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Review Article

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Honey between Traditional Uses and Recent Medicine

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Abstract

From ancient times, honey was not only used as a natural sweetener but also as a healing agent. Many health-promoting and curative properties attributed to it are the basis for some traditional folk medicine treatments throughout the world today.

Its beneficial effects in different disorders, rediscovered in recent decades , varying from its antibacterial effects and benefits in wound healing to its safe role in peptic ulcer, gastroenteritis, oncology, ophthalmology, dermatology and dental hygiene. This will be discussed in this review on the basis of a series of scientific studies conducted to investigate the therapeutic properties of this natural product.

Introduction

During the past decade there has been a worldwide increase in the use of traditional and complementary or natural systems of medicine [1-3]. Concomitant with this public interest has been a renewed interest in these therapies from both the scientific and medical communities. Whereas to date most research has focused on herbal and aromatherapy products, a number of other products show therapeutic promise. One such resource is honey.

Honey is a collection of nectar from many plantsprocessed by honey bees. This natural product is well known for its high nutritional and prophylactic medicinal value. Apitherapy (the medical use of honey bee products) has recently become the focus of attention as a form of folk and preventive medicine for treating certain conditions and diseases, as well as promoting overall health and well being [4].

There has been a renaissance in the usage of honey as a medicine in more recent times. It is widely available in most communities and although the

mechanism of action of several of its properties remains obscure and needs further investigation, the time has now come for conventional medicine to lift the blinds off this 'traditional remedy' and gives it its due recognition."

This review will analyse the therapeutic uses of honey as a folklore remedy and its recent uses.

Honey in history

Honey has had a valued place in traditional medicine for centuries. The prescription for a standard wound salve discovered in the Smith papyrus (an Egyptian text dating from between 2600 and 2200 BC) calls for a mixture of mrht (grease), byt (honey) and ftt (lint/fibre) as transliterated from hieroglyphic symbols [4].

The ancient Egyptians, Assyrians, Chinese, Greeks and Romans employed honey for wounds and diseases of the gut. Honey was the most popular Egyptian drug being mentioned 500 times in 900 remedies'. Whilst Hippocrates (3rd and 4th centuries BC) made little use of drugs in treatment he prescribed a simple diet, favouring honey given as oxymel (vinegar and honey) for pain, hydromel (water and honey) for 'thirst', and a mixture of honey, water and various medicinal substances for acute fevers [5]. During the Biblical era honey received religious endorsement by both Christianity and Islam. The holy Qur'an vividly illustrates the potential therapeutic value of honey [6, 7]: "Thy Lord has inspired the Bees, to build their hives in hills, on trees and in man's habitations, from within their bodies comes a drink of varying colours, wherein is healing for mankind ,verily in this is a sign, for those who give thought." (Chapter 16 – Bee).

The usage of honey as a medicine has continued into present-day folk-medicine. In India lotus honey is said to be a panacea for eye diseases [8]. The ancient usage of honey for coughs and sore throats has also continued into the traditional medicine of modern times [9]. Other examples of current day usage of honey in folk medicine are: as a traditional therapy for infected leg ulcers in Ghana [10]; as a traditional therapy for earache in Nigeria [11]; as a traditional therapy in Mali for the topical treatment in measles to prevent corneal scarring [12]. Honey also has a traditional folklore usage for the treatment of gastric ulcers [13]. Recently, scientific support has emerged with a proliferation in publications on the successful therapeutic use of honey in several general medical and surgical conditions.

Varieties of honey

There are more than 300 honey varieties - which also mean different flavours. Some have stronger tastes than others , some are milder and more delicate. In general, honey that is light in colour has a mild flavour and the ones with a darker colour usually have strong flavour. Experienced honey tasters can easily tell the differences between different honey varieties, although for some people it can be hard to tell one variety from another.

The main reason for the large number of honey varieties is the different types of nectar source. Different honey varieties also mean different flavours and aroma. Bees visit many kinds of plants and flowers, getting different qualities of nectar from these flowers [4].

Examples of these varieties include: acaciaalfalfa- avocado-basswood- blueberry-buckwheatclover-eucalyptus – fireweed- heather-ironbarkleatherwood-linden-macadamia- manuka - neem-orangeblossom- pumpukin blossom- rainforest-red gum- sagetualang-jungle honey.

Composition of Honey

The precise composition of honey varies according to the plant species on which the bee forages, but the main constituents are the same in all honeys. The average composition of honey is given in Table 1.

Table 1: Average composition of honey.

Component	Average (%)
Moisture	17.2
Fructose	38.19
Glucose	31.28
Sucrose	1.31
Disaccharides, calculated as maltose	7.31
Higher sugars	1.5
Free acid as gluconic	0.43
Lactone as Gluconolactone	0.14
Total acid as gluconic	0.57
Ash	0.169
Nitrogen	0.041

Data was collected from 490 samples of US honey [14].

More than 95% of the solids in honey are carbohydrate, and sensitive analytical and separation techniques have revealed honey to be a highly complex mixture of sugars, most of which are in the immediately digestible form in the small intestine. In addition to those

named in Table 1, the following have been identified as constituents of honey: isomaltose, nigerose, turanose, maltulose [15]; kojibiose [16); alpha beta-trehalose, gentiobiose, laminaribiose [17]; maltotriose, 1-kestose, panose, isomaltosyl glucose, erlose, isomaltosyltriose, theanderose, centose, isopanose, isomaltosyltetraose and isomaltosylpentaose [18]. Many of these sugars are not found in nectar but are formed during the ripening and storage effects of bee enzymes and the acids of honey.

The predominant acid found in honey is gluconic acid. Its presence in all honey originates largely from the activity of glucose oxidase which the bees add at ripening [19] and to a lesser extent from the bacterial action which occurs [20]. The pH of honey ranges from 3.2 to 4.5. The mineral and vitamin content of honey is very low, 0.02 % of its weight. Honey also contains a number of amino acids, proline, phenyalanine and aspartic acid with a concentration of greater than 200 ppm [21].

The main enzymes found in honey which are derived from the hypopharyngeal glands of worker honeybees, are invertase (which inverts sucrose to glucose and fructose); glucose oxidase (which oxidises glucose to gluconic acid and hydrogen peroxide in the presence of water); and amylase (diastase), which breaks down starch. Other honey enzymes originate from plants as catalase (a regulator of glucose oxidase activity); acid phosphatase; and a small proportion of amylase.

The enzyme glucose oxidase is of considerable interest because its activity causes the production of hydrogen peroxide which not only stabilizes the ripening nectar against spoilage but has microbicidal action [22, 23].

Honey and other bee products, such as royal jelly and propolis may be used as functional foods because of their naturally high antioxidant potential. Apart from sugars, honey contains many minor components with antioxidant activity [24].

According to Aljadi and Kamaruddin [25], the antioxidant capacity of honey is due mainly to the phenolic compounds and flavonoids it contains (Table 2), and there is a high degree of correlation between these substances and the antioxidant capacity of honey, although a synergic action between several compounds cannot be discounted [26]. Propolis, which also shows antioxidant activity, contains amino acids, phenolic acids, flavonoids, terpenes, steroids, aldehydes, and ketones [27].

Table 2: Principal flavonoids present in honey.

Group	Compound
Flavonoles	Quercetin, kaempherol, galangin, fisetin
Flavanones	Pinocembrin, naringin, hesperidin
Flavones	Apigenin, acacetin, chrysin, luteolin

Source: Cushnie and Lamb (28) and Fiorani et al. [29].

Several researchers [30, 31] reported that the composition of honey and so its antioxidant capacity depends on several factors, such as the flower source of the nectar, season, and environmental factors, such as soil type and climate, genetic factors, and processing methods. In other words, the possible health related effects due to the antioxidant activity of honey may depend on its origin [32].

Healing properties of honey - mechanism of action

The exact mechanism of the anti-microbial effect of honey remains obscure. Low pH, osmotic disruption of pathogens and the presence of bactericidal substances, collectively called inhibine [32] may all play a part, in addition to antioxidant properties. As mentioned previously, the antioxidant activity of honey is basically due to the presence of phenolic compounds and flavonoids, although the exact antioxidant action mechanism is unknown. Among the mechanisms proposed are free radical sequestrations, hydrogen donation, metallic ion chelation, or their acting as substrate for radicals such as superoxide and hydroxyl [30]. These biophenols may also interfere with propagation reactions [33] , or inhibit the enzymatic systems involved in initiation reactions [34].

The following are some examples of recent uses of honey:

Wound healing properties

It was found that, dry dressings adhere to the surface, causing pain and injure the granulating surface every time they are changed. Oily dressings prevent the surface secretions from escaping freely and may cause them to spread onto the neighbouring skin surfaces and cause undesirable reactions or toxic effects.

Conversely, honey is an effective treatment of wounds because it is non-irritating, non-toxic, self sterile, bactericidal, nutritive, easily applied and more comfortable than other dressings [35]. The treatment of wounds with honey has rendered them bacteriologically sterile within 7-10 days of the start of the treatment and

promoted healthy granulation of tissue [36]. Patients suffering from wound breakdown after operation for carcinoma of the vulva were treated by pouring honey into the wounds twice daily. The wounds became bacteriologically sterile within 3-6 days and *in vitro* studies of bacteria cultured from the wounds showed that undiluted honey not only failed to sustain growth of the bacteria (*Proteus mirabilis, Ps. aeruginosa, E.coli, Streptococcus faecalis, Clostridium perfingens* and *S. aureus*), but actually killed them. The *in vitro* anti-fungal activity of honey has been also tested on *Candida albicans, C. pseudotropicalis, C. stellatoidea* and *C.tropicalis*. They were all found to be susceptible [37]. Generous soaking of wounds and abscess cavities with honey, sometimes using castor oil to facilitate dressing, was found to include the following advantages: first, cross-infection of wounds often encountered with conventional therapy, was prevented because honey forms a mechanical and/or chemical barrier to infectious agents; second, the acceptance of grafts was prompt, in contrast to the inconsistent acceptance of grafts following antibiotic application; and third, a shorter duration of treatment and therefore hospitalization. Honey was also found to be more effective as an antibacterial agent against several *Pseudomonas* and *Staphylococcus* strains than the antibiotic, gentamicin [38].

In an extensive review on the antibacterial activity of honey (39), it was suggested that honeys intended for therapeutic use, should be assayed for their antibacterial activity as a form of quality assurance. It is also recommended that honey is protected from light to prevent possible reduction of its antibacterial activity.

Antibacterial activity of honey

The antibacterial activity of honey was first recognized in 1892 [40]. Honey has been used as a medicine in many cultures for a long time. However, it has a limited use in medicine due to lack of scientific support [41]. It has been rediscovered by the medical profession and it is gaining acceptance as an antibacterial treatment of topical infections resulting from burns and wounds [42]. It is well established that honey inhibits a broad spectrum of bacterial species.

More recently, honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, Gram positives, and Gram negatives [43]. There are many reports of bactericidal as well as bacteriostatic activity of honey especially against bacteria, which have developed resistance to many antibiotics [44].

Honey has been reported to be effective in the healing of infected postoperative wounds [45]. The *in vitro* antimicrobial activity of honey was reported by Radwan et al. [46] and by Chute et al. [47], who observed that honey stopped the growth of *Salmonella* and *Escherichia coli*. Honey has been useful in the treatment of infected surgical wounds, burn wounds, and decubitus ulcers (bedsores) [48]. It maintains a moist wound environment that promotes healing, and its high viscosity helps to provide a protective barrier to prevent infection. Low concentrations of this known antiseptic are effective against infectious bacteria and promote wound healing mechanism [49] through stimulation and proliferation of peripheral blood lymphocytic and phagocytic activity. The mild acidity and low level hydrogen peroxide release assists both tissue repair and contributes to the antibacterial activity [50]. In addition to presence of defensin1; a protein present in honey that acts as natural antibiotic [51].

Respiratory tract infection

Manuka honey has well-documented antimicrobial and antifungal properties and is currently being used by physicians across the world for a wide variety of medical problems especially in the respiratory tract. Low pH, hydrogen peroxide generation, and the hyperosmolarity mechanisms of antimicrobial action are ubiquitous for all honeys. In addition, manuka honey has been shown to contain high concentrations of methylglyoxal (MGO), contributing the relatively superior antimicrobial activity of manuka honey compared to non-MGO honeys that can be effective in respiratory tract infection. In high concentrations, manuka honey is effective in killing *Staphylococcus aureus* biofilms in vitro. Lower concentrations of manuka honey, however, are desirable for clinical use as a topical rinse in chronic rhinosinusitis [52]. In addition, topical manuka honey application in allergic fungal rhinosinusitis, showed symptomatic benefits [53]. Honey may be considered as an effective antitussive in children [54].

Gastroenteritis

According to the Muslim holy book “The Holy Hadith”, dating back to the 8 th century AD the prophet Mohamed recommended honey against diarrhoea [55]. Also, the Roman physician Celsus (ca. 25 AD) used honey as a cure for diarrhoea [56]. The use of honey for prevention and treatments of gastro-intestinal disorders such as peptic ulcers, gastritis, gastroenteritis has been

reported in various books and publications from Eastern Europe [57,58] and from Arab countries [59].

Pure honey has bactericidal activity against many enteropathogenic organisms, including those of the *Salmonella* and *Shigella* species, and enteropathogenic *E. coli* [60]. *In vitro* studies of *Helicobacter pylori* isolates which cause gastritis have been shown to be inhibited by a 20% solution of honey.

Even isolates that exhibited a resistance to other antimicrobial agents were susceptible [61]. A clinical study of honey treatment in infantile gastroenteritis was reported by Haffejee & Moosa [62] and Abdelrahman et al. [63], they found that honey shorten the duration of diarrhoea in patients with bacterial gastroenteritis caused by organisms such as *Salmonella*, *Shigella* and *E. coli*. They recommended that honey was a safe substitute for glucose as long as it provided 111 mmol/l each of glucose and fructose. The high sugar content of honey means that it could be used to promote sodium and water absorption from the bowel.

Propolis (a product of honey bee) has positive effects on intestinal giardiasis, a parasitosis which affects mostly children [64]. In some studies on rats, the intake of honey was effective against the onset of colitis.It was assumed that honey plays an important role in preventing inflammatory tissues from producing free radicals [65]. As regards the gastrointestinal tract, the intake of honey helps treat *Helicobacter pylori* infections, particularly difficult to eradicate, by fighting the bacteria's tendency to develop resistance to antibiotics [66], which is the primary cause of treatment failure.

In addition, honey is a traditional treatment for dyspepsia, highly recommended by physicians based on professional experience, although no scientific evidence exists to support its efficacy. It has been discovered, however, that *Helicobacter pylori* is probably the agent that causes dyspepsia: this suggested that the therapeutic action of honey at the systemic level may be attributable to antibacterial properties [67].

Gastric ulcers

Clinical and animal studies have shown that honey reduces the secretion of gastric acid. Additionally, gastric ulcers have been successfully treated by the use of honey as a dietary supplement. An 80% recovery rate of 600 gastric ulcer patients treated with oral administration of honey has been reported [68].

Radiological examination showed that ulcers disappeared in 59% of patients receiving honey. Animal experiments have shown that the administration of a honey solution via a tube in the stomach of rabbits prior to them being administered with 0.5 g ethanol per kg body weight, accelerated alcoholic oxidation. An animal study [69] showed that honey administered subcutaneously or orally before oral administration of ethanol affords protection against gastric damage and reverses changes in pH induced by ethanol. A controlled clinical trial demonstrated the use of fructose in the treatment of acute alcoholic intoxication. A small but significant increase occurred in the rate of fall of blood-ethanol levels and it was concluded that fructose may be beneficial in shortening the duration of alcoholic intoxication [70].

Immune function

It has been reported that Manuka honey increased IL-1beta, IL-6, and TNF-alpha production from Mono Mac6 cells or human monocytes [71, 72], and the active component was 5.8 kDa, which increased production of these cytokines via TLR4 [73]. In addition, it was reported that oral intake of honey augmented antibody productions in primary and secondary immune responses against thymus-dependent and thymusindependent antigens [74]. The effects of Jungle honey on immune functions and antitumor activity were investigated in mice. It was found that this honey increased peritoneal cell numbers and ROS production, enhanced chemotaxis for neutrophil and IL-1beta mRNA expression in peritoneal cells and Inhibited LL/2 tumour growth [75].

Diabetes

There is a need for sweeteners in the diabetic diet to improve overall dietary compliance. Since fructose is absorbed more slowly from the gastrointestinal tract than glucose and is rapidly taken up by the liver, blood sugar levels rise only minimally after fructose ingestion [76]. Bornet *et al*. [77] demonstrated the sucrose or honey at breakfast have no additional acute hyperglycaemic effect over amount of bread in type II diabetic patients. In addition, a clinical study by Katsilambros *et al*. [78], indicated that honey could be a suitable sweetener for the type II diabetic diet as honey causes less hyperglycemia than sugar with the additional benefit of a lower glycemic value. It was found that tualang honey exerts a hypoglycemic effect and ameliorates oxidative stress in kidneys of streptozotocininduced diabetic rats [79]. Another study [80] suggested that hypoglycemic effect of tualang honey

in streptozotocin (STZ)-induced diabetic rats might be attributed to its antioxidative effect on the pancreas. Moreover, combination of honey with metformin or glibenclamide might offer additional antioxidant effect to these drugs. This might reduce oxidative stress-mediated damage in diabetic kidneys [81] or improves glycemic control, and provides additional metabolic benefits, not achieved with either glibenclamide or metformin alone [82].

Oncology

In oncology, honey has been used as a barrier against the implantation of tumours in laparoscopic oncological surgical procedures. In the same field, the intake of honey reduces chemotherapy-related neutropenia fever by alleviating pancytopenia, of which chemotherapy fever is a symptom [83]. A study by the University of Bonn showed that the use of special honeybased preparations may provide protection from hospital infections in immunodepressed children with leukaemia [83]. In a Russian study, the use of a food product (Honey Laminolact), containing milk ferments, amino acids, fruit pectines and honey that proved effective in protecting the gastrointestinal tract from radiotherapy in women with cancer uterus [84].

In clinical trials, the anti-cancer properties of honey have been tested in rats. Honey proved to be moderately effective against tumours and significantly effective against metastatic growths. It also enhanced the anti-cancer activity of 5-fluorouracile and cyclophosphamide [85].

Dental Hygiene

Honey is also recommended in dental hygiene. The use of honey chewing-gum three times a day after meals significantly reduces plaque and the risk of gingivitis. It also has therapeutic properties in the treatment of gingivitis and periodontal disorders [86]. In a study on 10 cases of dental infections, the local use of natural honey in dental abscesses and chronic osteomyelitis proved to have antibacterial effects [87].

Dermatology

In dermatology, the use of mixtures containing honey, olive oil and bee wax is very helpful in the treatment of dermatitis and psoriasis vulgaris, as well as seborrheic dermatitis and dandruff (provided the treatment is applied topically every day for at least four weeks), by combining antibacterial activity with antifungal and antioxidant effects [88].

Recent studies have revealed that tea tree oil (Melaleuca oil), honey, and cinnamic acid have antifungal activity against Malassezia species, which may be of benefit in the treatment of seborrheic dermatitis [89]. Chrysin (5,7-dihydroxyflavone), a natural flavonoid occurring in various plants and foods such as propolis and honey, reportedly opposes inflammation and carcinogenesis, but has rarely been applied in skin care. In a study aimed to explore the roles of chrysin in protection against UV-induced damage in keratinocytes, results showed that chrysin can attenuate apoptosis, reactive oxygen species (ROS) production, and cyclooxygenase 2 (COX-2) expression induced by UVB and UVA. Chrysin predominantly reversed the downregulation of aquaporin 3 (AQP-3) by UVB with efficient percutaneous absorption and no skin irritation and suggested to be used in skin photoprotection [90].

Majtan et al. [91] demonstrated that keratinocytes, which are known to be involved in wound healing, are responsible for elevated production of mediators including cytokines (TNF-alpha, IL-1beta and TGF-beta) and matrix metalloproteinase-9 (MMP-9) after incubation with honey. Also, the increased level of MMP-9 in the epidermis following incubation with honey led to degradation of type IV collagen in the basement membrane. These data demonstrated that honey activates keratinocytes and support the findings that honey may accelerate wound healing process.

The activities of honey dilutions were investigated against three species of Leishmania. The results were compared with the effects of the same concentrations of sugar. Honey and sugar both have anti-leishmanial effects in vitro, but honey is superior to sugar [92].

Ophthalmology

It was found that short term use of honey on intact corneas can be safe. Honey has anti-angiogenic and anti-inflammatory properties that can be explored in several corneal inflammatory and infectious conditions.

In a study of topical application of honey to injured corneas; results indicated faster epithelial healing, this was suggested to be due to decreased expression of transforming growth factor beta (TGF-beta), interferon gamma (IFN-gamma), interleukin 12 (IL-12) and tumour necrosis factor alpha (TNF-á) in injured corneas [93].

Another study using topical application of a WEP 1% (water extract of propolis) found that it has an inhibitory effect on CNV (corneal neovascularisation) in the rabbit's cornea. The inhibitory effect of propolis was

shown to be comparable to that of topical dexamethasone 0.1%, a potent inhibitor of angiogenesis. It was suggested that the effect of propolis may partially be due to its inhibitory effect on the activity of both cyclo-oxygenase and lipo-oxygenase [94].

In an experimental study of alkali chemical injury on rabbit's cornea , both topical and oral Tualang honey had almost the equal effects when compared with the conventional treatment regarding clinical inflammatory and histopathological inflammatory features, in addition to level of total antioxidant and lipid peroxidation products in the aqueous humour, vitreous humour and serum [95].

Honey was reported to be effective in bullous keratopathy [96] and in reducing total colony-forming units for the eyelids and the conjunctiva of dry eye subjects [97]. Also, honey may act as a prophylactic agent of endophthalmitis following eye surgery [98].

The flavonol quercetin, one of the flavonoids present in honey, could reduce the risk of cataract formation via affecting multiple pathways pertinent to eye lens opacification, including oxidative stress, nonenzymatic glycation, the polyol pathway, lens calpain proteases, and epithelial cell signalling [99]. Flavonoides could be of help in glaucoma too [100]. It was found that orally administered combination of flavonoids, C. asiatica, and Melilotus could be beneficial in preserving retinal sensitivity in diabetic cystoid macular oedema without macular thickening [101].

Conclusion

The above information shows that in microbiological and clinical tests, honey offers advantages in controlling bacterial growth and in the treatment of different health problems. The ease of administration for the treatment of wounds, the absence of antibiotic resistance as found with conventional antibiotics, the lack of side effects in alleviating gastric pain and shortening the duration of diarrhoea and safe role as sweetener in diabetes are all desirable features.

The promising effects in oncology, dermatology, ophthalmology and dental hygiene make honey not only a traditional therapy but still has a place in modern day society.

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