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### HONEY AS COMPLEMENTARY MEDICINE: - A REVIEW

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### ABSTRACT

Honey is a natural sweetener, but it is not just a sweetener it's a nature's gift to mankind. Natural honey has various ingredients in it, that contribute to its incredible properties. It's antimicrobial properties have attracted researchers towards itself and now we can find many research papers published on this topic. Honey is normally used in our daily life for treatment of hearing loss, bad breath, fatigue, weight loss, pimples, influenza, ingestion, heart diseases, toothache, hair loss, bladder infections, infertility etc. Honey is used as a mixture with many natural products such as lemon, clover, milk, cinnamon and water for treatment of various ailments and other health disorders. Beside this, honey is now used in various industries that exploit nature's wonderful gift (honey). Commercially honey is used as moisturizer, hair conditioner, laxative, aphrodisiac, rooting hormone, cleansers etc. Honey mixed with ground almonds makes an excellent facial cleansing scrub.

## KEYWORDS

honey, types, commercial applications, antimicrobial, medicine.

## 1. INTRODUCTION

Honey is the substance made when the nectar and sweet deposits from plants are gathered, modified and stored in the honeycomb by honey bees. The definition of honey stipulates a pure product that does not allow for the addition of any other substance. This includes, but is not limited to, water or other sweeteners.[1] Fructose and glucose are the main carbohydrate constituents of honey. Honey is composed primarily of the sugar glucose and fructose; its third greatest component is water. Honey also contains numerous other types of sugars, as well as acids, vitamins, proteins and minerals.[2,3] The pure honey contains alkaloids, auroquinone glycosides, cardiac glycosides, flavonoids & reducing Compounds.[4] Substituting honey with sugars in processed food can inhibit harmful and genotoxic effects of mycotoxins and improves the gut microflora.[5] The medicinal and antimicrobial properties of honey in relation to wound treatment has been recognised for approximately 4500 years, where for instance, Prince Hal was treated with rose honey by John Bradmore, a London surgeon.[6] 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. [7] 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'[8,9]

### 2. Types:

- (i) Manuka honey,
- (ii) Pasture honey,
- (iii) Jelly bush honey,

- (iv) Jungle honey,
- (v) Chestnut honey,
- (vi) Rhododendron honey,
- (vii) Blossom honey.[10]

These varieties are due to components of the flower sources.[11] The overall amino acid profile did not enable the botanical origin of honey samples to be distinguished as a rather high variation among honeys from the same botanical source and between honey types from different floral origin was found. It was observed that all the samples contained sulphate and oxalate, and that differences of medium values between the honeydew and floral honeys group were significant. Anion analysis could allow the distinction of honeydew from floral honeys in combination with results of other physicochemical parameters.[12] The medical and nutritional properties of honey depend on its chemical composition. The chemical composition of honey varies depending on the plant source, season, and production methods.[10]

### 3. Physical aspects:

**i) Sensitivity to heat:** The loss of antibacterial activity on exposure of honey to heat was of complete loss of inhibition by 17% honey after exposure of 50% honey to 100°C for 5 min, 80°C for 10 min, or 56°C for 30 min.[13]

**(ii) Sensitivity to light:** Honey lost its ability to inhibit bacterial growth (tested in a 17% solution) after exposing a thin film of it to sunlight and it is confirmed that exposure of honey in a layer 1-2 mm thick to sunlight for 15 min was found to result in complete loss of non-osmotic activity[14]

**(iii) Storage effect:** Enzymatic activity, antimicrobial properties, microbial quality, color

and chemical composition are all influenced by heat and storage.[15]

#### **4. Microbiological aspects:**

##### **Antimicrobial activity**

The antibacterial effect of honey, mostly against gram-positive bacteria, both bacteriostatic and bactericidal effects have been reported, against many strains, many of which are pathogenic. Honey glucose oxidase produces the antibacterial agent hydrogen peroxide, while another enzyme, catalase breaks it down. Honey with a high catalase activity has a low antibacterial peroxide activity. Honey has both peroxide and non peroxide antibacterial action, with different non-peroxide antibacterial substances involved: acidic, basic or neutral (Bogdanov, 1997). Antimicrobial effect of honey is thus due to different substances e.g. aromatic acids (Russell et al., 1988) and compounds with different chemical properties (Dustmann, 1978; Dustmann, 1979; Bogdanov, 1997) and depends on the botanical origin of honey (Molan, 1992a; Molan, 1992b; Bogdanov, 1997; Molan, 1997). The high sugar concentration of honey (Mundo et al., 2004), and also the low honey pH (Yatsunami and Echigo, 1984) is also responsible for the antibacterial activity. Most experiments report on stop of bacterial growth after a certain time of honey action. The higher the concentration the longer is the period of growth inhibition. Complete inhibition of growth is important for controlling infections (Molan, 1992b). Honey has also antiviral activity Rubella (Zeina et al., 1996), Herpes virus (Al-Waili, 2004). Honey has also fungicide activity against different dermatophytes (Molan, 1997). Honey has been shown to have a prebiotic effect, i.e. its ingestion stimulates the growth of healthy specific Bifidus and Lactobacillus bacteria in the gut. Sour-wood, alfalfa, sage and clover honeys have been shown to have prebiotic activity (Shin and Ustunol, 2005). The prebiotic activity of chestnut honey is bigger than that of acacia honey (Lucan et al., 2009). Oligosaccharides from honeydew honey have prebiotic activity

(Sanz et al., 2005). Theoretically honeydew honeys, containing more oligosaccharides should have a stronger prebiotic activity than blossom honeys.[16]

##### **(i) As antibacterial agent**

The antibacterial properties of honey includes, the release of low lives of hydrogen peroxide, some honey have an additional phytochemical antibacterial compounds. The antibacterial property of honey is also due to osmotic effect of its high sugar content as it has an osmolarity sufficient to inhibit the microbial growth. [17] Hydrogen peroxide was responsible for the antibacterial activity of honey since both the antibacterial activity of honey and hydrogen peroxide were destroyed by light.[18] White and Subers reported that hydrogen peroxidase which is produced by the glucose oxidase of honey could be the inhibitory substance against bacteria. However, it is known that honey as well as bacteria produce a catalase that eliminates hydrogen peroxide. But although catalase is active with high concentration of hydrogen peroxide, it is of low activity with physiological levels.[19] Lavie found an additional group of lightsensitive, heat-stable antibacterial factors in honey which inhibited the growth of *Bacillus subtilis*, *B. alvei*, *Escherichia coli*, *Pseudomona pyocyanes*, *Salmonella* and *Staphylococcus aureus*. [20]

A comparison was made by Cortopassi-Laurino and Gelli between the physico-chemical properties and antibacterial activity of honey produced by Africanized honey bees (*A. mellifera*) and Melliponinae (stingless bees) in Brasil. For both types of honey at a concentration of 5-25%, *Bacillus stearothermophilus* was found to be the most susceptible and *E. coli* the least susceptible of the seven bacterial isolates tested (the other five being, *B. subtilis*, *B. subtilis* Caron, *Staphylococcus*, *Klebsiella pneumoniae* and *Ps. aeruginosa*). *Melipona subnitida* honey produced from *Mimosa bimucronata* and *Plebia* species honey produced from *Borreria/Mimosa*

exhibited the greatest antibacterial activities [21] Antibacterial activities of the two honey samples, produced by the honeybee (*Apis mellifera*), were assayed using standard well diffusion method. Both honey samples were tested at four concentrations (5%, 25%, 50% and 100% w/v) against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Escherichia coli*. [22] There are many reports of bactericidal as well as bacteriostatic activity of honey and the antibacterial properties of honey may be particularly useful against bacteria, which have developed resistance to many antibiotics. [23]

#### **(ii) As antifungal agent**

The synergistic action of starch on the antifungal activity of honey, a comparative method of adding honey with and without starch to culture media was used. *Candida albicans* has been used to determine the minimum inhibitory concentration (MIC) of five varieties of honey. [24] The antifungal action of three single samples of South African honey (wasbessie, bluegum and fynbos) against *Candida albicans* and found honey to inhibit on the growth of *C. albicans*, while the control, bluegum and fynbos honey produced only partial inhibition. [25]

#### **(iii) As antiviral agent**

Honey had good anti-Rubella activity, while thyme did not. These results may justify the continuing use of honey in traditional medicines from different ethnic communities worldwide and in some modern medications such as cough syrups. [26]

### **5. Nutritional aspects.**

#### **(i) Carbohydrates**

The main sugars are the monosaccharides fructose and glucose. Additionally, about 25 different oligosaccharides have been detected [27, 28]. The principal oligosaccharides in blossom honey are the disaccharides sucrose, maltose, trehalose and turanose, as well as some nutritionally relevant ones such as

panose, 1-kestose, 6-kestose and palatinose. The amount of glucose, fructose and sucrose in % present in honey is 30.31[29], 38.38[29] and 1.31[29] respectively and amount of Reducing Sugars in %- 76.75[30]. Compared to blossom honey honeydew honey contains higher amounts of the oligosaccharides melezitose and raffinose. In the process of digestion after honey intake the principal carbohydrates fructose and glucose are quickly transported into the blood and can be utilized for energy requirements by the human body. A daily dose of 20 g honey will cover about 3% of the required daily energy.

#### **(ii) Proteins, Enzymes and Amino Acids**

Honey contains roughly 0.5% proteins, mainly enzymes and free amino acids. The contribution of that fraction to human protein intake is marginal. The three main honey enzymes are diastase (amylase), decomposing starch or glycogen into smaller sugar units, invertase (sucrase,  $\alpha$ -glucosidase), decomposing sucrose into fructose and glucose, as well as glucose oxidase, producing hydrogen peroxide and gluconic acid from glucose. The amount of True Protein, mg/100g. 168.6[31]

#### **(iii) Vitamins, Minerals And Trace Compounds.**

The amount of vitamins and minerals is small and the contribution of honey to the recommended daily intake (RDI) of the different trace substances is marginal. It is known that different unifloral honeys contain varying amounts of minerals and trace elements [32]. From the nutritional point of view chromium, manganese and selenium are important, especially for 1 to 15 years old children. The elements sulphur, boron, cobalt, fluoride, iodide, molybdenum and silicon can be important in human nutrition too, although there are no RDI values proposed for these elements. [33-42]. Honey contains 0.3–25 mg/kg choline and 0.06 to 5 mg/kg acetylcholine [41]. Choline is essential for cardiovascular and brain function as well as for cellular membrane composition

and repair, while acetylcholine acts as a neurotransmitter.

#### **(iv) Aroma Compounds, Taste-Building Compounds and Polyphenols**

There is a wide variety of honeys with different tastes and colours, depending on their botanical origin [42]. The sugars are the main taste-building compounds. Generally, honey with a high fructose content (e.g. acacia) are sweeter compared to those with high glucose concentration (e.g. rape). The honey aroma depends also on the quantity and type of acids and amino acids present. In the past decades extensive research on aroma compounds has been carried out and more than 500 different volatile compounds were identified in different types of honey. Indeed, most aroma building compounds vary in the different types of honey depending on its botanical origin [43]. Honey flavour is an important quality for its application in food industry and also a selection criterion for the consumer's choice.

Polyphenols are another important group of compounds with respect to the appearance and the functional properties of honey. 56 to 500 mg/kg total polyphenols were found in different honey types [44,45]. Polyphenols in honey are mainly flavonoids (e.g. quercetin, luteolin, kaempferol, apigenin, chrysin, galangin), phenolic acids and phenolic acid derivatives [46]. These are compounds known to have antioxidant properties. The main polyphenols are the flavonoids, their content can vary between 60 and 460  $\mu\text{g}/100\text{ g}$  of honey and was higher in samples produced during a dry season with high temperatures [47].

#### **6. Glycemic Index and Fructose**

The impact of carbohydrates on human health is discussed controversially, especially the understanding of how the carbohydrates of a given food affect the blood glucose level. Today, the dietary significance of carbohydrates is often indicated in terms of the glycemic index (GI). Carbohydrates with a low GI induce a

small increase of glucose in blood, while those with a high GI induce a high blood glucose level. The only comprehensive data on honey GI are the one presented in, based mainly on data of different Australian honeys [48, 49]. There is a significant negative correlation between fructose content and GI, probably due to the different fructose/glucose ratios of the honey types tested. It is known that unifloral honeys have varying fructose content and fructose/glucose ratios [50]. Some honeys, e.g. acacia and yellow box, with relatively high concentration of fructose, have a lower GI than other honey types. There was no significant correlation between GI and the other honey sugars. The GI values of 4 honeys found in one study varied between 69 and 74 [51], while in another one the value of a honey unidentified botanical origin was found to be 35 [52]. As the GI concept claims to predict the role of carbohydrates in the development of obesity [53], low GI honeys might be a valuable alternative to high GI sweeteners. In order to take into consideration the quantity of ingested food, a new term, the glycemic load, was introduced. It is calculated as follows: the GI value is multiplied by the carbohydrate content in a given portion and divided by 100. Values lower than 10 are considered low, between 10 and 20 are intermediate and above 20 belong to the category high. For an assumed honey portion of 25 g the glycemic load of most honey types is low and some types are in the intermediate range.

Glycemic Index (GI) and Glycemic Load (GL) for a Serving (25 g) of Honey. The GI concept was developed to provide a numeric classification of carbohydrate foods, assuming that such data are useful in situations where the glucose tolerance is impaired. Therefore, food with a low GI should provide benefits with respect to diabetes and to the reduction of coronary heart disease [54]. The consumption of honey types with a low GI, e.g. acacia honey might have beneficial physiological effects and could be used by type-2 diabetes patients. An



intake of 50 g honey of unspecified type by healthy people and diabetes patients led to smaller increases of blood insulin and glucose than the consumption of the same amounts of glucose or of a sugar mixture resembling to honey [55,56]. It was shown that consumption of honey has a favourable effect on diabetes patients, causing a significant decrease of plasma glucose [57–59]. Honey was well tolerated by patients with diabetes of unspecified type [60] and by diabetes type-2 patients [61-63]. According to recent studies, long term consumption of food with a high GI is a significant risk factor for type-2 diabetes patients [64]. However, the GI concept for the general population is still an object of discussions [65].

Fructose is the main sugar in most honey types. A surplus consumption of fructose in today's American diet, mainly in the form of high-fructose corn syrup, is suspected to be one of the main causes for overweight problems [66]. By reviewing clinical studies these authors found that fructose ingestion causes a rise of de-novo lipogenesis, which has an unfavourable effect on energy regulation and on body weight. In rat feeding experiments the hypertriglyceridemic effect observed after intake of fructose does not take place after feeding of honey [67]. Compared to rats fed with fructose, honey-fed rats had higher plasma  $\alpha$ -tocopherol levels, higher  $\alpha$ -tocopherol/triacylglycerol ratios, lower plasma NOx concentrations and a lower susceptibility of the heart to lipid peroxidation. These data suggest a potential nutritional benefit of substituting fructose by honey in the ingested diets. Ingestion of both honey (2 g/kg body weight) and fructose prevented the ethanol-induced transformation of erythrocytes in mice [68]. In humans faster recovery from ethanol intoxication after honey administration has been reported while a higher ethanol elimination rate has also been confirmed [69, 70].

## **7. Medicinal Aspects:**

### **(i) As remedy for diarrhea**

Infections of the intestinal tract are common throughout the world, affecting people of all ages. The infectious diarrhoea exacerbates nutritional deficiencies in various ways, but as in any infection, the calorific demand is increased. Pure honey has bactericidal activity against many enteropathogenic organisms, including those of the Salmonella and Shigella species, and enteropathogenic E. coli.[71] 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.[72] In a clinical study, the administration of a bland diet and 30 mL of honey three times a day was found to be an effective remedy in 66% of patients and offered relief to a further 17%, while anaemia was corrected in more than 50% of the patients.[73]

### **(ii) As Appetite Increaser**

Honey consumption delayed the postprandial ghrelin response ( $p=0.037$ ), enhanced the total PYY ( $p=0.007$ ) response, and blunted the glucose response ( $p=0.039$ ) compared with consumption of the sucrose-containing meal.[74]

### **(iii) As Medicine for Gastric Ulcers**

Gastric ulcers have been successfully treated by the use of honey as a dietary supplement.[75] Honey administered subcutaneously or orally before oral administration of ethanol affords protection against gastric damage and reverses changes in pH induced by ethanol.[76]

### **(iv) For wound healing**

Honey is an effective treatment of wounds because it is non-irritating, non-toxic, selfsterile, bactericidal, nutritive, easily applied and more

comfortable than other dressings.[77] 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.[78] Anti-fungal activity of Honey has been also tested on *Candida albicans*, *C. pseudotropicalis*, *C. stellatoidea* and *C. tropicalis* and all were found to be susceptible.[79]

Honey was also found to be more effective as an antibacterial agent against several *Pseudomonas* and *Staphylococcus* strains than the antibiotic, gentamicin.[80]

In a clinical study involving 59 patients with wounds and ulcers, most of which had failed to respond to conventional treatments, 15-30 ml fresh honey was applied daily. The bacteria isolated from 58 of these wounds (*E. coli*, *S. aureus*, *P. mirabilis*, mixed coliforms, *Klebsiella* species, and *S. faecalis*) were all susceptible to honey in vitro.

One other bacteria, *Ps. pyocyanea* did not undergo complete lysis in vitro tests but it was completely sterilised in vivo. In one case in which the patient had a Buruli ulcer infected with *Mycobacterium ulcerans*, honey treatment was ineffective and in vitro tests showed the mycobacteria to be resistant to honey.[81]

Honey has cleansing action of wounds, stimulates tissue regeneration, reduces inflammation and honey impregnated pads act as non adhesive tissue dressing.[82]

- **Rapid Healing Agent**

In several reports the rapidity of healing seen with honey dressings is noted. One report[83] refers to wounds becoming closed in a spectacular fashion in 90% of cases, sometimes in a few days. Another [84] refers to healing being surprisingly rapid, especially for first and second degree burns. Hejase has also noted the rapid healing changes when honey is applied to Fournier's gangrene [85]. Blomfield [86] is of the opinion that honey promotes healing of ulcers and burns better than any other local application used before. Clinical

observations made are that open wounds heal faster [87,88] and are ready faster for closure by stitching[87] when dressed with honey (than when dressed conventionally).

- **Stimulation of the healing process**

Some wounds, termed chronic wounds, may go for long periods, sometimes for years, without the healing process taking place. Leg ulcers and diabetic ulcers are a common examples of this type of wound. Honey has been found to be effective in starting the healing process in non-healing ulcers [89-95] some of which had been present for a median time of 1 year<sup>51</sup>, or had been treated for up to 2 years<sup>36</sup>, or had shown no healing over more than 5 years despite usual measures including skin grafts[96]. Honey has also been used successfully on chronic foot ulcers in lepers and diabetic foot ulcers[97].

- **Clearance of infection**

Honey is effective in clearing infection in wounds where other treatments have failed. One report gave the results of treating with honey dressings 47 patients with wounds and ulcers which had been treated for 1 month to 2 years with conventional therapy (including antibiotics) with no signs of healing, or the wounds were increasing in size[98].

- **Cleansing action on wounds**

Several authors have reported the cleansing effect of honey on wounds[86],[98],[90],[93],[99],[100],[101]. The standard procedure for the treatment of wounds is to surgically remove any dead tissue (i.e. debride the wound) which would serve to support the growth of infecting bacteria. Otherwise these would produce toxins which would kill more surrounding tissue. Debridement is a painful procedure that usually requires anaesthesia of some sort.

- **Stimulation of tissue regeneration**

When a wound heals the dead or damaged tissue it is replaced by the growth of new

connective tissue and a new outer layer of skin (epithelium) spreads over the surface of the wound.

- **Reduction of inflammation**

The inflammation of surrounding tissues that results from infection of a wound, or directly from the damage to tissues caused by burns, is the major cause of the pain and discomfort associated with wounds. The process of inflammation involves blood capillaries opening up and allowing plasma from the blood to flow out into the surrounding tissues. This causes swelling of the tissues (oedema), the pressure giving rise to damage and discomfort in the healing area. It also causes plasma to exude from open wounds, sometimes in large quantities.[102]

- (vi) **As medicine for canine recurrent dermatitis**

The antibacterial activity of honeydew honey and propolis was evaluated in vitro against *Staphylococcus aureus* strains isolated from canine patients with dermatitis and found that the honey showed bactericidal effects against the bacterial tested *S. aureus* stains, but was less efficient than the propolis at certain concentrations.[103]

- (vii) **As skin disinfectant**

Typical honeys are about eight times more potent against coagulase-negative staphylococci than if bacterial inhibition were due to their osmolarity alone. Therefore, honey applied to skin at the insertion points of medical devices may have a role in the treatment or prevention of infections by coagulase-negative staphylococci.[104]

- (viii) **As immune inducer**

It has been reported that Manuka honey increased IL-1 $\beta$ , IL-6, and TNF- $\alpha$  production from Mono Mac6 cells or human monocytes [105,106], and the active component was 5.8 kDa, which increased production of these

cytokines via TLR4 [107]. In addition, it was reported that oral intake of honey augmented antibody productions in primary and secondary immune responses against thymus-dependent and thymus-independent antigens [108].

- (ix) **As antioxidant**

Honey contains a variety of phytochemicals (as well as other substances such as organic acids, vitamins, and enzymes) that may serve as sources of dietary antioxidants (Gheldof and Engeseth 2002; Gheldof et al. 2002). The amount and type of these antioxidant compounds depends largely upon the floral source/ variety of the honey (Gheldof et al. 2002). In general, darker honeys have been shown to be higher in antioxidant content than lighter honeys (Gheldof et al. 2002). Researchers at the University of Illinois Champaign/Urbana examined the antioxidant content (using an assessment technique known as Oxygen Radical Absorbance Capacity or ORAC) of 14 unifl oral honeys compared to a sugar analogue. ORAC values for the honeys ranged from 3.0  $\mu\text{mol TE/g}$  for acacia honey to 17.0  $\mu\text{mol TE/g}$  for Illinois buckwheat honey. The sugar analogue displayed no antioxidant activity.[109]

Free radicals and reactive oxygen species (ROS) have been implicated in contributing to the processes of aging and disease. Humans protect themselves from these damaging compounds, in part, by absorbing antioxidants from high-antioxidant foods. This report describes the effects of consuming 1.5 g/kg body weight of corn syrup or buckwheat honey on the antioxidant and reducing capacities of plasma in healthy human adults. It can be speculated that these compounds may augment defenses against oxidative stress and that they might be able to protect humans from oxidative stress. Given that the average sweetener intake by humans is estimated to be in excess of 70 kg per year, the substitution of honey in some foods for traditional sweeteners could result in



an enhanced antioxidant defense system in healthy adults.[110]

Antioxidant properties shown by volatile oil of propolis (VOP) from India were investigated by spectrophotometric methods and a photochemiluminescence method and it was found that from IC50 values it could be concluded that the efficiency of scavenging ABTS radicals by the VOP was more pronounced as compared to scavenging other radicals.[111]

#### **(x) As anti-diabetic agent**

In the past, people with diabetes were advised to avoid “simple sugars” including honey. It was thought that consuming simple sugars would cause a sharp and rapid elevation in blood glucose levels and an overwhelming insulin demand. Some even speculated that eating simple sugars could cause diabetes, a notion that has not been supported by scientific research. In fact, research has shown that some complex carbohydrates raise blood glucose levels more significantly than certain simple sugars (see Glycemic Index). Both honey and sucrose have been shown to produce a lower glucose response than starchy foods such as white bread. Moreover, it has been shown that the total amount

of carbohydrate consumed is probably more important than the type of carbohydrate when it comes to blood sugar levels. Thus, experts agree that diabetics may include moderate amounts of “simple sugars” in a balanced diet. Honey compared with dextrose caused a significantly lower rise in plasma glucose levels in diabetic subjects. It also caused reduction of blood lipids, homocysteine levels and CRP (C reactive protein) levels in normal and hyperlipidemic subjects.[112]

#### **(xi) As treatment for arthritis**

Apparently also boron stimulates in a positive way, hormonal factors for both men and women, resulting in healthy bones. If this

hormonal balance is disturbed, it will lead to osteoarthritis and as honey contains boron, it's routinely consumption can avoid such problems.[113]

#### **(xii) Antimutagenic and antitumor activity**

Mutagenic substances act directly or indirectly by promoting mutations of the genetic structure. During the roasting and frying of food heterocyclic amines are formed, e.g. Trp-p-1 (3-Amino-1,4-dimethyl-5H-pyridol [4,3-b] indole). The antimutagenic activity of honeys from seven different floral sources (acacia, buckwheat, fireweed, soybean, tupelo and Christmas berry) against Trp-p-1 was tested by the Ames assay and compared to a sugar analogue as well as to individually tested simple sugars [114]. All honeys exhibited a significant inhibition of Trp-p-1 mutagenicity. Glucose and fructose were found to have a similar antimutagenic activity as honey. Nigerose, another sugar, present in honey [115,116] has an immunoprotective activity [117]. The anti-metastatic effect of honey and its possible mode of anti-tumor action was studied by the application of honey in spontaneous mammary carcinoma in methylcholanthrene-induced fibrosarcoma of CBA mice and in anaplastic colon adenocarcinoma of Y59 rats [118]. A statistically significant anti-metastatic effect was achieved by oral application of honey. These findings indicate that honey activates the immune system and honey ingestion may be advantageous with respect to cancer and metastasis prevention. In addition, it is postulated that honey given orally before tumour cell inoculation may have a decreased effect on tumour spreading. In another study of the same group the effect of honey on tumour growth, metastasising activity and induction of apoptosis and necrosis in murine tumour models (mammary and colon carcinoma) was investigated [119]. A pronounced antimetastatic effect was observed when honey was applied before tumour-cell inoculation (per oral 2 g kg<sup>-1</sup>

for mice or 1 g kg<sup>-1</sup> for rats, once a day for 10 consecutive days).

In another study the anti-tumour effect of honey against bladder cancer was examined in vitro and in vivo in mice [120]. According to these results honey is an effective agent for inhibiting the growth of different bladder cancer cell lines (T24, RT4, 253J and MBT-2) in vitro. It is also effective when administered intralesionally or orally in the MBT-2 bladder cancer implantation mice models.

#### **8. Reasons for its activity:**

**(i)** The first factor is the osmotic effect of honey. Honey is a saturated or super-saturated solution of a mixture of fructose and glucose sugars (84%), therefore, no fermentation occurs in honey. Inhibition by the osmotic (water-withdrawing) effect of dilute solutions of honey obviously depends on the species of bacteria (Molan, 1992a).

**(ii)** The second factor for the antimicrobial activity of honey is its acidity. The pH being between 3.2 and 4.5 is low enough to be inhibitory to many pathogens. However, if honey is diluted, especially by body fluids, the pH will not be low enough to effectively inhibit bacteria (Cooper et al., 2002; Molan, 1992b).

**(iii)** The third factor is the presence of hydrogen peroxide in honey. Hydrogen peroxide is produced enzymatically in honey by glucose oxidase enzyme secreted by bees into the nectar. Although, hydrogen peroxide has been used as an antiseptic (Turner, 1983), it is not now as popular because it causes inflammation and damage to tissues (Halliwell and Cross, 1994; Saissy et al., 1995; Watt et al., 2004). In honey, the enzyme found is activated by dilution and the peroxide produced is too mild to cause tissue injury, and yet has antimicrobial activity (Bang et al., 2003; Bunting, 2001; Orrù et al., 2010).

**(iv)** The fourth factor is the presence of antibacterial phytochemical components (Molan and Russel, 1988; Mavric et al., 2008; Yao et al., 2004; Halawani, 2006).

**(v)** The fifth factor is the presence of defensin-1, which was recently found to contribute in the antibacterial activity of honey (Kwakman et al., 2010).

**(vi)** The sixth factor in the in vivo antibacterial activity of honey is the induction of increased lymphocyte and phagocytic activity. Recent studies showed that the proliferation of peripheral blood B-lymphocytes and Tlymphocytes in cell culture is stimulated by honey at concentrations as low as 0.1% and phagocytes are activated by honey at concentrations as low as 0.1% (Abuharfeil et al., 1999). Honey at a concentration of 1% also stimulates monocytes in cell culture to release cytokines, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6, which activate the immune response to infection (Alvarez-Suarez et al., 2010; Tonks et al., 2001; Tonks et al., 2003).[121]

**(vii)** The seventh factor is the antibacterially active fraction of honey derived from the native New Zealand manuka tree, *Leptospermum scoparium* (Myrtaceae). This fraction consists of derivatives of benzoic acids, cinnamic acids and flavonoids, all of which have been identified previously in honeys which do not exhibit non-peroxide residual antibacterial activity. The flavonoids had not previously been identified in manuka honey. Furthermore, the flavonoids were different from those found in the leaves of manuka trees but were the same as those found in European honeys and propolis. While most of these phenolic products possess antibiotic activity, they do not individually or collectively account for the antibacterial activity of 'active' manuka honey. Essentially all of this activity is associated with the carbohydrate fraction of the honey.[122]

### **Raw vs processed honey:**

The antibacterial activity of raw and processed honey was carried out on the extracts of honey using solvents such as methanol, ethanol and ethyl acetate and compared it with the popular antibiotics. The inhibitory action of extracts of honey were evaluated against six bacterial strains, Gram-positive bacteria viz., *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus* and Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhi* by agar well diffusion method and it was found that raw honey has more antimicrobial activity than processed one.[123]

### **9. Reasons for variance:**

The water activity of honey varies relatively little, and is not of much importance in the antibacterial effect of the dilute solutions of honey used to study the antibacterial activity of honey. Although the acidity of honey varies considerably, this too is likely to be of little consequence when the honey is in dilute solution in nutrient broth for testing its effect on bacterial cultures, as the broth buffers the acidity. The major variations seen in overall antibacterial activity are due to variation in the level of hydrogen peroxide achieved, and in some cases to the level of non-peroxide factors. The latter was found to be responsible for much of the activity in honeys with high levels of antibacterial activity in a study of 64 samples[124]. The content of non-peroxide factors is obviously related to the floral source, and sometimes it can account for the major part of the antibacterial activity in a honey, as is found with manuka honey[125]. The level of hydrogen peroxide achieved can also be related to the floral source, as components from some floral sources can affect both the production and the destruction of hydrogen peroxide (discussed below). There is a dynamic equilibrium: the level of hydrogen peroxide depends upon the balance between the rate of its production and the rate of its destruction.

Hydrogen peroxide obviously must be degraded, or else full-strength honey would contain substantial amounts of it, and any dilution of honey would eventually achieve inhibitory levels. From the first work demonstrating that hydrogen peroxide is responsible for antibacterial activity in honey, it was realized that hydrogen peroxide is destroyed by components of honey. When testing *Staphylococcus aureus* for its susceptibility to added hydrogen peroxide, it was found that higher levels had to be added to achieve an inhibitory effect if honey was present'. Hydrogen peroxide was found to rapidly disappear when added to dilute honey, and, except in samples accumulating very high levels, the level of hydrogen peroxide accumulated from enzymatic action was seen to decline with time.[126]

Of the factors possibly involved in the destruction of hydrogen peroxide, an obvious component to consider was catalase. This enzyme had long been thought to be present in honey[127], and was unequivocally shown to be present by Scheparte in 1966. Catalase comes from the pollen and nectar of certain plants; more coming from the nectar[128] Honeys from some floral sources have been found to have very high levels of catalase, and these honeys accumulate low levels of hydrogen peroxide: the ones accumulating high levels of hydrogen peroxide had low levels of catalase[128,129] There was some deviation from the inverse correlation seen in these studies, but this could well have been the result of non-peroxide antibacterial factors giving higher levels of activity, or prior denaturation of glucose oxidase giving lower levels. The latter would probably have been the explanation for the group of honeys with low antibacterial activity and low catalase activity found in another study of 28 samples[130]. Excluding this group, in this study a highly significant inverse correlation was found between catalase activity and accumulation of hydrogen peroxide.

Not all the variation, however, in the destruction of hydrogen peroxide associated with floral sources is due to the plants contributing catalase to the honeys. It has been found that the disappearance of hydrogen peroxide added to honey occurs even if honey is boiled beforehand to inactivate the catalase, indicating that a chemical degradation is involved as well as the enzymatic destruction[131].

The floral source can influence the production as well as the destruction of hydrogen peroxide, thus affecting the balance between these and lowering the level of accumulation. Very large differences have been found between honeys from different floral sources in the thermal stability of their glucose oxidase content. A similar finding has been made in respect of the sensitivity of glucose oxidase to denaturation by light, a photosensitizing component responsible for the photo-oxidation of the enzyme being partially characterized in this study. Of course, the influence of these factors on the antibacterial activity depends on the degree of exposure of honey samples to heat and light before they are assayed, but it is likely that much of the variation seen in the antibacterial activity of honeys reflects the history of those honeys. The level of antibacterial activity in a honey has for a long time been taken as an indication of whether or not a honey has been subjected to heating in its processing, although with the realization that it depends on other factors as well, this measure is no longer recommended[132]. The agar diffusion assay demonstrated that Ulmo 90 honey had greater antibacterial activity against all MRSA isolates tested than manuka honey and similar activity against *E. coli* and *P. aeruginosa*. and unlike manuka honey, Ulmo 90 honey activity is largely due to hydrogen peroxide production[135]. Honey from different phytogeographic regions exhibited differential antimicrobial activity and susceptibility of yeasts to honey of either species was greater than that of bacteria.[136]

### ***Infection:***

Activity levels of four bee midgut proteolytic enzymes were measured in adult honey bees 3, 8, and 24 days after dosing with spores of *Nosema apis*. Trypsin and chymotrypsin activity levels were significantly lower in *N. apis*-dosed bees than in the controls at each time point. Elastase levels were significantly lower than controls in dosed bees examined at 8 and 24 days, but not at 3 days. Leucine aminopeptidase levels were lower in dosed bees at days 3 and 8, but not at day 24. In both the dosed and the control bees, levels of each of the four enzymes were significantly higher at days 3 and 8 than at day 24.[135]

### ***10. Commercial applications of honey:***

More than \$15 billion a year in U.S. crops are pollinated by bees, including apples, berries, cantaloupes, cucumbers, alfalfa, and almonds. U.S. honey bees also produce about \$150 million in honey annually. But fewer bees means the economy takes a hit: The global economic cost of bee decline, including lower crop yields and increased production costs, has been estimated at as high as \$5.7 billion per year.[136]

Honey has good nutritive value as it contains many fats, vitamins, minerals and various other components and it is used as food in different parts of the world. Honey has the capacity to serve as a natural food preservative. Research has demonstrated the potential for honey to reduce enzymatic browning in fruits and vegetables and prevent lipid oxidation in meats. Most of the antibacterial activity of the honeys occurs due to hydrogen peroxide generation. Other researchers have identified the flavonoids in honey, particularly caffeic acid and ferulic acid, as the most likely contributors. Honey can be used as laxative and it is shown that eating natural, unheated honey every day means you won't need a laxative.[137] The honey is used for increasing shelf-stability of a product containing peanut butter and honey.[138]



Honey has been commercially used in soaps, biscuits and other healthcare supplements. Dried honey products are now a days commonly used and are made by converting liquid honey through a drum/roller or spray-drying process. Other technologies such as microwave vacuum/freeze drying are also used. Dried honey is mixed with sweeteners: Corn syrup, high fructose corn syrup, maltodextrins, non-nutritive sweeteners, sugar, sugar syrup and processing aids, drying aids, bulking agents, anti-caking agents: Calcium stearate, bran, dextrins, lecithin, soy flour, wheat starch. The role of honey in quality improvement of oil-free potato chips.[138]

### **11. Harmful effects of honey:**

Honey usually contains yeasts and bacteria in it, that can lead to various diseases such as botulism. Total plate counts from honey samples vary from zero to tens of thousands per gram for no apparent reason. Most samples of honey contain detectable levels of yeasts. Although yeast counts in many honey samples are below 100 colony forming units per gram (cfu/g), yeasts can grow in honey to very high numbers. Standard industry practices control yeast growth. Bacterial spores, particularly those in the *Bacillus* genus, are regularly found in honey. The spores of *C. botulinum* are found in a fraction of the honey samples tested normally at low levels.[139]

### **Contaminants and Toxic Compounds**

As any other natural food, honey can be contaminated by the environment, e.g. by heavy metals, pesticides, antibiotics etc. [140]. Generally, the contamination levels found in Europe do not present a health hazard. The main problem in recent years was the contamination by antibiotics, used against the bee brood diseases, but at present this problem seems to be under control. In the European Union antibiotics are not allowed for that purpose, and thus honey containing antibiotics is also not permitted to be traded on the market.

A few plants used by bees are known to produce nectar containing toxic substances. Diterpenoids and pyrazolidine alkaloids are two main toxin groups relevant in nectar. Some plants of the Ericaceae family belonging to the sub-family Rhododendron, e.g. *Rhododendron ponticum* contain toxic polyhydroxylated cyclic hydrocarbons or diterpenoids [141]. The substances of the other toxin group, the pyrazolidine alkaloids, found in different honey types and the potential intoxication by these substances is reviewed [142]. Cases of honey poisoning have been reported rarely in the literature and have concerned individuals from the following regions: Caucasus, Turkey, New Zealand, Australia, Japan, Nepal, South Africa, and also some countries in North and South America. Observed symptoms of such honey poisoning are vomiting, headache, stomach ache, unconsciousness, delirium, nausea and sight weakness. In general the poisonous plants are known to the local beekeepers and honey, which can possibly contain poisonous substances, is not marketed. To minimise risks of honey born poisoning in countries where plants with poisonous nectar are growing tourists are advised to buy honey in shops and not on the road and from individual beekeepers.

## **12. CONCLUSION**

Honey is a low-cost natural product that can be used for different purposes. Now, commercially honey is used in various industries for product formation and this trend is increasing day by day as industrialists are finding honey to be cheap source of sweetening agent without any side-effects as in case of synthetic sweeteners. Due to variation of botanical origin honey differs in appearance, sensory perception and composition. It contains mainly carbohydrates. The glycemic index of honey varies from 32 to 87, depending on botanical origin and on fructose content. The main nutrition- and health relevant components are the carbohydrates, which make it an excellent energy source





especially for children and sportsmen. Besides its main components, the carbohydrates fructose and glucose, honey contains also a great number of other constituents in small and trace amounts, producing numerous nutritional and biological effects: antimicrobial, antioxidant, antiviral, anti-parasitic, anti-inflammatory, anti-mutagenic, anticancer and immunosuppressive activities. Different nutritional studies have confirmed various effects after honey ingestion, e.g. enhanced gastroenterological and

cardiovascular health. Besides, honey showed physiological effects on blood health indicators as well as effects on hepatitis A and radiation mucositis patients. However, it should be pointed out that most of these studies were based on relatively high honey intakes of 50 to 80 g. Honey compositions, and also its different biological effects, depend to a great extent on the botanical origin of honey. This fact was often not considered in the reviewed studies.

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