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Tualang Honey: A Sweet Remedy from Nature

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Honey is a sweet and sticky biological liquid that is produced by bees following the collection from plant nectars. Honey is enjoyed as a popular food product across the globe for its sweetness, flavour, and texture. The benefits offered by honey as food and medicine to mankind are immense with its virtues being documented in ancient religious, medical, and secular texts. The source and composition of honey greatly influence its biochemical properties while the therapeutic value of honey has been relatively associated with its antioxidant properties. Tualang honey is a Malaysian multi-floral jungle honey produced by the rock bee (*Apis dorsata*). Although there are various types of honey being marketed globally such as Manuka honey, less attention was given to Tualang honey as a commercially available food product. Also, Tualang honey is less extensively studied and characterised, unlike Manuka honey. At present, there is a growing interest in the use of honey as a nutraceutical and therapeutic agent to develop new methods of treatment. Therefore, this paper narratively reviews the selected functional and therapeutic properties, such as the antioxidant, anticancer, antimicrobial, antinociceptive, and hepatoprotective activity of the Tualang honey suggesting its use as potential functional food or functional food ingredient.

Keywords: Tualang honey; therapeutic; antioxidant activity; functional food

I. INTRODUCTION

Honey can be defined as a natural biological product obtained from nectar that offers great benefit to mankind due to its attributes as a nutraceutical, energy, and medicinal food. Honey is often enjoyed as a food product for its sweetness, flavour, and texture. Apart from small quantities of proteins, minerals, organic acids, and vitamins, honey is known to contain glucose, fructose, and water (White Jr, 1978; Nolan *et al.,* 2019). The variation of these components gives rise to the smell, taste, appearance, and biological properties of honey (Bocian *et al.,* 2019). For example, there are several known types of honey including Acacia honey, Manuka honey, Buckwheat honey, Sourwood honey, and many others.

The composition of honey is highly dependent on the diversity of the floral source used by the bees to harvest the nectar, entomological origin, climate, and storage time (Ramón-Sierra *et al.,* 2022). The processing of honey involves filtration and heating to remove undesirable materials such as pollens, beeswax, and yeast before being packed into bottles to assure better product quality and shelf life (Subramanian *et al.,* 2007). Several important physicochemical properties such as moisture content, pH, hydroxymethylfurfural (HMF) value, and antioxidant properties can be used as an indicator to determine the quality of honey. A lower pH is desirable to prolong the shelf life of honey because most of the spoilage microorganisms are incapable to withstand acidic conditions. For example, the pH range of Manuka honey and Tualang is between 3.2 – 4.2 and 3.5 – 4.0, respectively. Likewise, the low moisture content in honey is necessary to prevent fermentation.

The freshness of honey can be determined based on the HMF value whereby rigorous processing of honey with high temperatures or long periods of storage can lead to a higher HMF value. Mohammad and Hassan (2021) stated that the HMF values for Tualang honey ranged from 0.75 to 8.08

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mg/kg. Although this value is higher when compared to Kelulut honey (0.05 – 2.27 mg/kg), the HMF values are within the limit for the freshness of tropical honey (80 mg/kg). The HMF values of honey can also be influenced by the variation of types and content of sugar as well as the fructose and glucose ratio (Wu *et al.,* 2020).

The importance of honey for medicinal purposes is well documented in some of the world's oldest literature whereby honey is well-studied for its antimicrobial properties. Johnston *et al.* (2018) stated that the medicinal properties in honey originate from the floral source used by bees. Manuka honey which is derived from nectar collected by honeybees (*Apis mellifera*) foraging on the manuka tree (*Leptospermum scoparium*) in New Zealand is an example of an internationally popular honey (Henriques *et al.,* 2010). Apart from being widely consumed, Manuka honey has been extensively researched for its medicinal and nutritional properties.

Likewise, in Malaysia, Tualang honey is gaining recent interest due to its therapeutic and functional properties. This narrative literature review aims to summarise the selected functional and therapeutic properties of Tualang honey such as the antioxidant, anticancer, antimicrobial, antinociceptive, and hepatoprotective activity. The probable underlying mechanisms of its therapeutic effects are also discussed suggesting the potential use of Tualang honey as functional food or functional food ingredient.

II. CHARACTERISTICS OF TUALANG HONEY

Tualang honey is collected from hives of wild honey bees (*Apis dorsata*) on Tualang trees (*Kompassia excelsa*) (Figure 1) found in the Malaysian rainforest (Mohamed *et al.,* 2010). These Tualang trees are also found in Sumatra, Borneo, and South Thailand. Tualang trees are characterised by their height which reaches up to 250 feet and can harbour more than a hundred nests of wild honey bees on a single tree (Figure 2).

Approximately 450 kg of honey can be harvested from a single Tualang tree (Othman *et al.,* 2015). The specific physical properties of Tualang honey include high colour intensity, a pH value of 3.55 to 4.00, and a specific gravity value of 1.335. Fructose (41.73%), glucose (47.13%), sucrose (1.02%), and maltose (4.49%) constitute the sugar composition of Tualang honey (Chua & Adnan, 2014). Mohamed *et al.* (2010) stated that Tualang honey can be filtered, concentrated, and subjected to gamma irradiation to remove the contaminating microorganisms from the honey.

Figure 1. Tualang tree (*Kompassia excelsa*)

Figure 2. Beehive of *Apis dorsata* on Tualang tree

The fractionation of Tualang honey found that 65% of the component in this honey is sugar comprising of monosaccharides such as glucose and fructose (Moniruzzaman *et. al.,* 2013; Chew *et al.,* 2018). Also, Mohamed *et al.* (2010) stated that Tualang honey contains polyphenol compounds that possess relatively high antioxidant activities. Gallic, benzoic, syringic, transcinnamic, p-coumaric, and caffeic acids constitute the phenolic acids of Tualang honey (Mohamed & Alfarisi, 2017). Likewise, catechin, naringenin, kaempferol, luteolin, and apigenin constitute the flavonoids in Tualang honey (Talebi *et al.,* 2020). The major volatile compounds in Tualang honey were also identified and profiled by Sakika *et al.* (2022) using gas chromatography-mass spectrometry (Table 1). The identified volatiles belong to different chemical classes such as oxygenated compounds, hydrocarbon, and heterocyclic compounds. Furan derivatives such as furfural are produced due to sugar degradation (Sakika *et al.,* 2022).

Table 1. Major volatile compounds in Tualang honey

Compound	**Molecular Formula**	**Molecular Weight [M-W]**
Formic acid	CH_2O_2	46
Acetic acid	$C_2H_4O_2$	60
Glycolaldehyde dimethyl acetal	$C_4H_{10}O_3$	106
Furfural	$C_5H_4O_2$	96
2-Furanmethanol	$C_5H_6O_2$	98
1,2-Cyclopentanedione	$C_5H_6O_2$	98
2-Furancarboxaldehyde, 5-methyl	$C_6H_6O_2$	110
2,5-Dimethyl-4-hydroxy-3(2H)-furanone	$C_6H_8O_3$	128
5-Hydroxymethylfurfural	$C_6H_6O_3$	126
Linoleic acid ethyl ester	$C_{20}H_{36}O_2$	308

III. THERAPEUTIC PROPERTIES OF TUALANG HONEY

A. Antioxidant Activity

The therapeutic properties of Tualang honey can be mainly attributed to the phenolic compounds such as the polyphenols including flavonoids and phenolic acids that are abundantly found in the Tualang honey (Table 2) which act as free radical scavengers, peroxy-radical scavengers, and metal chelators.

Table 2. Reported quantitative data of phenolic and flavonoid compounds found in Tualang honey

Polyphenolics	**Quantity (µg/100 g honey)**
Catechin	12.9 – 35.6
Caffeic acid	2.5 – 3.2
Benzoic acid	0.2 – 1.0
Naringenin	0.6
Trans-cinammic acid	0.01 – 0.5
Gallic acid	0.4
Kaempferol	0.02 – 0.2
Syringic acid	0.02 – 0.1
p-Coumaric acid	0.04

Ferreira *et al.* (2009) stated that there is a positive correlation between the antioxidant properties and the phenolic content of honey. Also, the dark brown appearance of Tualang honey corresponds to a high value of ferric-reducing power which is positively correlated to the high concentrations of phenolic acids and flavonoids (Talebi *et al.,* 2020). For instance, the total phenolic and flavonoid content of Malaysian Tualang honey ranged from 305.47 to 419.86 mg gallic acid equivalents per kg (GAE/kg) and from 135.29 to 165.34 mg catechin equivalents per kg (CEQ/kg), respectively (Khalil *et al.,* 2012).

According to Chew *et al.* (2018), fractionation of Tualang honey after acid hydrolysis improved the bioactivities of Tualang honey to scavenge free radicals and inhibit inflammation. Approximately 35 to 165 times increase in the ability to scavenge free radicals was observed in Tualang honey fractionated with ethyl acetate. The free radical-scavenging activity of Tualang honey measured in a ferric reducing/antioxidant power (FRAP) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay was found to be from 273.46 to 292.34 µM Fe(II)/kg and from 28.48% to 36.94%, respectively (Khalil *et al.,* 2012). Likewise, the FRAP and DPPH analysis of Tualang honey conducted by Mohamed *et al.* (2010) ranged from 322.1 ± 9.7 µM Fe(II) per 100 g and 41.3 ± 0.78 %, respectively. These values were higher than that of Indian forest and pineapple honey (Kishore *et al.,* 2011). The outcomes of the DPPH and FRAP assays confirm the high antioxidant activities of Tualang honey.

The antioxidant activities of Tualang honey *in vivo* were demonstrated by the reduction of elevated malondialdehyde (MDA) levels and restoration of the activities of catalase (CAT) and superoxide dismutase (SOD) in streptozotocin-induced diabetic rats (Erejuwa *et al.,* 2012). Another study by Erejuwa *et al.* (2010) showed that a combination of Tualang honey with glibenclamide or metformin delivered an additional antioxidant effect on the kidneys of diabetic rats by upregulating the catalase and downregulating the glutathione peroxidase gene expression level, respectively.

B. Anticancer Activity

Tualang honey was found to actively participate in the scavenging of free radicals and may consequently prevent the onset of cancer. Fauzi *et al.* (2011) reported that Tualang honey induced apoptosis of breast (MDA-MB-231 and MCF-7) and cervical (HeLa) cancer cell lines in a dose- and time-dependent manner. The MDA-MB-231 and MCF-7 cancer cells treated with 5% and 10% of Tualang honey exhibited apoptosis within 24 hours of treatment. A 51.2% of apoptosis was observed at 48 hours for MDA-MB-231 cells treated with Tualang Honey while 56.2% of apoptosis was observed in the HeLa cells treated with Tualang Honey within 72 hours of treatment. The Tualang honey was also found to increase the leakage of lactate dehydrogenase (LDH) from the cell membranes of breast and cervical cancer cells with effective concentrations (EC50) ranging from 2.4% to 2.8%.

On the other hand, Ahmed and Othman (2017) demonstrated a reduction in the size of palpable tumours from 1.47 cm3 to 0.26 cm3 in cancer-induced female Sprague-Dawley rats treated with 0.2 g kg-1 of Tualang honey. The haematological parameters such as haemoglobin concentration, packed cell volume, red blood cell, red blood cells distribution width, mean corpuscular haemoglobin, polymorphs, and lymphocytes values were modulated close to normal in cancer-induced female Sprague-Dawley rats treated with 0.2 to 2.0 g kg-1 of Tualang honey. Treatment with Tualang honey also exhibited lower anti-apoptotic protein (E2, ESR1, and Bcl-xL) expression and a higher pro-apoptotic protein (Apaf-1 and Caspase-9) expression at serum and cancer tissue levels in cancer-induced female Sprague-Dawley rats.

Likewise, Tualang honey was found to induce apoptotic nuclear changes like nuclear shrinkage, chromatin condensation, and fragmented nuclei in oral squamous cell carcinoma and osteosarcoma cell lines (Ghashm *et al.,* 2010). Tualang honey may have also inhibited cell proliferation by arresting the cell cycle at the sub-G1 phase (Pichichero *et al.,* 2010). The activation of caspase-3 and DNA laddering-induced apoptotic activity (Jaganathan & Mandal, 2010) may also be a possible mechanism pertaining to the anticancer activity of Tualang honey. Thus, a combination of drug treatment with Tualang honey which stops cells at different cell cycle checkpoints (G1 and/or S phases) could be a promising strategy to inhibit tumour survival. Although the mechanism of Tualang honey to prevent cancer is still unclear, studies have shown that honey alters the expression of certain genes related to cell growth and apoptosis (Amruta *et al.,* 2020). The use of cancer cell lines such as K562 and MCF7 allows the investigation of potential anticancer substances such as Tualang honey in a simplified, controlled, and reproducible environment (HogenEsch & Nikitin, 2012). However, the inability of cell cultures to behave like tumours and their interactions with the host (HogenEsch & Nikitin, 2012) means that the efficacy of Tualang honey as an anticancer agent in human clinical trials may not be the same. Future studies using human cancer cell lines combined with *in vivo* testing in a model that closely approximates the targeted human cancer have a greater chance of success in evaluating the anticancer activity of Tualang honey.

C. Antimicrobial Activity

Tualang honey was found to exhibit bactericidal and bacteriostatic activities against various species of wound and enteric bacteria. Tan *et al.* (2009) demonstrated that the minimum inhibitory concentration (MIC) for Tualang honey ranged from 8.75% to 25% (w/v) against bacteria such as *Streptococcus pyogenes* (ATCC 19615), local clinical isolates of coagulase-negative Staphylococci, Methicillin-resistant *Staphylococcus aureus* (ATCC 33591), local clinical isolates of *Streptococcus agalactiae*, *Staphylococcus aureus* (ATCC 25923), local clinical isolates of *Proteus mirabilis*, local clinical isolates of *Shigella flexneri*, *Escherichia coli* (ATCC 25922) and *Enterobacter cloacae*. Likewise, Tualang honey exhibited a better (11.5%) MIC against *Acinetobacter baumannii* in comparison to manuka honey (12.5%). Tualang honey was also found to have a lower 95% inhibition value in comparison to Manuka honey when tested against coagulase-negative Staphylococci, Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Salmonella Typhi*. Nasir *et al.* (2010) also demonstrated the antibacterial activities of Aquacel wound dressing incorporated with Tualang honey to prevent bacterial infection during the management of burn wounds. Similarly, Hbibi *et al.* (2020) suggested that honey may be used as an adjunctive antimicrobial agent for mechanical periodontal treatment due to the promising comparable antimicrobial value of honey with chlorhexidine.

The antimicrobial effects of honey are mainly attributed to the osmotic effect of the sugars, pH, and peroxidase activity (Ghazali, 2009; Ahmed & Othman, 2013). The antimicrobial effects are also due to the presence of non-peroxidase substances such as phenolic acids, flavonoids, and lysozymes (Alnaqdy *et al.,* 2005). The antimicrobial activity of honey may also be due to its adverse effects on the structure, function, and cellular membrane permeability of the microbes which eventually leads to cell death (Čanadanović-Brunet *et al.,* 2011). Ramón-Sierra *et al.* (2022) demonstrated that some antibacterial proteins or peptides in honey induce changes in the transmembrane potential that affects the membrane permeability of bacteria. Likewise, the protein component in honey may inhibit the synthesis of a bacterial protein or may induce the expression of enzymatic activity such as proteases that leads to bacteria lysis. Although Gram-negative and Gram-positive bacteria could be affected by these antibacterial compounds (Wiese *et al.,* 2003), the bactericidal or bacteriostatic effect of honey is highly dependent on the bacterial strain. Hence, the specific underlying cellular and molecular mechanism of the antimicrobial activity of Tualang honey should be investigated in future studies.

D. Antinociceptive Activity

The analgesic effects of Tualang honey were investigated by Abd Aziz *et al.* (2014) by determining the antinociceptive effects of Tualang honey in comparison to the inflammatory drug, prednisolone. The antinociceptive effects of Tualang honey measured using the tail-flick test were found to be dose-dependent and comparable to prednisolone. For instance, a significant increase in the tail flick latency time was observed in the groups administered with Tualang honey at 1.2 g/kg and 2.4 g/kg indicating the potential analgesic activity of Tualang honey.

Similarly, Tualang honey was found to exhibit a reversal of neuronal damage in the spinal cords from the off-springs of prenatally stressed Sprague-Dawley rats (Abd Aziz *et al.,* 2019). The histopathology of the spinal cord of the prenatally stressed rats displayed visible large multipolar neurons with big nuclei. Upon treatment with Tualang honey, the histopathology of the spinal cord of these rats was found to exhibit normal multipolar neurons with clear cell boundaries and a regular-shaped nucleus. The Tualang honey-treated rats also displayed improvement in the activity of oxidative stress markers such as plasma glutathione, catalase, and malondialdehyde activity (Abd Aziz *et al.,* 2019) which may benefit the pain-modulating structures in the central nervous system, including the spinal cord (Azman *et al.,* 2021). Akanmu *et al.* (2011) stated that the action of Tualang honey on opioid receptors in the spinal cord may contribute to the antinociceptive effects. Inhibition of voltage-gated Na^+ channels and stimulation of the noradrenergic inhibitory system or serotonergic system has also been suggested as a mode of mechanism that may confer the analgesic properties of honey.

In a clinical study, oral consumption of 4 mL Tualang honey (thrice daily for seven days) combined with sultamicillin antibiotic was found to stimulate rapid early postoperative pain relief among patients who underwent tonsillectomy (Abdullah *et al.,* 2015). Minimal pain scores were also observed in these patients through a lower frequency of nighttime awakening. The use of painkillers was lower in patients given Tualang honey in combination with sultamicillin compared to patients who received sultamicillin alone indicating the soothing effect of the Tualang honey on the mucosa. Kishore *et al.* (2011) mentioned that antinociceptive effects may also be due to its antioxidant property whereby per gram of Tualang honey is equivalent to 53.06 ± 0.41 mg of ascorbic acid. Likewise, the antioxidants in Tualang honey may have inhibited nociceptive transmission by interacting with the glutamate receptors in the central nervous system (Abd Aziz *et. al.,* 2014; Azman *et al.,* 2021).

E. Hepatoprotective Activity

Elevations of transaminases and alkaline phosphatase (ALP) are examples of hepatic abnormalities, especially among patients with diabetes mellitus. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentration in blood circulation serve as an indicator of hepatotoxicity (Harris, 2005). Streptozotocin-induced diabetic rats treated with Tualang showed significantly ($p<0.05$) lower levels of AST (170.0), ALT (100.0), and ALP

(470.0) in comparison to the diabetic control group which exhibited AST, ALT, and ALP levels of 302.2, 153.0, 730.0, respectively (Erejuwa *et al.,* 2012). The hepatoprotective activity of Tualang honey may be due to its protective effect against hyperglycemia as demonstrated by Ali *et al.* (2020). Tualang honey was found to display a high (74.83% at 100 μg/mL) percentage of inhibition of α-amylase activity which may impart the antidiabetic activity followed by hepatoprotective mechanism (Ali *et al.,* 2020). A similar study by Eraslan *et al.* (2010) found that pine honey improved hepatic function by ameliorating hepatic oxidative stress. Also, Tualang honey was found to improve lipid abnormalities (Mohamed *et al.,* 2017) which may have contributed to its hepatoprotective activity. Apart from the therapeutic properties that have been discussed above, Tualang honey is also known to possess anti-inflammatory, anti-asthma, anti-lipidemic, wound-healing, memory-improving, and fertility-improving activities substantiating the potential use of Tualang honey as a medicinal food.

IV. CONCLUSION

Honey is one of the most appreciated food products in the world due to its sweet flavour and texture. At present, a range of studies is being conducted to evaluate the potential benefits offered by numerous types of honey as medicine to mankind. Although the biochemical properties of honey are highly dependent on its source and composition, the therapeutic value of honey has been comparatively associated with its antioxidant properties. Tualang honey, the multi-floral honey from Malaysia, was found to exhibit antioxidant, anticancer, antimicrobial, antinociceptive, and hepatoprotective activity. Apart from the therapeutic activities that were discussed in this review, Tualang honey is also known to demonstrate which clearly shows its great potential as functional food or functional food ingredient. Therefore, sufficient quantities of Tualang honey should be produced to cater to the needs of the food industry. Future studies could be conducted to improve the existing resources of Tualang honey using biotechnological tools such as genetic engineering to facilitate the sustainable production of Tualang honey. Likewise, *in vivo* studies should be conducted on the bioavailability and metabolism of Tualang honey to fetch valuable insights into the molecular pathways that cater to the effective use of Tualang honey as a dietary supplement and alternative medicine.

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VI. CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

VII. REFERENCES

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