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Review

Biological and therapeutic effects of honey produced by honey bees and stingless bees: a comparative review

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ABSTRACT

Honey is a natural product produced by both honey bees and stingless bees. Both types of honey contain unique and distinct types of phenolic and flavonoid compounds of variable biological and clinical importance. Honey is one of the most effective natural products used for wound healing. In this review, the traditional uses and clinical applications of both honey bee and stingless bee honey – such as antimicrobial, antioxidant, anti-inflammatory, anticancer, antihyperlipidemic, and cardioprotective properties; the treatment of eye disorders, gastrointestinal tract diseases, neurological disorders, and fertility disorders and wound healing activity are described.

Introduction

Honey is a natural sweetener that is widely available across the world. Among natural products, it is extensively used for various applications, some clinical (Ahmed and Othman, 2013), and contains approximately 200 distinct chemical compounds (Ramanauskiene et al., 2012). Honey bee honey is a viscous solution containing various molecules, including fructose and glucose (80–85%); water (15–17%); ash (0.2%); proteins and amino acids (0.1–0.4%) and trace amounts of enzymes, vitamins and other substances, such as phenolic compounds. However, honey composition varies depending on the types of plants from which the bee consumes nectar. Nevertheless, nearly all honey worldwide contains similar types of phenolic acids, including caffeic, ellagic, ferulic and *p*-coumaric acids; flavonoids, such as apigenin, chrysin, galangin, hesperetin, kaempferol, pinocembrin and quercetin; and antioxidants, such as tocopherols, ascorbic acid, superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH). Each constituent has unique nutritional and medicinal properties, and the components act synergistically, lending honey utility in a variety of applications (Patricia et al., 2015a). Nevertheless, the physical properties and chemical composition of honeys fluctuate based on the plants from which the bees collect raw material. In addition, differences in the type of flora, climatic conditions and geographical region also influence honey's physical and chemical properties. In a recent study, different methods were used for discrimination of the entomological origins of sting bee and stingless bee honeys (Patricia et al., 2011, 2015b) as well as authentication of commercial honeys by nuclear magnetic resonance (Schievano et al., 2015).

Several research studies of honey have confirmed its biological properties, such as antioxidant, anti-inflammatory, anti-bacterial, antiviral, anti-ulcer activities; and antihyperlipidemic, antidiabetic and anticancer properties (Erejuwa et al., 2010; Kishore et al., 2011; Viuda-Martos et al., 2008). It has been reported that honey lowers cardiovascular risk in both healthy patients and in those with increased risk factors. Various parameters, such as plasma glucose, plasma insulin, cholesterol, triacylglycerides (TG), blood lipids, C-reactive proteins and homocysteine, were investigated following *in vivo* administration of natural and artificial honeys; natural honey was found to have significant ameliorative effects on the aforementioned parameters (Al-Waili, 2004). In particular, Tualang (*Koompassia excelsa*) honey has been reported to have protective effects in learning and memory, including enhanced morphology of memory-related brain areas, increased levels of brain-derived neurotrophic factor, reduced brain oxidative stress, increased acetylcholine concentration, and reduced acetyl cholinesterase activity in brain homogenates (Al-Himyari, 2009; Othman et al., 2015).

Stingless bee honey is a precious bee product of the stingless bee. Stingless bee honey is different from that produced by the bees of

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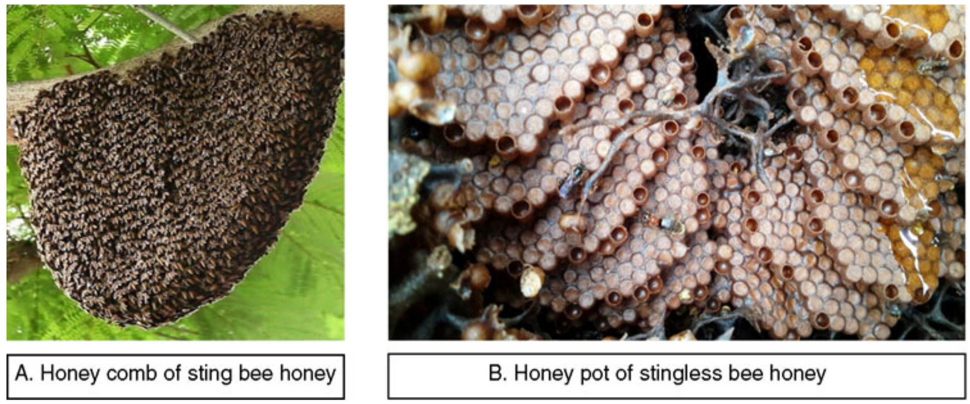


Fig. 1. Honey comb (A) of sting bee honey and pot (B) of stingless bee honey.

the genus *Apis* (*i.e.*, the honey bee) in terms of its color, taste and viscosity (Almeida-Muradian et al., 2014; Guerrini et al., 2009). This valuable bee product has traditionally been consumed directly and used in numerous medical practices: both traditional methods, in which honey is harvested directly from the forest, and in the more well-established meliponary (Souza et al., 2006). The honey comb of sting bee honey and honey pot of stingless bee honey are represented in Fig. 1. The aim of this review is to summarize information on the traditional and clinical uses of honey bee and stingless bee honey to augment various biological activities and to treat diseases.

Chemical constituents of honey bee and stingless bee honey

Honey contains approximately 200 compounds, such as vitamins, enzymes, amino acids and minerals, with the major content being water and sugars. Sugars comprise approximately 95–99% of honey's dry matter. Of the sugars in honey, fructose is the most prevalent, comprising approximately 32–38% of its total sugar. In addition to fructose and glucose, several other disaccharides and oligosaccharides, including sucrose, maltose, maltotriose and panose, can be found. Organic acids, minerals and trace elements such as calcium, potassium, sodium, magnesium, phosphorus, sulphur, iron, zinc, copper and manganese are other components present.

In addition, various vitamins, including ascorbic acid (Vitamin C), thiamine (Vitamin B1), pantothenic acid (Vitamin B5), riboflavin (Vitamin B2), nicotinic acid (Vitamin B3), pyridoxine (Vitamin B6), biotin (Vitamin B8), folic acid (Vitamin B9) and cyanocobalamin (Vitamin B12), are present (Ciulu et al., 2011). Enzymes and proteins are minor constituents, with the enzymes playing a vital role in various activities, including antimicrobial activity and facilitating calcium absorption (Ariefdjohan et al., 2008). Many studies have reported (Can et al., 2015; Escriche et al., 2014; Flores et al., 2015; Habib et al., 2014) that the antioxidant capacity of honey is dependent not only on the presence of total phenolic compounds but also on the presence of flavonoids, which play an important role in ameliorating oxidative stress. Interglycosidic linkages in *O*-glycosil flavones from *Tetragonula carbonaria* have previously been detected by high-performance liquid chromatography/photodiode-array (Truchado et al., 2015).

A variety of flavonoids and terpenoids have been reported in various honeys. In manuka honey, pinocembrin (**1**), chrysin (**2**), pinobanksin (**3**), 8-methoxykaempferol (**4**), luteolin (**5**), isorhamnetin (**6**), galangin (**7**), kaempferol, sakuranetin (**8**), quercetin and magniferolic acid (**9**) and 3β-hydroxy-24-methylenecycloartan-26-oic acid (**10**) have been identified (Ahmed and Othman, 2013). The various physicochemical properties of honey bee and stingless bee honey are summarized in Tables 1 and 2. Various types of therapeutic efficacies of honey are depicted in Fig. 2.

Table 1
Physicochemical properties of honey bee (Tualang and Manuka honey) and stingless bee honey.

Physico-chemical properties	TH (Erejuwa et al., 2010)	MH (Stephens et al., 2010)	Stingless bee honey (Souza et al., 2006)	IHC guideline (Bogdanov et al., 1999)
Appearance	Dark brown	Light-dark brown	Amber brown	Colorless to dark brown
Moisture content	23.30% (Ahmed and Othman, 2013)	18.70%	25.02	<20.00
pH	3.55–4.00	3.20–4.20	3.05–4.55	3.40–6.00
Total reducing sugars	67.50%	76.00%	55.00–86.00%	>60.00
Glucose	30.00%	36.20%	8.20–30.98	23.00–32.00
Fructose	29.60%	40.00%	31.11–40.20	31.20–42.40
Sucrose	0.60%	2.80%	0.31–1.26%	0.00–2.80
Maltose	7.90%	1.20%	NA	NA
Calcium	0.18%	1.00%	NA	NA
Potassium	0.51%	1.00%	NA	NA
Sodium	0.26%	0.0008%	NA	NA
Magnesium	0.11%	1.00%	NA	NA
Specific gravity	1.34	1.39	NA	NA
Electrical conductivity (mS/cm)	0.75–1.37	0.53	0.49–8.77	0.80–4.40
HMF (mg/kg)	46.17	40.00	8.80–69.00	<80
Ash content (g/100 g)	0.19	0.03	0.01–0.12	<0.6

TH, Tualang honey; MH, Manuka honey; HMF, hydroxylmethylfufural; IHC, International Honey Commission; NA, not available.

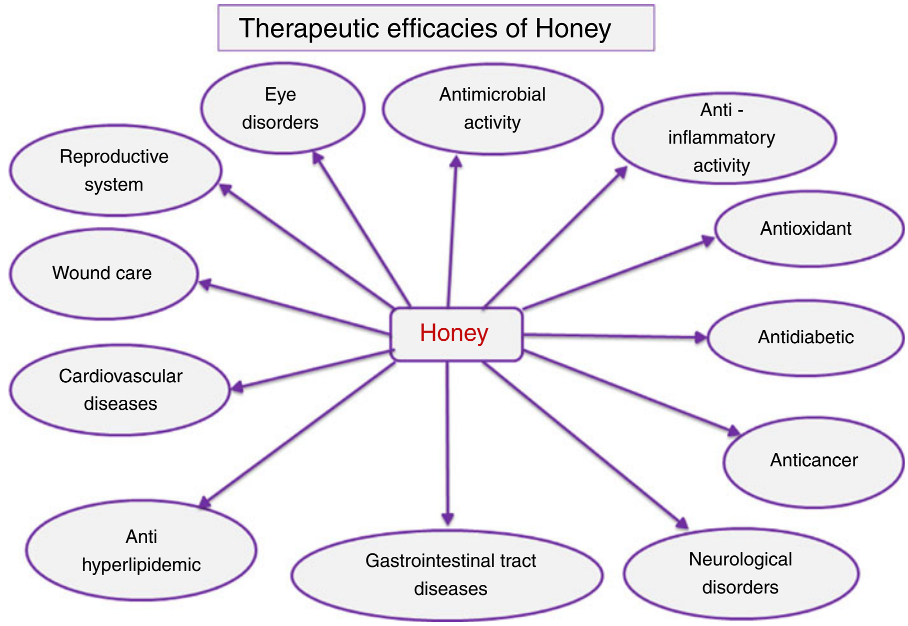


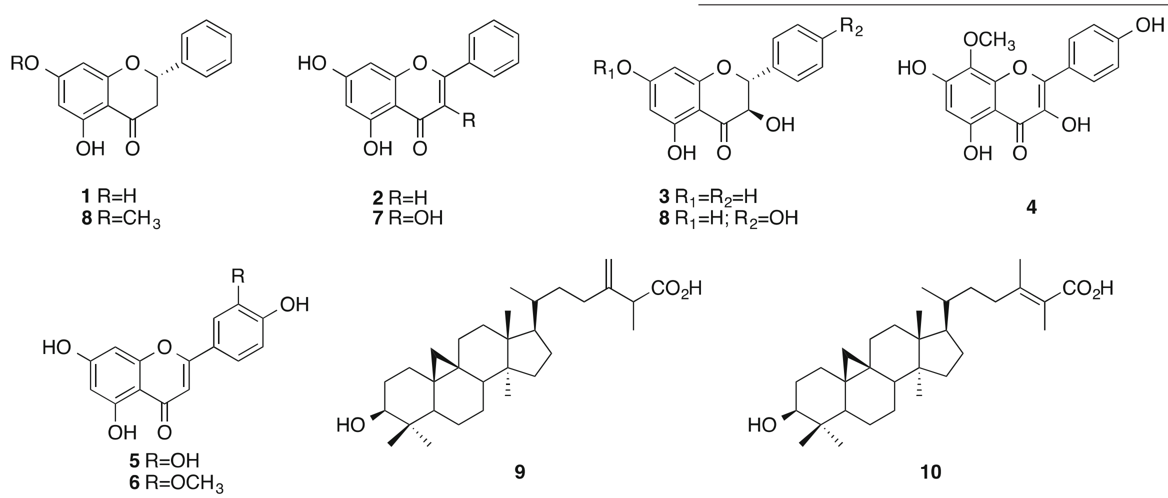
Fig. 2. Schematic representation of the therapeutic effects of honey.

Table 2
Color quality analysis of honey bee and stingless bee honey samples.

Color	Pfund scale (mm)
Water white	<08
Extra white	09–17
White	18–34
Extra light amber	35–50
Light amber	51–85
Amber	86–114
Dark amber	>114

Source: The National Honey Board (2007).

Honey is among the best wound healers available in the nature. The ancient Chinese, Egyptians, Greeks, Assyrian and Romans utilized different types of honey to treat wounds and diseases of the intestine. Honey exerts known antibacterial effects against several microorganisms, including *Escherichia coli*, *Shigella* spp., *Helicobacter pylori* and *Salmonella* spp. (Al Somal et al., 1994; McGovern et al., 1999). In addition, honey is reported to have anti-inflammatory (Kassim et al., 2010; Nasuti et al., 2006) and anti-cancer activities against breast, cervical (Fauzi et al., 2011) and prostate cancers (Samarghandian et al., 2011) as well as osteosarcoma (Ghashm et al., 2010). Furthermore, honey is traditionally used as an anti-diabetic (Erejuwa et al., 2012b) and hypolipidemic agent (Adnan et al., 2011) and to ameliorate thyroid disturbances (Adewoye and Omolekulo, 2014).



Traditional uses of honey

Honey has held a place of importance in traditional medicine for ages (Jeffrey and Echazarreta, 1996; Patricia et al., 2004, 2013). For many years, honey has been a pivotal player as an antioxidant, and it has been reported that honey can be used as a hepatoprotective and cardioprotective agent (EL-Kholy et al., 2009; El Denshary et al., 2012; Erejuwa et al., 2012a). In addition, honey has protective effects against gastrointestinal ailments (El-Arab et al., 2006; Salem, 1981).

Antimicrobial activity

Tetragonisca angustula (*T. angustula*) is a stingless bee widely available in Brazil and Mexico. The biological activity of *T. angustula* honey – particularly its antimicrobial activity – has been well documented and was found to possess good antimicrobial activity against the bacterium *S. aureus* (Miorin et al., 2003). Another study revealed that *T. angustula* honey has significant antimicrobial activity against several different bacterial strains, including *Bacillus cereus* (Gram positive bacteria) and *Pseudomonas aeruginosa* (Gram negative bacteria), as well as against yeasts such as *Candida albicans* and *Saccharomyces cerevisiae* (DeMera and Angert, 2004). A recent study has confirmed the antibacterial activity of *T. angustula* honey on Gram positive bacteria such as *Staphylococcus aureus* and *Enterococcus faecali*, as well as coagulase-negative methicillin-sensitive and Gram negative bacteria such as *P. aeruginosa* and *E. coli* (Sgariglia et al., 2010).

A recent study reported that the eleven types of stingless bee honey, including that of *Trigona carbonaria*, have potential antimicrobial activity against several types of microorganisms collected from thirteen clinical samples in addition to standard reference strains (Boorn et al., 2010). Furthermore, *Trigona laeviceps*, a stingless bee found in Thailand, produces honey with antimicrobial activity against several types of bacteria (*E. coli* and *S. aureus*) and the fungal strain *Aspergillus niger*, as well as two types of yeasts (*Auriobasidium pullulans* and *C. albicans*) (Chanchao, 2009).

Honey bee honey also displays a wide range of antimicrobial activities against various types of bacteria, fungi and viruses (Aggad and Guemour, 2014; Cooper et al., 1999; Nasir et al., 2010). Manuka honey is one of the most potent and well-investigated honeys for its antimicrobial and wound healing activities (Al Somal et al., 1994; Willix et al., 1992). Tualang honey from Malaysia was also reported to have significant antimicrobial and wound healing activities (Bergman et al., 1983; Efem, 1988). In our previous study (Tan et al., 2009), both Tualang and Manuka honey were effective against *Stenotrophomonas maltophilia* (Tan et al., 2009). However, Tualang honey had a lower MIC (11.25%) against *Acinetobacter baumannii* compared with manuka honey (12.5%).

Antioxidant activities

Two types of stingless bee honeys (*T. angustula* and *Plebeia wittmanni*) have been reported to have good antioxidant activity (Vattuone et al., 2007). A study conducted in the Northeastern regions of Brazil revealed that stingless bee honey from *Melipona (Michmelia) seminigra merrillae* possesses antioxidant potential (da Silva et al., 2013). Furthermore, *T. carbonaria*, *Melipona fasciculate*, *Melipona subnitida* and *Melipona aff. Fuscopilosa* honeys showed significant antioxidant activity *in vitro*. Among all stingless bee honey samples, *T. carbonaria* had the best antioxidant activities, indicating that the antioxidant potential of honey varies based on type.

Several studies have indicated that honey bees from different geographical regions have sufficient but variable antioxidant activity. In a study by Kishore et al. (2011), it was reported that the radical scavenging activity of Tualang honey bees is high, and their honey had the highest antioxidant activity among the honey types compared. Tualang honey collected from forests in Malaysia showed substantial antioxidant activity, as indicated by several tests including the 1,1-diphenyl-2-picrylhydrazil (DPPH) and FRAP assay (Henderson et al., 2015), ORAC assay (The Oxygen Radical Absorbance Capacity), ABTS [2,2-azinobis (3-ehtylbenzothiazoline-6-sulfonic acid) diammonium salt assay, TEAC (Trolox-equivalent antioxidant capacity) assay and ascorbic acid content assay (Bashkaran et al., 2011; Erejuwa et al., 2012a,b; Ferreira et al., 2009; Khalil et al., 2012, 2015; Moniruzzaman et al., 2012, 2013, 2014). Algerian and Bangladesh honeys have also been reported to have good antioxidant activity (Khalil et al., 2012; Moniruzzaman et al., 2014). Flavonoids and polyphenols found in honey also have been reported to have antioxidant activity (Pérez-Pérez et al., 2013).

Anti-inflammatory activity

Melipona marginata is an endangered stingless bee species from Brazil. It produces honey with unique physicochemical properties and a distinctive flavor. In one study, the honey extracted from *M. marginata* showed anti-inflammatory effects when applied to the skin (Borsato et al., 2014).

The efficacy of Manuka honey and its components as anti-inflammatory agents have also been reported. The production of various inflammatory cytokines has been assessed by exposing human monocytes to Manuka honey (Tonks et al., 2003). The results of this study revealed that the honey stimulated the production of inflammatory cytokines interleukin-1β (IL-1β) and IL-6 as well as tumor necrosis factor-α (TNF-α) through a toll-like receptor 4 (TLR4)-dependent pathway. In particular, one of the main components of Manuka honey, a protein with a molecular weight of 5.8 kDa, is reported to be responsible for the stimulation of different types of cytokines in human monocytes through the TLR4 pathway (Tonks et al., 2007).

Tualang honey has been shown to possess anti-inflammatory activities in animals. The administration of Tualang honey to a chemically induced injury on rabbit cornea yielded effects similar to those of conventional treatment (Bashkaran et al., 2011) indicating its potential to treat ailments of the eye. Another study reported the effects of Tualang honey on early biomarkers of photocarcinogenesis in the PAM212 mouse keratinocyte cell line. Keratinocytes treated with Tualang honey were protected against exposure to ultraviolet-B radiation. The same study also noted the anti-inflammatory capacity of Tualang honey (Ahmad et al., 2012).

Eye diseases

Stingless bee honey also plays an important role in treating chemically induced cataracts. Honey from the stingless bee *Melipona favosa favosa* exhibited activity against sodium selenite-induced cataracts in Wistar rats. Furthermore, the application of stingless bee honey as an eye wash agent has led to the retardation of selenite-induced cataracts in rats (Patricia, 2002). In addition, *Meliponini* honey has been used as an eyedropper to treat eyesight problems. Honey from the stingless bee species *Tetragonisca* is also used in the treatment of glaucoma and cataracts (Costa-Neto and Oliveira, 2000).

Gastrointestinal tract diseases

Another important medicinal use of honey is in the treatment of gastrointestinal tract diseases. Some honey preparations have shown beneficial effects in dyspepsia and in the treatment of periodontal diseases. Honey also has beneficial effects in children with gastroenteritis. The continuous treatment with honey of a group of children resulted in a reduction in the duration of diarrhea (Haffejee and Moosa, 1985). One study reported the potential of honey to treat ethanol-induced increased vascular permeability and gastrointestinal disturbances (Ali and Al-Swayeh, 1997). Nevertheless, to our knowledge, no scientific report is available on the utility of stingless bee honey for treating gastrointestinal disorders.

Neurological disorders

Oxidative stress is one of the major causes of neuroinflammation, which leads to neuronal apoptosis and death. A recent study on Tualang honey from Malaysia in the context of neurodegenerative disorders reported that honey may have significant activity against chronic cerebral hypoperfusion, which is one of several factors contributing to Alzheimer's disease (Saxena et al., 2014). Several studies have confirmed the beneficial effects of honey on memory and learning processes. A long-term study on the efficacy of honey in treating dementia in humans found that honey and the components present in honey may prevent dementia and other cognitive diseases (Al-Himyari, 2009). Another study in which honey was continuously administered to animals revealed that memory is enhanced and there is increased proliferation of neurons in hippocampal regions (Al-Rahbi et al., 2014). However, to our knowledge, there is lack of investigation of the neurological effects of stingless bee honey; thus, more studies should be conducted.

Effect on fertility

Honey has beneficial effects on fertility as well as in ameliorating the hormones related to fertility. A recent study on rats exposed to auditory stress reported that a decrease in fertility could be ameliorated with 0.2 ml of 5% honey dissolved in water. Noise is a natural teratogenic factor that severely impacts human health, reproductive fitness, and the function of reproductive organs. This study indicated that honey consumption ameliorated altered levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. In addition, positive effects of vitamin E on these parameters have been reported (Rajabzadeh et al., 2015a,b).

Stress plays a vital role in many diseases, disorders and dysfunctions. Alterations in reproductive function are a common feature of increased levels of stress. In one study, the administration of Tualang honey to restraint-stressed pregnant rats at 1.2 g/kg daily conferred beneficial effects on various parameters, such as corticosterone level, pregnancy outcome and adrenal histomorphometry (Haron et al., 2014). Mosavat et al. (2014) reported that honey supplementation at 1 g/kg resulted in a significant restorative effect on altered gonadotropin levels in female rats (Mosavat et al., 2014). Another study reported that smoke-induced reproductive toxicity was ameliorated by the oral administration of honey at 1.2 g/kg/day, which improved the percentage of successful intromission and ejaculation in rats. By extension, this results in increased fertility and mating rates (Mohamed et al., 2013). However, to our knowledge, reports on the effects of stingless bee honey on fertility are lacking, and the possible effects require further investigation.

Antidiabetic activity

The antihyperglycemic effects of honey in rabbits with chemically induced diabetes have been confirmed. One study found that different doses of honey (as low as 5 ml/kg) produced a significant reduction in blood glucose levels and other related parameters. The study indicated that even at low doses (5 ml/kg), honey may be a good alternative to sucrose as a natural sweetener for diabetic patients (Akhtar and Khan, 1989). Honey and its components were found to have several health benefits with long-term usage. Honey showed beneficial effects in one report, including weight improvement and reduction in blood glucose levels.

Honey contains a high concentration of fructose, a monosaccharide capable of elevating blood glucose levels through oral absorption. It is therefore a paradox that researchers and nutritionists have encouraged the use of honey as a nutrition supplement in diabetic individuals (Adesoji and Oluwakemi, 2008). A recent review has been published with a detailed information on the antidiabetic action of honey (Erejuwa et al., 2012b). To our knowledge, no data have been reported on the antidiabetic activities of stingless bee honey.

Anticancer activity

Cancer is one of the most important and dreadful diseases. Numerous studies (Fauzi et al., 2011; Hawley et al., 2014; Kustiawan et al., 2014; Othman, 2012) on the efficacy of honey on various types of cancers have shown that honey has debriding potential and stimulates angiogenic action. A study on the efficacy of honey against cancerous cells regarding their stability, viability and even metastasis showed significant anti-angiogenic effects (Fauzi et al., 2011). Several studies on honeys from Malaysia reported good activities against various cancers, including oral, bladder (Swellam et al., 2003), cervical (Fauzi et al., 2011), liver (Baig and Attique, 2014), bone and breast (Fauzi et al., 2011) cancers.

Experimental evidence also shows that Tualang honey protects non-cancerous cells from the adverse effects of tamoxifen through a DNA repair mechanism in Michigan Cancer Foundation 10 A (MCF-10A) cells compared with MCF-7 cells (Yaacob and Ismail, 2014). In addition, Manuka honey has been reported to possess anticancer activities (Fernandez-Cabezudo et al., 2013). A study on the effect of Manuka honey on improving post-radiation symptoms of esophagitis indicated its preventive effect on lung cancer (Berk et al., 2014). In a study related to squamous cell carcinoma, Manuka honey exhibited significant preventive effects, including a reduction in inflammation and odor from wounds in the oral cavity (Drain and Fleming, 2015). To our knowledge, although reports on the anticancer effects of stingless bee propolis are available (Choudhari et al., 2013; Kustiawan et al., 2014), the information on the anticancer effects of stingless bee honey is lacking and further investigation is required.

Cholesterol and lipid-lowering effects in cardiovascular diseases

One of the most noticeable applications of honey is in reducing cholesterol levels in hyperlipidemic patients. For example, the continuous administration of 75 g of honey dissolved in 250 ml water for 15 days significantly reduced lipid levels (Al-Waili, 2004). Another study by Yaghoobi et al. (2008) reported the effects of honey on fasting blood glucose (FBG), body weights, low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triacylglycerol, and C-reactive protein (CRP) in 55 patients and showed that oral administration of 70 g of honey for 30 days leads to a reduction in LDL, triacylglycerols, and cholesterol in overweight patients (Yaghoobi et al., 2008). In addition, HDL-C levels were elevated following the consumption of 10% honey over a prolonged period of time, suggesting that regular honey consumption has the health benefits of glycemic control and an improvement in the lipid profile, which directly or indirectly leads to a reduction in the occurrence of cardiovascular disease (Chepulis and Starkey, 2008). Tualang honey administration (3 g/kg/day) for 45 days showed an effect on myocardial ischemia in rats. Amelioration of the disturbance in cardiac marker enzymes [creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), and aspartate transaminase (AST)] has been reported (Khalil et al., 2015).

Wound healing activity

Many studies have examined the wound healing effects of honey. The wound healing activity of honey on experimental mice, which received topical application of honey, has been positive. Histopathology findings showed significant improvement in granulation tissue thickness and open wound size. This study also suggested that the topical application of honey to wounds may exhibit a wound healing capacity (Bergman et al., 1983). In a human study of 59 patients, honey was found to improve wound healing. Honey also acts as debriding agent when applied directly to a wound. One study reported that honey ameliorates granulation tissue thickness, epithelialization, and edema around wounds (Efem, 1988).

A randomized clinical study of 25 patients with wounds was conducted to investigate the efficacy of honey for wound healing. This study indicated that honey heals wounds rapidly and acts as an antiseptic agent (Subrahmanyam, 1998). A study by Cooper et al. (1999) demonstrated the antibacterial effects of Manuka honey on wounds (Alvarez-Suarez et al., 2014; Cooper et al., 1999). Another study revealed the substantial antimicrobial activity of Australian stingless bee honey and suggested that stingless bee honey would also possess wound healing activity (Boorn et al., 2010).

Conclusions and future prospects

Honey possesses numerous biological, biochemical and physiological activities in animals as well as in humans. The efficacy of these properties depends on the types of phenolic compounds present in the honey. Different types of honey have been investigated for their antimicrobial, anticancer, antidiabetic, anti-hypercholesterolemic, anti-inflammatory, antioxidant, and wound healing properties. Unfortunately, research on stingless bee honey has not been conducted systematically, so little information is available. A small number of reports have documented the beneficial effects of stingless bee honey in different contexts, such as antimicrobial, antioxidant, and cataract studies and anti-inflammatory activity. The information provided in this review makes clear the need for evaluation of the many potential biological and pharmacological activities of stingless bee honey, including in the treatment of diabetes, metabolic and neurological disorders, cancer, cardiovascular-disease-related complications and hypercholesterolemia and in wound healing.

Authors' contributions

PVR wrote the manuscript, drawn the structures of the compounds, KT contributed in the honey analytical part, tabulations, NS made contributions in correcting the manuscript, GSH has proofread the manuscript and given several inputs to improve the manuscript technically.

Conflicts of interest

The authors declare no conflicts of interest.

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