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Review Paper

THERAPEUTIC PROPERTIES OF HONEY

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Abstract

Honey was mentioned as medicine by Shen Nang, since 2000 BC. It has been extensively used as healing agent throughout the human history in addition to its widespread usage as popular food. Honey used in various foods and beverages as a sweetener and flavoring. It also has a role in religion and symbolism. Flavors of honey vary based on the nectar source, and various types and grades of honey are available. It is also used in various medicinal traditions to treat ailments. The global prevalence of chronic diseases such as hypertension, diabetes mellitus, atherosclerosis, and cancer are on the rise. These diseases constitute the major causes of death globally. Honey is a natural substance with many medicinal properties such as antibacterial, hepatoprotective, hypoglycemic, reproductive, antihypertensive, anticancer and antioxidant.

Key words: Honey, Therapeutic properties, Antibacterial, Antioxidant, anticancer.

INTRODUCTION

Honey is a sweet food made by bees using nectar from flowers. Honey bees transform nectar into honey by a process of regurgitation and evaporation. They store it as a primary food source in wax honeycombs inside the beehive. Honey gets its sweetness from the monosaccharide's, fructose, and glucose, and has approximately the same relative sweetness as that of granulated sugar. It has attractive chemical properties for baking and a distinctive flavor that leads some people to prefer it over sugar and other sweeteners. Honey has a long history of human consumption and is used in various foods and beverages as a sweetener and flavoring. It also has a role in religion and symbolism. Flavors of honey vary based on the nectar source, and various types and

grades of honey are available. It is also used in various medicinal traditions to treat ailments. The health effects of honey have long been noted by humans. The nutritional and medicinal qualities of honey have been documented in Vedic, Greek, Roman, Christian, Islamic and other texts. Physicians of ancient times, such as Aristotle (384–322 BC), Aristoxenus (320 BC) Hippocrates, Porphyry, Cornelius Celsus (early first century AD) and Dioscorides (c. 50 AD), and Arab physicians have referred to the healing qualities of honey. Honey contains powerful antioxidants with antiseptic and antibacterial properties. Honey has been reported to contain about 200 substances. The composition of honey varies depending on the plants on which the bee feeds. Honey is composed primarily of fructose and glucose but also contains fructo-oligosaccharides and many amino acids, vitamins, minerals and enzymes [1 and 2]. However, almost all-natural honey contains flavonoids (such as apigenin, pinocembrin, kaempferol, quercetin, galangin, chrysin and hesperetin), phenolic acids (such as ellagic, caffeine, p-coumaric and ferulic acids), ascorbic acid, tocopherols, catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), Millard reaction products and peptides. Most of those compound work together to provide a synergistic antioxidant effect [3 and 4]. Honey has had a valued place in traditional medicine for centuries [5and 6]. However, it has limited use in modern medicine due to lack of scientific support [7]. For a long time, it has been observed that honey can be used to overcome liver, cardiovascular and gastrointestinal problems [8]. Ancient Egyptians, Assyrians, Chinese, Greeks and Romans employed honey for wounds and diseases of the intestine [9]. Since a few decades ago, honey was subjected to laboratory and clinical investigations by several research groups. The most remarkable discovery was the antibacterial activity of honey that has been mentioned in numerous studies [10]. Natural honey exhibits bactericidal activity against many organisms including *Salmonella*, *Shigella*, *Escherichia coli* [3 and 11]. *Helicobacter pylori* [6]. The healing properties of honey can be ascribed to the fact that it offers antibacterial activity, maintains a moist wound environment that promotes healing, and has a high viscosity which helps to provide a protective barrier to prevent infection [12]. Research has also indicated that honey may possess anti-inflammatory activity and stimulate immune responses within a wound [13 and 14] demonstrated anti-inflammatory effects of honey in human after ingestion of honey [15]. Honey, interestingly, has been shown to prevent reactive oxygen species (ROS)-induced low- density lipoprotein (LDL) oxidation in some *in vitro* studies, thus

exhibiting beneficial cardiovascular protection [16 and 17]. Honey also had antineoplastic activity in experimental bladder cancer [18]. This article has reviewed important the therapeutic properties of honey.

Therapeutic properties of Honey

Mechanisms of Antimicrobial Activity

Many of characteristics of honey contribute to its antimicrobial activity. The enzymatic glucose oxidation reaction and some of its physical properties are considered to be the major factors. Other factors include high osmotic pressure/low water activity (A_w), low pH/acidic environment, low protein content, high carbon to nitrogen ratio, low redox potential due to the high content of reducing sugars; a viscosity that limits dissolved oxygen and other chemical agents phytochemicals [19].

Antibacterial Activity:

Several studies are investigating the antimicrobial activity of honey. The antibacterial activity of honey is usually associated with the release of hydrogen peroxide, from the oxidation of glucose to glucolactone and then to gluconic acid in the presence of the enzyme glucose oxidase. This activity was called peroxide-activity and constitutes, at variable extent, the mode of action of some honey[20]. The use of honey as a traditional remedy for microbial infections dates back to ancient times (Table 1).

Diabetic Benefits

The honey has an intermediate glycemic index. In an experimental study, combination of Tualang honey with oral hypoglycemic agents resulted in an improvement of glycemic control. Not just this but also resulted in an improvement of lipid and renal profiles which indicates its synergistic effect to oral hypoglycemic agents. This can suggest that the combination of honey with oral hypoglycemic agents may be a valuable adjuvant therapy to achieve and/or maintain glycemic control and possibly reduce or delay the onset of diabetic complications [24]. FDA-approved Manuka honey product, Medi honey, has proven beneficial for healing foot ulcers in diabetic patients. Diabetics with foot ulcers that do not heal sometimes require foot amputation [25]. Voiced that honey is good for diabetics. This is unlikely to find confirmation because of its high sugar content. However, it is better than products made with cane sugar. It revealed that insulin levels were lower when compared to the uptake

of equal caloric values of other foods, but blood sugar level was equal or higher than in the other compared products shortly after eating [26]. Some tests were carried out to confirm that honey reduced effects of diabetes on animals. Where reported that honey produces a lower glycemic response in both diabetic and non-diabetic rabbits [27 and 28].

Table 1: List of bacteria that were found to be sensitive to honey [21, 22and 23].

Gram Positive Strains	Gram Negative Strains
Streptococcus pyogenes	*Stenotrophomonas maltophilia*
Coagulase negative staphylococci	*Acinetobacter baumannii*
Methicillin-Resistant *Staphylococcus aureus (*MRSA*)*	*Salmonella enterica* serovar *typhi*
Streptococcus agalactiae	*Pseudomonas aeruginosa*
Staphylococcus aureus	*Proteus mirabilis*
Coagulase-negative *Staphylococcus aureus (*CONS*)*	*Shigella flexneri*
Hemolytic streptococci	*Escherichia coli*
Enterococcus	*Enterobacter cloacae*
Streptococcus mutans	*Shigella sonnei*
Streptococcus sobrinus	*Salmonella typhi*
Actinomyces viscosus	*Klebsiella pneumonia*
Streptococcus faecalis	*Stenotrophomonas maltophilia*
Streptococcus pneumoniae	*Burkholderia cepacian*
Mycobacterium tuberculosis	*Helicobacter pylori*
Bacillus anthracis	*Campylobacter* spp.
Corynebacterium diphtheriae	*Porphyromonas gingivalis*

Glycemic Index of Sugar and Honey

The glycemic index (GI) is a measure of how carbohydrates deal with glucose in the blood. A carbohydrate with a low GI allows for only a small increase in blood glucose, while a carbohydrate with a high GI leads to a high blood glucose level. The average glycemic index for honey is 55 ±5 and this can be compared to the glycemic index of normal sugar, which is 68±5. Honey is a lower GI than sugar. Research has

shown that foods with a low GI, a small increase in blood glucose, may provide reduced risk of coronary heart disease and type 2 diabetes [29 and 30].

Gastrointestinal Effect

Honey shows promise for healing peptic ulcers caused by *Helicobacter pylori* bacteria, in the research cited by the University of Waikato in New Zealand. It is also effective against various strains of bacteria that cause gastroenteritis [25]. Honey has prebiotic effects: increasing the population of bacterial microflora important for the health of the gastrointestinal tract. According to Ustunol [31], the consumption of honey increases the population of normal flora called Bifidobacteria, where its constituents were found to pose a prebiotic effect that resembles the effect of fructo-oligosaccharides (FOS).

Osteoporosis and Arthritis

Honey showed its ability to increase bone density and restore osteoporotic bones in ovariectomized rats which could be attributed to the effect of gluconic acid and carbohydrate constituents of honey that may enhance calcium absorption in the bone of rats. Also, it could be due to kaempferol (flavonoids compounds in honey) which has osteogenic effect in ovariectomized rats [32]. Daily consumption of 20 mg/day of Tualang honey by postmenopausal women for four months produced a comparable result to the hormonal replacement therapy on bone density. Accordingly, Tualang honey with its antioxidant and anti-inflammatory activities can be used as an alternative therapy for postmenopausal osteoporosis with minimal side effects [32]. In a recent research done at the Copenhagen University, it was found that when the doctors treated their Arthritis patients with a mixture of one tablespoon honey and half teaspoon cinnamon powder before breakfast, they found that within a week out of the 200 people so treated practically 73 patients were totally relieved of pain and within a month, mostly all the who could not walk or move around because of arthritis started walking without pain [25].

Anti-inflammatory action and Wound Healing

Many studies have been done previously on different types of wounds to determine the effectiveness of honey in the healing process. Its effectiveness was clear

in full-thickness as well as partial-thickness wounds. Honey showed better results than hydrofibre silver and aquacel plain dressings in full-thickness burn wounds, both in wound size reduction and efficacy of healing [33]. It also limits the growth of partial-thickness wounds infected with *Pseudomonas aeruginosa, Acinetobacter baumanii* or *Klebsiella pneumonia* [33]. In addition to its significant results in controlling of *Pseudomonas aeruginosa*-infected wounds [34], and in the treatment of diabetic foot in patients suffer from diabetes [35]. Another study mentioned that the time taken for the complete repair of the wound (superficial burns) created by red hot pins was much less when honey was applied to it as compared to sucrose of same composition [36]. It is also mentioned that the infection experiment procedure was with additional artificial infection created by injecting *Staphylococcus aureus* two days before wounding. The wounds thereafter were dressed with honey, ampicillin ointment and saline as control. Results revealed that honey demonstrated the fastest rate of healing as compared to the other treatments and control [14].

Immune System

A study for Molan, it has been suggested that the consumption of honey can exert several beneficial effects on the human immune response and its associated mechanisms. Honey has been reported to promote the multiplication of human peripheral blood B- and T-lymphocytes and the activation of neutrophils under conditions of cell culture [37]. In monocytic cell line culture, honey has been shown to stimulate the release of inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1β and interleukin-6 [38], which are involved in triggering many functions of the immune response to infection [39]. Moreover, in mice, it has been found that the intake of a honey-supplemented diet stimulates the production of antibodies during the primary and secondary immune responses against thymus-dependent and -independent antigens [10].

Antioxidant properties

Unlike synthetic compounds, honey represents a natural product that does not carry side effects which can be harmful to health. Among the compounds found in honey; vitamin C, phenol compounds, catalase, peroxides, glucose oxidase enzymes have antioxidant properties [40]. Various polyphenols are reported in honey. Some of the

polyphenols of honey like Caffeic acid, Caffeic acid phenyl ester, Chrysin, Galangin, Quercetin, Acacetin, Kaempferol, Pinocembrin, Pinobanksin and Apigenin have evolved as promising pharmacological agents in the treatment of cancer [41]. It was also observed that administration of honey with alcohol prevent to great extent the lesions caused by only chronic alcohol administration [42]. Honey also contains flavonoids and carotinoids. High levels of these indicators ensure a high level of antioxidants in honey. Antioxidant properties of honey act as an antidepressant during high emotional, physical and intellectual stress [43].

Reproductive and fertility benefits

Honey can protect against vaginal epithelial atrophy and uterine atrophy in ovariectomised rats (the animal model of menopause) [44]. It also can reduce testicular damage by reducing lipid peroxidation in rats exposed to oxidant cigar smoke, and it has a protective effect against cigar smoke-induced abnormal sperm parameters [45]. Besides, honey showed clinically its ability to improve sperm concentration, motility, and morphology among oligospermic males [46]. Honey has a marked role in reduction of Bisphenol A (BPA)-induced ovarian toxicity in prepubertal rat through decreasing follicular morphological abnormalities in the ovary and improving the normal estrous cycle [47]. Many data suggested that honey may protect or ameliorate CS-induced testicular damage in rats via its antioxidant effect. The authors in one of their previous studies also reported that honey supplementation in normal rats improved Spermatogenesis [45]. A recent study also demonstrated the beneficial effects of honey on sperm motility and morphology in rats [48]. A study by Abdul-Ghani and colleagues also indicated that honey supplementation in rats caused increased epididymal sperm count and improved the activity of testicular marker enzymes for spermatogenesis, as evidenced by increased sorbitol dehydrogenase and reduced lactate dehydrogenase [49]. Available data in ovariectomised female rats also suggest that honey may produce beneficial effects in female reproductive organs [44]. A similar beneficial effect of honey on oxidative stress was also reported in human subjects. A study investigated the effects of 8-week honey supplementation on seminal plasma cytokines, oxidative stress and antioxidants in male road cyclists during intensive cycling training. The study found that honey supplementation significantly increased the concentrations of seminal SOD, CAT and TAS. This antioxidant effect of honey was also associated with lower elevations in

the seminal IL-1beta, IL-6, IL-8, TNF-alpha, ROS and MDA levels [50]. Another study on mice the results showed significant ($P<0.05$) increase in oocyte maturation, fertilization by *in vitro* fertilization (IVF) and cleavage of the oocyte by IVF between the three groups. Also, there is a significant increase in sperms motility. Decreased percentage of dead sperms between control and treated in two different doses i.e. 1.2 and 1.8 g/kg body weight for 35 days groups and a significant decrease in abnormalities of sperms in mice between the three groups [51]. A preliminary clinical study was conducted involving post-menopausal women aged 45 to 65 years. Hundreds healthy post-menopausal women were given 20 g/day of Tualang honey and followed up for 6 months. The results showed that there were significant changes in the diastolic blood pressure, serum total cholesterol and LDL levels between the two groups after 6 months. Other clinical findings and laboratory investigations were not significant. Honey cocktail has slightly better effects than Tualang Honey in improving the physiological profile of post-menopausal women [52].

Cancer

Generally, evidence from cell culture and animal studies look promising for honey in terms of chemo prevention, as well as an adjunct therapy to cancer drugs. Studies have demonstrated that phenolics sourced from honey are bioavailable in humans [53], however, it remains to be seen whether the concentration achieved in blood is sufficient to intercept the cancer processes *in vivo*. Findings from the *in vitro* and *in vivo* animal studies mentioned suggest a positive impact of honey on several aspects of cancer. There are, however, several modifiers of metastasis which are yet to be studied for the effects of honey. For example, cancer-associated fibroblasts play an important role in tumour progression; honey has been shown to increase their proliferation during wound healing and was also reported to protect from radiation-induced damage to human diploid fibroblasts [54]. Therefore, further studies should examine the effects of honey on cancer-associated fibroblasts. The effect of honey on extracellular-degrading proteases i.e., matrix metalloproteinases, of which fibroblasts are an important source, has not been studied extensively to date. Honey's effects on the growth signaling pathways and on the invasive properties of cancer cells are also under-researched areas. Direct injection of honey into a tumour appears to be an attractive option, however, further research is needed to evaluate the overall effectiveness of this

approach. Although cancer cells feed on sugars, the high sugar content of honey, if injected directly into the tumour site, may influence the tumour stroma through the osmolarity effect. It would also be interesting to examine if such an approach could prevent neoplastic lesions from becoming invasive, as well as to measure the length of time during which these effects are sustained after treatment. Therefore, further mechanistic studies are needed to verify the anticancer potential of honey before recommendations for its use in clinical trials can be made [55].

Hepatoprotective effect

Honey supplementation in STZ-induced diabetic rats reduced elevated levels of AST, ALT and ALP. These data suggested that besides its antidiabetic and antioxidant effects, honey also produced a hepatoprotective effect in STZ-induced diabetic rats. In addition, it may be suggested that co-administration of honey with other therapeutic agents may be effective in minimizing the side effects of synthetic drugs. The actual mechanisms by which honey reduced elevated serum levels of liver enzymes in STZ-induced diabetic rats remain unclear [24]. The beneficial effects of antioxidants in ameliorating oxidative stress and suppressing or reducing elevated blood pressure in experimental and clinical studies further corroborate the role of oxidative stress in hypertension [56]. The combination of diabetes mellitus and hypertension is associated with increased cardiovascular risk factors [57]. Besides other factors, evidence suggests that diabetes mellitus may exacerbate hypertension via increased oxidative stress [58] also study revealed that the antioxidant effect of honey resulted in further reductions in blood pressure of diabetic SHR but not of diabetic [24]. Generally, antioxidant and hepatoprotective properties correlate well with each other, as decreasing harmful radicals will protect the liver from them. The amelioration of oxidative stress, as a result of honey administration, was accompanied by significant reductions in the size of enlarged hepatocytes and edema, restoration of bile canal iculidilatation and reduced number of apoptotic cells [59]. Similar hepatoprotective effect of honey was also reported in rats with obstruction of the common bile duct [60]. Honey can be used as an effective hepatoprotective agent against paracetamol-induced liver damage [61].

Cardioprotective effects

In an experimental study, honey prevented the development of myocardial infarction induced by soproterenol which appeared clearly by normal level of cardiac enzymes and normal histology of honey treated group in comparison to soproternol treated group. Furthermore, honey improved levels of antioxidant enzymes levels in cardiac muscle and reduced lipid peroxidation. The cardioprotective effect of honey against soproterenol-induced oxidative stress is through its contribution to endogenous antioxidant enzymes via inhibition of lipid peroxidation [62]. Honey ingestion improves experimental heart weaknesses as extrasystoles, arrhythmia and tachicardia of rats [63].

Analgesic action

Pain soothing action can come into being by direct anti-inflammatory action and by action on the brain. The analgesic action of honey has been shown to be due to the anti-inflammatory action but also to an action on the brain via the opioid system, due possibly to honey flavonoids [64].

Links to other diseases

In a review by Erejuwa et al., the antioxidant properties of honey are reviewed and honey is praised as a "novel antioxidant". This review presents findings that indicate honey may ameliorate oxidative stress in the gastrointestinal tract (GIT), liver, pancreas, kidney, reproductive organs and plasma/serum. Besides, the review highlights data that demonstrate the synergistic antioxidant effect of honey and antidiabetic drugs in the pancreas, kidney and serum of diabetic rats. This is strengthened by the finding that honey potentiates the antioxidant effects of herbs [65 and 66]. These data suggest that honey, administered alone or in combination with conventional therapy, might be a novel antioxidant in the management of chronic diseases commonly associated with oxidative stress. In view of the fact that the majority of these data emanate from animal studies, there is an urgent need to investigate this antioxidant effect of honey in human subjects with chronic or degenerative diseases. The authors go on to suggest that honey might be the better antioxidant than accepted antioxidants such as vitamin C and E, as the latter act also as oxidants [66].

CONCLUSION

Honey has antibacterial and antioxidants activities, antidiabetic activities, antiproliferative and antineoplastic activities and wound healing properties. It restores osteoporotic bones. Honey has beneficial effects on the Immune system and reproductive systems. Furthermore, it has hepatoprotective, cardioprotective, and cancer activities.

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