualang honey compared to untreated rats	[26]
	Young and adult male Sprague Dawley rats (n = 12 per group)	70% honey concentration, forced feeding, 12 weeks	Improved spatial memory performance in honey-treated rats compared to untreated rats	[27]
	Adult male Sprague Dawley Rats (n = 12 per group)	200 mg/kg/bwt, oral, 14 days	Tualang honey pre-treatment showed protective effects against hypoxia-induced memory deficits compared to untreated rats	[28]
	Adult male Sprague Dawley Rats (n = 18 per group)	200 mg/kg/bwt, (methanolic fraction MTH 150mg/kg), IP, 14 days	Tualang honey and MTH improved spatial and recognition memory in LPS-induced memory deficits comparable to memantine	[29]
	Chronic cerebral hypoperfusion male Sprague Dawley Rats (n = 10 per group)	1.2 g/kg, oral, 10 weeks	Improved spatial memory performance in honey-treated cerebral hypoperfusion rats compared to untreated rats	[30]
	Adult male Sprague Dawley Rats (n = 18 per group)	TH pre-treatment (1.0 g/kg bwt) five times every 12 h	Improvement in locomotor activity in kainic acid-induced rats pre-treated with TH compared to without TH	[31]

Notes: bwt: body weight; MVAVLT: Malay Version of Auditory Verbal Learning Test; LPS: lipopolysaccharide; MTH: methanolic fraction of Tualang honey; KA: kainic acid.

The mechanisms underlying the nootropic effects of Tualang honey in the above studies are illustrated in **Figure 2**. Tualang honey improves the antioxidant system, thus enhancing the morphology of the brain, reducing neurodegeneration, and thereby improving cognition.

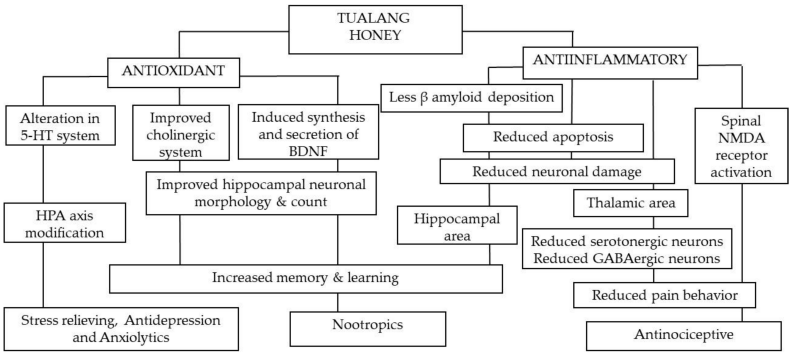

Figure 2. The putative neuroprotective mechanism of Tualang honey. Tualang Honey can strengthen the cellular antioxidant defence system and prevent neuroinflammation. Both antioxidant and anti-inflammatory contributed to the nootropics effects and antinociceptive effects while antioxidant is a major contributing factor to stress-relieving, antidepression and anxiolytics effect.

2.2. Antinociceptive Effects of Tualang Honey

Findings from studies of Tualang honey in both human and animal models present promising effects as an antinociceptive agent, as listed in **Table 3**.

Table 3. Antinociceptive effects of Tualang honey supplementation on human and animal models.

Study Models	Subject	Dose, Method of Administration and Duration of Tualang Honey Supplementation	Findings	Reference
Humans	**Patients (3–18 y/o) underwent tonsillectomy (n = 38 each group)**	**Topical 2–3 mL Tualang Honey (applied on both tonsillar bed by a 3 mL syringe) + 4 mL Tualang honey three times daily for 7 days**	**Early postoperative pain was relieved slightly faster in Tualang honey and antibiotic group compared to the antibiotic only group**	**[32]**
	Patients (13–65 y/o) underwent skin grafting (n = 35)	**Honey hydrogel (Tualang honey was added to a mixture of 15% polyvinyl pyrrolidone (Kollidon 90), 1% protein-free agar (Oxoid) solution and 1% polyethylene glycol)**	**Tualang honey hydrogel may be effective in the treatment of split-skin graft donor sites with minimal pain, discomfort and pruritus.**	**[33]**
	Neonates more than 37 weeks gestation, birth weight more than 2.5 kg, (n = 78)	**2 mL of Tualang honey, oral, blinded sampling, pre-packed in 3 mL syringe, administered directly onto dorsum of infants tongue over 30 secs duration of procedure (during venepuncture)**	**Tualang honey was effective in relieving venepuncture pain compared to 24% sucrose**	**[34]**
Animal models	**Adult male Sprague Dawley rats (n = 24)**	**0.2, 1.2 or 2.4 g/kg, oral, 5 and 10 days**	**Preemptive administration of Tualang honey 1.2 g/kg for 5 days and 1.2, as well as 2.4 g/kg for 10 days, had a reduction in the pain behaviour score comparable to prednisolone in formalin-induced rats**	**[35][36][37] [38]**
	Male rat offsprings (n = 24)	**1.2 g/kg, oral, 3 weeks**	**Tualang honey treated group had a significant reduction in the formalin test score in phase 1 and phase 2 compared to the stressed only group.**	**[39][40]**

2.3. Stress-Relieving Effects of Tualang Honey

Asari et al., (2019) [41] showed that male rats induced with chronic stress had reduced corticosterone levels (24.5 ng/mL) following oral administration of Tualang honey. Acute and chronic stress may abnormally modify the cytokines level such as increased tumour necrosis factor-α (TNF-α) and IL-6, as well as decreased interferon-γ (IFN-γ) at peripheral and central levels [41]. Consequently, these alterations may increase the risk of getting cardiovascular, neurodegenerative, and

autoimmune diseases. Tualang honey successfully lowered these proinflammatory cytokines in the rat brain exposed to chronic stress [41]. In another study, Haron et al. (2014) [42] demonstrated that supplementation of Tualang honey similarly reduced serum corticosterone levels in pregnant rats exposed to chronic stress (3.0 ng/mL from 4.5 ng/mL in stress group). Tualang honey might have partly minimized the adverse effects of stress on the thickness of zona fasciculata of the adrenal glands by reducing the occurrence of lipid peroxidation in the adrenal glands of the prenatal stress rat. Additionally, adverse pregnancy outcomes of the prenatally stressed rat, including a lower gestational period, were reduced after administration of Tualang honey, possibly due to its phytoestrogen effects [40].

2.4. Antidepressive Effects of Tualang Honey

Ovariectomised rats with depressive-like states demonstrated reduced depressive-like behaviour following the oral administration of Tualang honey, as manifested by reduced mean immobility time and increased mean swimming time [43]. After menopause, prolonged ovarian hormone deprivation may augment the effects of chronic unpredictable stress on depressive-like behaviour [44]. Besides, the ovariectomy causes a lower level of BDNF mRNA in the hippocampus of the rat [43][45]. Following supplementation with Tualang honey, the ovariectomised rat exposed to stress showed an increment in the brain BDNF concentration level (1.2 pg/mL) [43]. The antidepressant effect of Tualang honey is believed to be associated with its phytoestrogen properties, attributed to a high flavonoid content that possibly restores the HPA axis and improves mood in this rat model, hence preventing the depressive symptoms in the postmenopausal period.

2.5. Anxiolytic Effects of Tualang Honey

The first study investigating the anxiolytic effect of Tualang honey was on ovariectomised rats exposed to stress. This study revealed that Tualang honey increased the number of rearing events and locomotive activity, reduced mean freezing and grooming time, and decreased the autonomic nervous system response, indicating an improvement of anxiety-like behaviour [46]. The anxiolytic effect of Tualang honey could be attributed to a decrease in the brain oxidative stress that consequently modulates the brain 5-hydroxytryptamine system (**Figure 2**). As various phenolic acids/flavonoids were discovered in Tualang honey, such as gallic acid, kaempferol, naringenin, luteolin, syringic acid, p-coumaric acid, hyacinthim, trans-cinnamic acid, and caffeic acid, the cumulative antioxidant properties help in modifying and reducing anxiety-like behaviour [43]. As similarly reported by Azman et al. (2019) [47], Tualang honey supplementation elevated the mean activity or level of GR, glutathione S-transferases (GST), and total antioxidant capacity (TAC), and decreased the mean activity or level of oxidative stress markers, such as protein carbonyl and MDA, in the brain of the ovariectomised rat. Since postmenopausal women are prone to anxiety due to the deprived source of oestrogen, Tualang honey has the potential to act as an alternative anxiolytic agent, as its effects are comparable to those of oestrogen as demonstrated in an animal study [48][25].

3. Conclusions

Herein reports the possible neurological mechanisms of Tualang honey pertaining to its antioxidant and anti-inflammatory properties. These findings could aid in the development of new therapeutic roles for Tualang honey, such as in multiple sclerosis, amylotropic lateral sclerosis, and Parkinson's disease, as well as in determining how to get the most out of this brain supplement. In order to develop this new prospective quality standard, more research is needed to describe Tualang honey's bioactive chemicals, molecular mechanisms, and critical components that affect nootropic action. Furthermore, proper apicultural techniques should be promoted, particularly in regions rich in tropical rain forests.

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