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Honey and its Anti-Inflammatory, Anti-Bacterial and Anti-Oxidant Properties

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Abstract

Honey mainly consists of sugars and water. Apart from sugars, honey also contains several vitamins, especially B complex and vitamin C, together with a lot of minerals. Some of the vitamins found in honey include ascorbic acid, pantothenic acid, niacin and riboflavin; while minerals such as calcium, copper, iron, magnesium, manganese, phosphorus, potassium and zinc are also present. Honey has been used for its healing, nutritional and therapeutic properties since ancient times. Its antibacterial potentials even against multi-drug resistant bacteria, such as *Staphylococcus aureus, Pseudomonas aeruginosa and Acinetobacterbaumanni* have been proved. Honey is well known for its anti-inflammatory and antioxidant capacities, which may be useful for the prevention of chronic inflammatory process like atherosclerosis, diabetes mellitus and cardiovascular diseases. The antibacterial, anti-inflammatory and antioxidant properties of honey will be reviewed here.

Keywords: Honey; Inflammation; Anti-bacterial properties

Introduction

Honey mainly consists of sugars and water. Sugars in honey comprises predominantly of monosaccharides and oligosaccharides. The most abundant sugar in honey is fructose, while sugars in it are sweeter and give more energy than artificial sweeteners [1-3]. Apart from sugars, honey also contains several vitamins, especially B complex and vitamin C, together with a lot of minerals. Some of the vitamins found in honey include ascorbic acid, pantothenic acid, niacin and riboflavin; while minerals such as calcium, copper, iron, magnesium, manganese, phosphorus, potassium and zinc are also present [4]. Honey contains at least 181 constituents [2,5]. The other constituents of honey are amino acids, antibiotic-rich inhibine, proteins and phenol antioxidants [6]. It also contains other bioactive substances such as phenolic constituents, flavonoids, organic acids, carotenoid-derived compounds, nitric oxide (NO) metabolites, amino acids and proteins [7,8]. Evidence indicates that some varieties of honey contain kynurenic acid (a tryptophan metabolite with neuroactive activity) which may contribute to its antimicrobial properties [9]. The presence of enzymes such as glucose oxidase, diastase, invertase, phosphatase, catalase and peroxidase has also been documented in honey [10].

Anti-Bacterial and would Healing Activity

The medicinal importance of honey has been known since ancient times and its antimicrobial property as well as wound-healing activities was well-known long ago. The first written reference for honey was a Sumerian tablet writing dating back to 2100-2000 BC, which mentioned honey's use as a drug and an ointment. Aristotle (384-322 BC), when discussing different honeys, referred to pale honey as being "good as a salve for sore eyes and wounds" [11]. The healing property of honey is due to the fact that it offers anti-bacterial activity, maintains a moist wound condition, and its high viscosity helps to provide a protective barrier to prevent infection. Its immune-modulatory property is relevant to wound repair, too [12].

Nowadays, with the presence of multi-drug or pan-drug-resistant microbes, alternative anti-microbial strategies are urgently needed. This need has led to a re-evaluation of the therapeutic use of ancient remedies, such as plants and plant-based products, including honey [13-15]. The antimicrobial activity in most honeys is due to the enzymatic production of hydrogen peroxide [13]. However, another kind of honey, called non-peroxide honey (e.g. manuka honey), displays significant anti-bacterial effects even when the hydrogen peroxide activity is blocked. Its mechanism may be related to the low pH level of honey and its high sugar content (high osmolarity) that is enough to hinder the growth of microbes. Honey traditionally has an acidic pH, between 3.2 and 4.5, which is low to be inhibitory for many bacteria [15,16]. The anti-bacterial property of honey is also derived from the osmotic effect of its high sugar content and low moisture content, along with its acidic properties of gluconic acid and the antiseptic properties of its H_2O_2 [17]. A recent study examining the antimicrobial properties of honey *in vitro* found that H_2O_2, methylglyoxal and an antimicrobial peptide, bee defensin-1, are distinct mechanisms involved in the bactericidal activity of honey [18]. The medical grade honeys have potent *in vitro* bactericidal activity against antibiotic-resistant bacteria causing several life-threatening infections to humans. Nevertheless, there is a large variation in the antimicrobial activity of some natural honeys, which is due to temporal variation in sources of nectar. Thus, identification and characterization of the active principles may provide valuable information on the quality and possible therapeutic potential of honeys.

Currently, many researchers have reported the anti-bacterial activity of honey and found that natural unheated honey has some broad-spectrum antibacterial activity when tested against pathogenic bacteria, oral bacteria as well as food spoilage bacteria [12,19]. At present a number of honeys are sold with standardized levels of anti-bacterial activity. The *Leptospermum scoparium* honey, the best known of the honeys, has been reported to have an inhibitory effect on around 60 species of bacteria, including aerobes and anaerobes, gram-positives and gram-negatives [20]. Manuka honey is produced from the manuka bush (*Leptospermum scoparium*) indigenous to New Zealand and Australia. Exceptionally high concentrations of the anti-

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bacterial compound methylglyoxal have been found in manuka honey, but the exact contribution of this and possible other compounds to the bactericidal activity of manuka honey remains largely unknown [21,22]. In a report testing anti-bacterial activity of two different honeys, after 24 hours of incubation, both honeys killed all tested bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), but manuka honey retained activity up to higher dilutions than RS honey (unprocessed Revamil source usually from the Netherlands honey). Bee defensin-1 and H_2O_2 were the major factors involved in rapid bactericidal activity of RS honey. These factors were absent in manuka honey, but this honey contained 44-fold higher concentrations of methylglyoxal than RS honey. Methylglyoxal was a major bactericidal factor in manuka honey, but after neutralization of this compound, manuka honey retained bactericidal activity due to several unknown factors. RS and manuka honey have highly distinct compositions of bactericidal factors, resulting in large differences in bactericidal activity [23].

There are several reports that Tualang honey has variable broad-spectrum activities against many different kinds of gram positive and enteric bacteria [24-26]. Unlike glucose oxidase, the antibacterial properties from *Leptospermum* spp. honeys are light- and heat-stable. Natural honey of other sources can vary as much as 100-fold in the potency of their antibacterial activities, which is due to hydrogen peroxide. In addition, honey is hygroscopic, which means that it can draw moisture out of the environment and dehydrate bacteria, and its high sugar content and low level pH can also prevent the microbes from growth.

Most deaths in severely burn-injured patients are due to burn wound sepsis or complications due to inhalation injury. Currently, the emerging antimicrobial resistance trends in burn wound bacterial pathogens are a serious challenge [27]. Thus, honey with effective antimicrobial properties against antibiotic-resistant organisms such as MRSA (methicillin-resistastant *Staphylococcus aureus*), vancomycin-resistant *Enterococcus spp* (VRE) and multiple-resistant Gram-negative rods such as *Pseudomonas aeruginosa*, *Acinetobacter spp*. and members of the family *Enterobacteriaceae*, which have been associated with infections of burn wounds and sites of major thermal injury and in nosocomial infections, is much anticipated [28-30].

The honey has been used from ancient times as a method of accelerating wound healing. It's potential to assist with wound healing has been demonstrated repeatedly [31,32]. Honey is gaining acceptance as an agent for the treatment of ulcers, bed sores and other skin infections resulting from burns and wounds [33,34]. The healing properties of honey can be ascribed to the fact that it offers anti-bacterial activity, maintains a moist wound environment that promotes healing, and has a high viscosity which helps to provide a protective barrier to prevent infection [35]. There are many reports suggesting that honey is very effective as a dressing of wounds, burns, skin ulcers and inflammations; the anti-bacterial properties of honey speed up the growth of new tissue to help healing the wound [36]. The medihoney and manuka honey have been shown to have *in vivo* activity and are suitable for the treatment of ulcers, infected wounds and burns [37,38].

More specifically, the honey, when applied topically, rapidly clears wound infection to facilitate healing of deep surgical wounds with infection [39]. The application of honey can promote the healing in infected wounds that do not respond to the conventional therapy, (*i.e.*, antibiotics and antiseptics), including wounds infected with MRSA or multi-drug resistant *Pseudomonas aeruginosa* [40-43]. Moreover, it has been used on skin grafts and infected skin graft donor sites successfully [44]. The removal of exudate in wounds dressed with honey is of help in managing inflammatory wounds.

The manuka, jelly bush and pasture honeys are capable of stimulating the monocytes, the precursors of macrophages, to secrete TNF-α [29,45]. Also, glycosylated proteins in honey can induce TNF-α secretion by macrophages, and this cytokine is known to induce the mechanisms of inflammation, the formation of granulomatosus tissue and of wound repairing [46]. Thus, the immune-modulatory properties of honey, when topically applied, are relevant to wound repair.

The notion for using honey as a treatment regimen for peptic ulcers and gastritis comes from traditional folklore as well as from reports in modern times [11]. Honey may promote the repair of damaged intestinal mucosa, stimulate the growth of new tissues and work as an anti-inflammatory agent [37-39]. Manuka honey has been reported to exhibit antimicrobial activity against pathogenic bacteria *Helicobacter pylori* making this honey a promising functional food for the treatment of wounds or stomach ulcers [47].

Anti-Inflammatory Effects

As mentioned above, raw honey contains substantial amounts of compounds such as flavonoids and other polyphenols which may function as anti-oxidants [7,8].

In Malaysia, there are several types of honey, including Tualang, Nenas, Coconut, and Gelam. Among these, Tualang and Gelam honeys are well known in Malaysia for their potential health benefits, such as anti-oxidant and anti-inflammatory activities [48,49]. Mohamed et al. have shown that Tualang honey contains highly phenolic compounds that possess relatively good anti-oxidant activity. In an animal model, a topical dressing of Tualang honey showed a positive effect for treating full-thickness burn wounds [41,50,51]. As previously reported, Gelam honey has anti-oxidative and radical scavenging activities, which are mainly attributed to its phenolic content.

In a recent study, it has been reported that honey reduced the activities of cyclooxygenase-1 and cyclooxygenase-2, thus showing anti-inflammatory effects. Furthermore, ingestion of diluted natural honey has produced reductions on concentrations of prostaglandins such as PGE_2 (prostaglandin E_2), $PGF_{2\alpha}$ (prostaglandin $F_{2\alpha}$) and thromboxane B_2 in plasma of normal individuals [52]. Interestingly, in an inflammatory model of colitis, honey was as effective as prednisolone treatment [53]. While NSAIDS and corticosteroids may have many serious side effects, honey has an anti-inflammatory action free from major side effects.

Recently, Gelam honey has been demonstrated to decrease inflammatory mediators such as COX-2 and TNF-α via attenuating NF-κB translocation to the nucleus and thus inhibiting the activation of the NF-κB pathway [54]. It is widely known that the activation of NF-κB plays a key role in the pathogenesis of inflammation [55,56]. Therefore, Gelam honey has just been documented to inhibit the inflammatory process by inhibiting NF-κB pathway.

Anti-Oxidant Activity of Honey

Natural honey contains many flavonoids (such as apigenin, pinocembrin, kaempferol, quercetin, galangin, chrysin and hesperetin), phenolic acids (such as ellagic, caffeic, p-coumaric and ferulic acids), ascorbic acid, tocopherols, catalase, superoxide dismutase, reduced glutathione, Maillard reaction products and peptides, most of which work together to provide a synergistic antioxidant effect [57-59].

It is noteworthy that the botanical origin of honey has the greatest influence on its anti-oxidant activity, while processing, handling and storage affects its anti-oxidant capacity only to a minor degree [60-65]. The anti-oxidant activity has been shown to strongly correlate with the

content of total phenolics [66-70]. In addition, a strong correlation has been found between anti-oxidant activity and the color of honey. Many researchers have reported that dark honey has a higher total phenolic content and consequently a higher anti-oxidant capacity [71]. Blasa et al. have shown that the anti-oxidant activity is located in both the ether and the water fractions, indicating that the flavonoids of honey may be available to various compartments of the human body, where they may exert different physiological effects [67,72].

The presence of free radicals and reactive oxygen species (ROS) is of the outmost importance in the process of cellular dysfunction, pathogenesis of metabolic and cardiovascular diseases as well as aging. The consumption of foods and substances rich in anti-oxidants may protect against these pathological changes and consequently prevent the pathogenesis of chronic inflammatory disorders. Researches have reported that honey contains several important substances and these include mainly anti-oxidants [73,74]. The qualitative and quantitative composition of honey (including the anti-oxidants constituent and the other phytochemical substances) is a reflection of the floral source as well as the variety of the particular honey [75]. In their analysis of the phytochemical composition of mono-floral Cuban honeys, Alvarez-Suarez et al. [71] have concluded that Cuban honeys contain important phenolic, flavonoid and carotenoid concentrations with high substantial anti-oxidant capacity [72,76]. Researchers in California have also advocated the consumption of the anti-oxidants from foods such as honey highly-rich.

A report in which two buckwheat honey treatments were administered to 37 healthy human adults at the rate of 1.5 g/kg body weight, with corn syrup as control, has demonstrated increased ($p < 0.05$) plasma total-phenolic content and plasma anti-oxidant. This study has supported the notion that phenolic anti-oxidants from processed honey are bioavailable and that they increase the anti-oxidant activity of plasma. Therefore, they advocated for the substitution of honey in some foods as traditional sweetener for enhanced anti-oxidant defense system in healthy human adults [77].

It has been shown that honey intake ameliorates risk factors of metabolic and cardiovascular diseases in patients and healthy individuals at risk. Unlike refined sugars, diabetic patients can safely and harmlessly eat this natural and sweetest sugar (fructose)-containing product, natural honey. Recently, researchers have fed male and female rats with honey or sugar (golden syrup) supplemented diet for 12 weeks from 7 days of age to compare their metabolic response, and see if honey is protective against metabolic syndrome. In male rats, golden syrup has significantly increased ($p<0.05$) blood levels of metabolic substrates (glucose and triglycerides); and caused enhanced ($p<0.001$) visceral adiposity, hypercholesterolemia, hyper-insulinemia, hepatomegaly and fatty liver. These cardiovascular diseases and metabolic diseases' risk factors were not observed in the honey fed rats in this trial. They concluded that honey is cardio-protective, and its consumption may ameliorate risk factors of metabolic and cardiovascular diseases in patients and healthy individuals at risk. Unlike refined sugars, diabetic patients can safely and harmlessly eat this natural and sweetest sugar (fructose)-containing product, natural honey. These results confirmed the conclusion drawn from earlier study that substituting honey for refined carbohydrates was beneficial [78]. Earlier researches from other laboratories and clinical trials further affirmed the metabolic and cardiovascular health significance of eating honey by recording some health profiles. These were reduction in the plasma levels of risk factors which include total cholesterol, LDL-cholesterol, triglycerides,

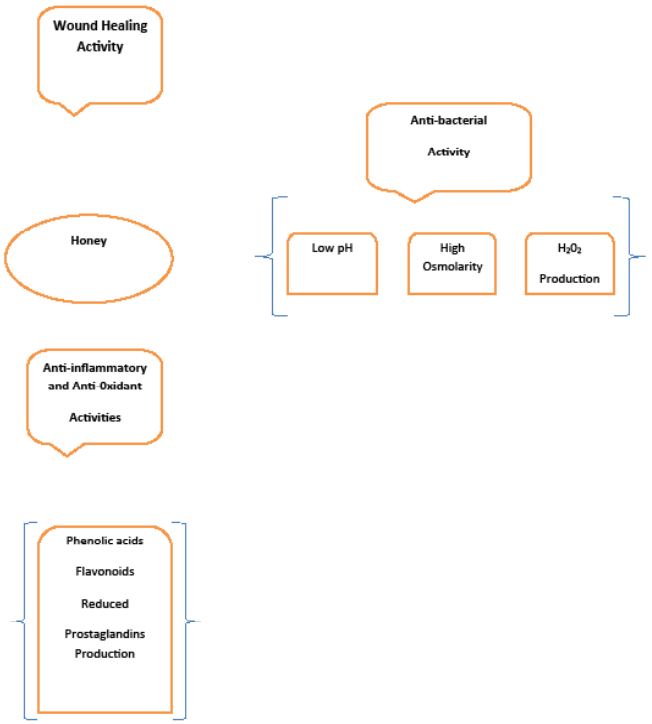

Figure 1: The anti-bacterial, anti-inflammatory, anti-oxidant and wound healing properties of Honey.

glucose in normal and diabetic patients, C-reactive protein, while the health indices elevated in the blood were HDL cholesterol [79-81]. Besides that, other researchers recorded higher plasma anti-oxidants levels in rats nurtured with natural honey relative to fructose-fed rats, and consequently low susceptibility of these subjects to cardiovascular diseases. Another study has demonstrated that the combination of glibenclamide or metformin with honey improves glycemic control, and provides additional metabolic benefits, not achieved with either glibenclamide or metformin alone in streptozocin-induced diabetic rats.

Conclusion

Honey mainly consists of sugars and water, but also contains several vitamins, especially B complex and vitamin C, together with a lot of minerals. Honey has been used for its healing, nutritional and therapeutic properties since ancient times. It possesses anti-bacterial, anti-inflammatory and anti-oxidant properties that may be beneficial for combating multi-drug resistant bacteria as well as for preventing chronic inflammatory processes, such as atherosclerosis and diabetes mellitus (Figure 1).

Teaching Points

Honey has antibacterial properties.Honey has wound healing activity.Honey possesses anti-oxidant and anti-inflammatory capacities, which may be useful in chronic inflammation process such as atherosclerosis and diabetes mellitus.

Conflicts of Interest

There are no conflicts of interest regarding this manuscript. Also, there was no funding. Ethical approval was not required.

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