Anti-inflammatory and wound healing properties of Malaysia Tualang honey

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Inflammation is a biological response and a defence mechanism by the body to remove harmful stimuli followed by healing process. Healing is a process of skin and other soft tissue repair at the site of injury. However, uncontrolled inflammation could lead to serious illnesses such as cancer and cardiovascular diseases, which cause great impact on public health and economy. This necessitates supplementation with anti-inflammatory properties to prevent or remove unnecessary inflammation and damage. For ages, Tualang honey (TH) has been used as a natural remedy for inflammation and wounds. TH also exhibits antioxidant, antibacterial and reproductive properties. This review collates the various studies on anti-inflammatory and wound-healing properties of TH. It also presents findings that indicate that honey may ameliorate ultraviolet-induced inflammation of the skin, chemical-induced inflammation of the eyes and oxidative stress on the eyes. Besides, wound-healing properties have also been highlighted here. These data suggest that TH might be a therapeutic agent in the management of inflammation and wound healing. However, there is a need to study the underlying mechanism of action of TH *in vitro* and *in vivo*, to develop a better understanding of its potential benefits.

Keywords: Anti-inflammatory properties, natural remedy, Tualang honey, wound healing.

HONEY is a natural food obtained from bee hives[1]. There are two types of honey: blossom honey, made by the bees from nectar in flowers[2]; and honeydew honey, comes mainly from excretions of plant-sucking insects on the living parts of plants, or secretions of living parts of plants[3]. Honey has been used for ages as a cure for multiple illnesses and as a common food amongst most people around the world[4]. It has captured the interest of many owing to its numerous biological activities. These may be partly attributed to high antioxidant levels due to phenolic acids, flavonoids, vitamin C and vitamin E in the honey[5–8]. The two main biological effects of honey are its antiseptic and healing properties[9]. Antiseptic effect, for instance, bacteriostatic or bactericidal, could be due to high osmolarity, acidity, hydrogen peroxide and non-peroxide components[10,11].

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Examples of non-peroxide component are methylglyoxal (MGO)[12] and bee defensin-1 (ref. 13). These two components have been documented to contribute towards the antibacterial activities; however, MGO has been questioned on the grounds of safety issues for usage on diabetic patients, due to the production of advanced glycation end-products[12]. On the other hand, the healing activity is partly contributed by anti-inflammatory, antibacterial and the capability to stimulate immune responses in a wound. The honey reduces infection and promotes the wound healing process. As honey possesses numerous pharmacological actions, it is becoming acceptable as an effective therapeutic agent by practitioners of conventional medicine and by the general public.

Malaysian Tualang honey is a wild multifloral honey obtained from the branches of *Koompassia excelsa*, known as the Tualang tree[14]. This tree belongs to the Fabaceae family and is commonly found in the tropical rainforests of Malaysia[15]. The honey is produced by *Apis dorsata*, also known as Asian rock bees[16]. These giant bees build their hives high up on the Tualang tree. The bee hive may be up to 6 ft high and each hive may have an average of 30,000 bees[15].

Tualang honey (TH) has been reported to have higher phenolic, flavonoid and ascorbic acid content, which in turn intensifies its antioxidant activity[17,18]. The dark colour of TH could be related to higher total phenolic content[19,20]. The pH of TH is between 3.2 and 4, which accounts for its high antibacterial activity[19]. In addition, less moisture content present in TH makes it suitable for wound dressing. In addition, a high content of glucose, fructose, sucrose and maltose is present in TH (Table 1).

Table 1. Physico-chemical characteristics of Tualang honey

Appearance	Dark brown
Specific gravity	1.335
pH	3.20–4.00
Moisture content (%)	23–30
Total reducing sugar (%)	67.50
Fructose (%)	29.60
Glucose (%)	30.00
Sucrose (%)	0.60
Maltose (%)	7.90

Source: Refs 21, 22.

Table 2. Phytochemical constituents/bioactive compounds detected in Tualang honey

Phytochemical constituents	Activity
5-(Hydroxymethyl) 2-furancarboxaldehyde	Antioxidant
3-Furaldehyde	Antioxidant
Beta-D-glucopyranose, 1,6-anhydro-	–
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	Antimicrobial, anti-inflammatory, antioxidant
1,6-Anhydro-beta-D-glucofuranose	–
Methyl 2-furoate	–
Phenylacetaldehyde	Antioxidant
Formic acid	–
Levoglucosenone	Anticancer, treatment for autoimmune system and cardiovascular diseases
2-Furancarboxaldehyde, 5-methyl-	–
Acetic acid	Antihistamine
2(5H)-Furanone	–
2-Furanmethanol	Antioxidant
Maltol	Antioxidant, anticonvulsant, depressant, anti-aging
2(3H)-Furanone, dihydro-4-hydroxy-	–
Propanoic acid, 2-hydroxy-, ethyl ester	–
2(5H)-Furanone, 5-methyl-	–
2-Propanone, 1,3-dihydroxy-	–
2-Propanone, 1-hydroxy- (CAS) acetol	–
Hydrogen chloride	–
Propanoic acid, 2-oxo- (CAS) pyruvic acid	–

Source: Ref. 23.

Tan *et al.*[23] conducted a gas chromatography-mass spectroscopy (GC-MS) study on TH sample. The data revealed that TH contains numerous phytochemical compounds. It had the highest phytochemical content of 5-(hydroxymethyl) 2-furancarboxaldehyde compared to any other honey in Malaysia[15]. This compound is known to have high antioxidant activity[6]. TH also contains 3-furaldehyde, 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-, phenylacetaldehyde, 2-furanmethanol and maltol (Table 2). These compounds are known to contribute to the antioxidant properties of this honey. High antioxidant activity may partly contribute to the anti-inflammatory properties of TH.

Anti-inflammatory properties

Inflammation is the reaction of a normal living tissue to local injury and it plays an important role in the defence mechanism which helps to protect us from infection or injury[24]. The function of inflammation is to eliminate the foreign bodies or injurious agents. Furthermore, it removes damaged tissue components, so that the body can begin to heal and recover. However, if the inflammation is left untreated or uncontrolled, it will lead to many acute and chronic human diseases[25]. Honey is used for different purposes in traditional medicine around the world. Honey exhibits anti-microbial, anti-inflammatory and antioxidant activities as well as boosting of the immune system[26–29]. The anti-inflammatory and wound-healing properties are known to be the vital bioactivities of honey[30]. Almost all types of honey have been proven to have anti-inflammatory and wound healing properties in both *in vitro* and *in vivo* settings, which includes Manuka honey, Gelam honey[31], and Malaysian TH[8,32]. TH also exhibits antioxidant, antibacterial, antiproliferative and anti-cancer properties[33–37].

Several studies have reported suppression and relief symptoms of inflammation following the application or consumption of honey. Ahmad *et al.*[32] reported that Malaysian TH exhibits protective effect against ultraviolet (UV)-induced inflammation and DNA damage on human keratinocytes. The UVB component from solar UV radiation is known to be the main cause of a number of cutaneous disorders and it is potent in damaging DNA directly or via production of reactive oxygen species. In addition, UVB irradiation activates the transcription factor NF-κB (ref. 38) and cyclooxygenase-2 (COX-2)[39]. Overall, UVB irradiation leads to skin inflammation, gene mutation, immune suppression and even skin cancer[40,41]. However, Ahmad *et al.*[32] showed that TH reduced the effects of UVB-induced inflammation on PAM212 keratinocytes cell line via modulation in early biomarkers of photocarcinogenesis; this includes inhibiting epidermal COX-2 protein expression and PGE2 production.

The high phenolic content of TH, which is attributed to its antioxidant properties, may partly contribute to the protective effect against UVB-induced inflammation on keratinocytes. Kishore *et al.*[18] reported that the elevated radical scavenging and antioxidant properties of TH are

due to its high phenolic content. In addition, high flavonoid or phenolic content of honey is able to down-regulate the expression of MMP-9 induced by tumour necrosis factor (TNF-α) on keratinocytes[42]. Thus, the data suggest that TH provides significant protection from adverse effects of UVB radiation in PAM212 keratinocytes[32].

TH was found to be equally effective in treating alkali-induced injury in rabbits[33]. In this study, TH was administered orally and topically for 7 days after induction of alkali injury on the cornea of the rabbits. Alkali injury of the cornea leads to two phases of inflammation: infiltration of polymorphonuclear (PMN) leukocytes during the first phase and second wave of inflammatory cell infiltration which begins on day 7 (ref. 43). The injury that was caused by alkali is mostly due to oxidative stress in the eye. The parameters measured were conjunctival hyperemia, corneal edema and epithelial healing after alkali induction. Surprisingly, in the TH-treated group, positive results were seen in all the parameters which include the reduction of degree of inflammatory cell infiltration. The data showed that the anti-inflammatory properties of TH are comparable to conventional treatment. However, further studies are needed to elucidate the anti-inflammatory mechanism of TH.

A similar study on human corneal cell has shown that 0.4% of TH improved human corneal epithelial progenitor cell (HCEP) migration. In addition, it also assisted in minimizing oxidative stress in HCEP cells *in vitro*. Oxidative stress is the production of inequality between free radicals and reactive metabolites, which leads to the damage of vital biomolecules and cells that cause chronic inflammation[44]. Moreover, the literature showed oxidative stress causes chromosomal instability, shortening of telomeres and cellular replicative senescence in stem cells *in vitro*[45,46]. TH-induced enhancement of the oxidative stress tolerance of HECP cells may partly be contributed by the antioxidant active phytocompounds, such as 5-(hydroxymethyl) 2-furancarboxaldehyde, 3-furaldehyde, 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-, phenylacetaldehyde, 2-furanmethanol and maltol present in TH[23]. By decreasing oxidative stress via direct radical scavenging activity, TH helps in preventing chronic inflammation[47].

Wound healing properties

Skin is constantly exposed to oxidants; both to endogenous and environmental prooxidants which eventually lead to inflammatory responses[44]. Wound healing is a process of skin and other soft tissue repair following injury. Three stages are involved in the process of wound healing: inflammation, proliferation and remodelling[48]. Unhealed wounds and ulcers have a great impact on the public health and economy. Thus, an intervention that exhibits therapeutic effects on achieving significant wound healing and to eliminate infections is of great value and is necessary. Honey is well known for its use in treating edema and inflammation, the common consequences that present in most wounded tissues. Studies have been carried out to establish the wound healing property of all types of honey.

Some types of honey are being used in the clinical setting for wound healing. For instance, a blend of Manuka and jelly bush honey is medically certified and licensed as medical product for wound care in Europe, America and Australia[49,50]. Also, honey is applied as a wound dressing under controlled and sterilized conditions in Australia and New Zealand[51]. A recent study showed that the healing efficacy of Malaysian TH as a dressing is superior to modern hydrofibre and silver dressings on full thickness burn wounds[52]. Wound contraction in fresh wound is one of the markers of wound healing[53]. Studies showed that wound contraction in animals treated with TH was markedly greater than modern dressing[52]. Moreover, wound size of the TH-treated group showed a significant reduction of 12.86% by day 3 and 33.94% by day 9. On the contrary, the wound size of hydrofibre silver-treated wounds showed a reduction in size with only 2.2% by day 3 and 13.74% by day 9. In addition, scabs formed by the TH-treated wounds were thinner than those developed by conventional treatments. The reason for this is due to the moist environment of honey, due to its viscosity and high sugar content that prevents infection[31].

Furthermore, Lazim *et al.*[54] documented wound healing properties of TH in human setting. The study stressed on the enhancement of the wound healing process of TH in post-tonsilectomy patients. In this clinical trial, the selected patients were treated with TH and antibiotics, whereas another group of patients received only antibiotics. Interestingly, a significant healing process was observed in the patients treated with TH and antibiotics. In addition, all patients from the TH–antibiotics group recovered completely by day 14. These clinical trial data showed that TH can be an excellent adjunct therapy for post-operative patients. Imran *et al.*[55] reported that TH may be effective in the treatment of split-skin graft donor sites. Patients preferred TH hydrogel dressing as the treatment gave a soothing sensation and a pleasant odour compared with the conventional dressing. Moreover, they also experienced minimal pain when using TH hydrogel dressing. Healing properties of TH can be ascribed to the fact that it exhibits strong antibacterial activity. This activity speeds up the growth of new tissue to heal the wound[56]. Also, it has high viscosity and is capable of maintaining a moist environment[57] which makes it a potent antibacterial, wound-healing and anti-inflammatory agent.

Conclusion

Different types of honey contain different phytochemical compounds and thus exhibit multiple biological activities. From this review, it can be concluded that Malaysian

Tualang honey possesses strong anti-inflammatory properties and can be used as a preventative medicine. It is suggested that antioxidant properties play a major role in promoting anti-inflammation, wound healing and radical scavenging properties of this honey. Despite these findings, the use of Tualang honey in clinical practices as an anti-inflammatory agent has not reached its potential. Further research and clinical trials are required to develop a better understanding of its potential health benefits.

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