

Review

Honey as a potent natural supplement for diverse human ailments

¹Surekha L. Chavan, ¹Revati S. Deshmukh, ²Harsh Parekh and ²Pratap N. Mukhopadhyaya*

¹Department of Oral Pathology and Microbiology, Bharti Vidyapeeth University Dental College and Hospital, Dhankawadi, Katraj, Pune, India.

²Interdisciplinary Science, Technology and Research Academy/Department of Microbiology, Abeda Inamdar Senior College, Hidayatullah Road, CAMP, Pune, India

*Corresponding author email: pnm.istra@yahoo.com; Tel.: +91 9881153425

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Abstract

The use of natural honey (NH) as a medicinal agent is associated with a vast range of health benefits and therapeutic promises. The tradition of using honey as a potent food supplementation and medicinal component exist in several countries cutting across traditions and civilizations. This review revisits the wide spectrum of medicinal properties that are associated with honey in the light of modern research and attempts to impart the much needed data required to provide this natural food the status of evidence based medicine. Subjects as diverse as diabetes, cardiology and ophthalmology were covered where beneficial medical properties of honey has been demonstrated and the review was concluded by identifying few safety aspects that are required to be known while using natural, unprocessed honey.

Key words: Honey, medicine, diabetes, cardiovascular, dental

INTRODUCTION

Honey is a sweet fluid made by honeybees from the nectar of flowers. It is generally made by wild or cultivated honeybees bearing the scientific name '*Apis mellifera*'. These bees collect nectar from flowering or other living part of the plants as its primary source of food for their colonies. This material, colloquially called 'nectar', is stored in hives where it is transformed into honey by the action of bees in due course of time. Over ages, honey has gradually emerged from being a natural

sweetener to a natural food product of significant nutritional value. It finds application not only like that of a drug for its antibacterial and antifungal activity, but also as an ointment (Jones, 2001). Honey has a soothing effect when applied on open wounds, and also has been used in many places as a remedy for ulcers, burns, wound healing (Coulston, 2000). The term 'Apitherapy' is now used when honey and its products are used to treat various human ailments.

Table 1. Constituents found in 100 gms of honey

Energy	304 Kcal
Carbohydrate (mainly sugars)	82.4gm
Protein	0.3gm
Water	17.10gm
Fibre	0.2gm
Vitamin B2	0.038mg
Vitamin B3	0.121mg
Vitamin B5	0.068mg
Vitamin B6	0.024mg
Vitamin B9	2µg
Vitamin C	0.5mg
Ca	6mg
Fe	0.42mg
Mg	2mg
Ph	4mg
K	52mg
Na	4mg
Zn	0.22mg

Composition

Honey being a natural compound exhibits a reasonable degree of content variations which is unavoidable. This depends on the type of flora used by the bees as well as other seasonal and environmental factors. Honey is mainly a solution of supersaturated sugars such as glucose (~31%) and fructose (~38%) and with a water content of around 17%. Apart from sugars and water, honey also contains a wide range of other minor but valuable constituents. The composition of typical honey is summarized in Table 1 (Coulston, 2000).

Carbohydrates present in honey are majorly a mixture of sugar comprising of about 95% of its dry weight. Apart from fructose and glucose many other forms of sugars such as panose, erlose, isopanose, centose, gentiobiose have been reported to be present in very minute quantity in honey. However many of these sugars are not found in nectar but are formed during the ripening process of honey (Jeffrey and Echazarreta, 1996). Protein accounts for 0.5% of total composition, mainly comprising of enzymes and free amino acids. Three different enzymes have been reported to be present in honey, namely, invertase (converts sucrose into fructose and glucose), diastase (converts starch or glycogen into smaller units) and glucose oxidase (responsible for production of hydrogen peroxide and gluconic acid from glucose) (Bogdanov et al., 2008). Proline is the major amino acid constituent of honey contributing for around 50% of the total 1% (w/w) content of amino acids (Iglesias et al., 2004). Many other amino acids have been reported to be

present in honey which depend upon its botanical and geographical origin (Iglesias et al., 2004; Pérez et al., 2007; González-Paramás et al., 2006). The vitamin content (Table 1) of honey was found to be very low but their contribution to its nutritional effect is high (Bogdanov et al., 2008). The assessment of concentration of trace elements and minerals reveals the presence of Al, Ba, Sr, Cr, Ti, Ni, Co, Mo and Ca, Cu, Fe, Na and Zn respectively (Conti, 2000; Stocker et al., 2005). The presence of high amount of polyphenolic compounds make honey a potential antioxidant candidate. Polyphenols in honey are in the form of flavonoids such as quercetin, kaempferol, chrysin and epigenin (Ferrerres et al., 1991; Truchado et al., 2008; Michalkiewicz et al., 2008) while other polypehonlic compounds include phenolic acid and their derivatives (Ferrerres et al., 1991; Gil et al., 1995). In a comparative study between honey originating from Argentina and that from other parts of the world, some useful composition of honey has been published. (Table 2). (Cantarelli et al., 2008).

Health effects of honey

Practitioners of conventional medicine as well as general public have accepted honey being an effective therapeutic agent. This is only possible because of extensive laboratory as well as literature research. There are many evidences in literature which clearly indicate the beneficial effect of honey being from wound healing to antibacterial activity as well as even antitumor effect.

Table 2. Major compositions of honey.

Parameters	Range
Moisture (%)	14.28 – 18.60
pH	3.34 – 4.70
Free acidity (meq kg-1)	21.23 – 43.20
Lactone (meq kg-1)	0.10 – 6.46
Reducing sugar (%)	63.20 – 73.24
Sucrose (%)	0.41 – 6.22
Diastase number	41.04 – 10.07
Ash (%)	0.06 – 0.21
Hydroxymethylfurfural content (meq kg-1)	1.48 – 34.08

Antibacterial activity of honey

The antibacterial activity of honey is attributed to its high percentage of sugar content since sugar, by the phenomenon of osmosis, draws water out from the bacterial cells depriving them from one of the most essential component of life. Interestingly, in a study conducted by Sackett and co-workers (Sackett, 1991) it was demonstrated that honey either retained or demonstrated enhanced antibacterial property even when used in dilute form. This suggested that apart from high sugar content there are other active components in honey which is responsible for its anti bacterial properties. Later it was found that apart from other components, the effect of hydrogen peroxide made honey a potent antibacterial agent (White et al., 1963).

The usual water content of honey is about 15-21% with 17% being an optimum level below which appropriate fermentation of nectar does not occur (Cantarelli et al., 2008). Hence, apart from high sugar, low water content significantly contributes to its antibacterial effect. The enzyme glucose oxidase which helps in maintaining the ratio of gluconic acid to glucose in honey further enhances antibacterial activity. The pH of honey is maintained at an acidic value between 3.2 to 4.5 (Cantarelli et al., 2008) which creates an anti microbial environment.

An important by-product of glucose oxidase enzyme is hydrogen peroxide. This compound is generated when glucose is converted to gluconic acid. In a study by Adcock (Adcock, 1962), the role of hydrogen peroxide was assessed by adding catalase enzyme to different honey samples which destroys Hydrogen peroxide. Following this treatment it was found that most of the honey samples lost their antibacterial activity while few still retained them. Similar study by Allen (Allen et al., 1991) demonstrated non-peroxide mediated antibacterial activity which is primarily because of the presence of polyphenolic compounds such as flavonoids, phenolic

acids and lysozyme. As water is an essential component of an enzyme activity, honey becomes dependent of adequate water content for exhibiting its hydrogen peroxide-based anti microbial activity. On the other hand, similar activity, based on its non enzymatic properties, which far less sensitive to heat and light, although low in activity, demonstrates a prolonged effect in controlling microbes and is considered more essential than the former in providing anti microbial property to honey (Taormina et al., 2001).

In a study different types of pathogens were incubated at 37°C for 8 hours in varying concentration of different types of honey. Results showed that Manuka honey (Willix et al., 1992) was more effective against wide variety of pathogens such as *S. aureus* and *E. coli*, inhibiting the former at a concentration of 1.8% v/v as compared to 4.5% v/v by other types of honey. On the contrary, opposite effect was found in case of *Proteus mirabilis* where a concentration of 7.8% (v/v) of Manuka honey was required to inhibit its growth as compared to 3.3% (v/v) by other types of honey. Several studies has been undertaken to evaluate the effect of honey on helicobacter pylori, the causative agent for human gastric ulcer. Several authors by way of published reports indicated that honey inhibits this pathogen at varying concentrations (Chute et al., 1992), (Ali et al., 1991). In a specific study using Manuka honey, it was found that *H. pylori* was inhibited at a final concentration of 5% (v/v) (Somal et al., 1994).

Another prominent honey, originally found in Malaysia and popularly known as Tualang honey (Hafizah et al., 2005) (Ref) inhibits a broad range of microbes including *Salmonella typhi*, *streptococcus pyogenes*, pathogenic *Escherichia coli*, *Streptococcus species* and *Staphylococcus aureus* at concentrations ranging from 6.25% - 25% (Hafizah et al., 2005; Norizah et al., 2004). Though not comparable to antibiotics, honey has been consistently reported to exhibit a prominent albeit low inhibitory effect against various pathogenic microbes

(Farouk et al., 1988).

Antioxidant property

The antioxidant capacity of honey is primarily due to the presence of polyphenol compounds and flavonoids present in it. (Alzahrani et al., 2012) Variations in the content of honey have been observed in different types collected from different places. The fact that antioxidant potential of honey depends on its polyphenolic content makes it evident that different honey will have different antioxidant potentials and the evidences found in literature also support this fact. For example, honey originating from Germany (Alzahrani et al., 2012) was found to have higher antioxidant capacity (1.366 μ molTE/g) compared to that from Chile (0.260 μ molTE/g) (Mejias and Montenegro, 2012). Even honey collected from two different regions in Brazil was found to demonstrate huge difference in their antioxidant potential with Brazil 'multi-floral' and 'orange blossom' honeys showing an antioxidant potential of 172.96 μ mol TE/g and 305.92 μ mol TE/g respectively. (Alzahrani et al., 2012).

Anticancer potential of honey

Uncontrolled cell growth (cellular proliferation) and inadequate apoptotic turnover are two main characteristics of a cancerous cell. Apoptosis is mainly characterized by three distinct phases, viz., (i) an induction phase when pro-apoptotic signals are generated (ii) an effector phase when the mitochondrion brings about the cell death and (iii) a degradation phase comprising of associated nuclear and cytoplasmic events (Mejias and Montenegro, 2012) (Ref). Loss of function in any one of the above mentioned three phases leads to cancer generation. Honey has been reported to induce apoptosis directly by depolarizing the mitochondrial membrane (Fauzi et al., 2011). In one of the study on human colon cancer cell line, honey was found to elevate caspase-3 activation along with increase in poly ADP-ribose polymerase cleavage (Jaganathan and Mandal, 2009). It was also found to interact with various pro and anti-apoptotic proteins related to colon cancer such as up-regulation of caspase-3, p53 and pro-apoptotic protein BAX 3 while down regulating protein Bcl2 (Jaganathan and Mandal 2010). The combination of honey with *Aloe vera* extract had similar kind of effects on BAX3 and Bcl2 proteins (Tomasin and Gomes-Marcondes, 2011).

Various *in-vitro* studies on different cancer cell lines are

also been conducted to show the anti-cancer efficacy of honey. Honey significantly reduces the proliferation of different bladder cancer cell lines at different concentrations. At 1-25% concentration, honey reduces proliferation of T24 and MBT-2 cell lines while at a concentration of 6-25%, it reduces proliferation RT4 and 253J cell line (Swellam et al., 2003).

In a study, Greek honey extracts *i.e.* fir, thyme and pine honey were checked for their oestrogenic activity and cell viability on MCF-7 breast cancer cell line as well as PC-3 prostate cancer cell line. Fir honey reduced the viability of PC-3 cell line where as thyme honey reduced the viability of MCF-7. This effect of both types of honey varied depending on their respective phenolic content (Tsiapara et al., 2009).

The presence of hydroxymethylfurfural in thyme honey has been attributed for its anti tumour activity (Michail et al., 2007). The presence of many other biologically active compounds in honey have been reported which demonstrate inhibitory effect on tumour progression by directly interacting with tyrosine kinase, ornithine decarboxylase and cyclooxygenase. These compounds include caffeic acid, caffeic acid phenethyl ester and flavonoid glycones (Oršolić and Bašić, 2007). In a study of rats having murine tumours and treated with honey for 10 days, the metastatic effect of these tumours were found to be reduced. Further in this study, metastases in lungs were induced by injecting viable cells intravenously within the animals. The above mentioned effect of honey was seen before the inoculation of tumour cell, but when honey was administered after tumour cell inoculation the metastatic effect of honey diminished (Oršolić et al., 2003). In another study honey was combined with various chemotherapeutic drugs such as 5-fluorouracil and adriamycin and the chemotherapeutic toxicity of these drugs were found to be lower in leukemic populations (Oršolić and Bašić, 2004).

The assessment of jungle honey in mice showed enhanced immune functions and anti-tumour activity. In a study, C57B/L6 mice were treated with jungle honey intraperitoneally at a dose of 1mg/mouse/day for seven days and tumour incidence as well as weight of each mouse checked to find that they had decreased (Fukuda et al., 2009).

The very first use of honey in cancer patients dates back to 1970, where 12 patients with wound breakdown following radical excision of vulval carcinoma were treated with topical application of household honey and improved healing rates of wound recorded as early as in 3-4 days (Cavanagh et al., 1970). Many cancer patients undergoing chemotherapy suffer from mucositis, a side effect that attacks the entire gastro-intestinal tract and

caused by the imbalance between cell proliferation and cell loss. Honey has been found to be effective in addressing radiation induced mucositis (Biswal et al., 2003), periodontal gum disease (English et al., 2004), radiotherapy induced skin reaction (Moolenaar et al., 2006), stomatitis (Chiba et al., 1985) and malignant ulcers (Simon et al., 2006).

Biswal et al. (2003), in a study investigated use of honey in patients suffering from head and neck cancer. In all, 40 patients were advised to take 20 ml of pure honey from *Camellia sinensis*, 15 minutes before and 6 hours after radiation therapy. Reduction in grade 3/4 mucositis was observed in honey-treated patients as compared to controls (Biswal et al., 2003). A similar kind of study was carried out in Iran where head and neck cancer patients were divided into two groups. One group received honey (20 ml, 15 min before, 15 after and 6 hours after the radiation therapy), while the control group received normal saline (20 ml). The results were same as that reported by Biswal et al. (2003); (motallebnejad et al., 2008). In another study, 30 cancer patients on chemotherapy and suffering from grade 4 neutropenia were treated with CSF (colony stimulating factor). After one cycle of chemotherapy the CSF treated patients were subjected to the same cycle but with addition of honey (Life-Mel honey) in the regimen for 5 days. It was found that anaemia was better treated in patients receiving honey (60%) as compared to only CSF (40%) and further, some patients reported improvement in quality of life after intake of honey (Zidan et al., 2006). Honey stimulates the healing process by facilitating an increase in lymphocytes and phagocytes and thereby aids the monocytes to release cytokines and interleukins e.g. TNF- α , IL-6 and IL-1 β (Tonks et al., 2003; Tonks et al., 2007).

Cardiovascular effects of honey

Beneficial effects of honey in healthy individuals as well as patients with increased cardiovascular risk factors have also been reported. Honey was administered to healthy male and female patients to check the effect on blood pressure (both systolic and diastolic) and heart rate. A significant reduction in systolic blood pressure was observed after 15, 30 and 60 mins of administration of honey in males and similar effects was observed in females after 15 mins of administration. The overall reduction in blood pressure in females was more as compared to males after oral administration of honey (Olusola et al., 2013). It is believed that the effect of sex hormones are responsible for the varying effects of

honey in males and females (Raghvendra et al., 2002). In another study involving 55 patients, the effect of natural honey was tested on total cholesterol, LDL, HDL, C-reactive protein and triglycerides. The patients were divided into two different groups, viz., control (17 subjects) and experimental (38 subjects). The control group received a daily dose of 70 g of sucrose for 30 days while the experimental group received 70 g of natural honey for the same span of time. Honey showed reducing effects on body weight, body mass index, body fat, total cholesterol, LDL, triglycerides and CRP and increased HDL in healthy individuals and similar effects were observed in patients with other elevated variables except for body weight and body mass index in overweight or obese patients (Yaghoobi et al., 2008). In a similar kind of comparative study between natural and artificial honey, their effect on insulin was assessed along with the above mentioned parameters. Elevation of insulin and CRP was higher in group receiving artificial honey as compared to natural honey (Al-Waili, 2004).

Anti-diabetic effect of honey

It has been discussed earlier that major constituent of honey is carbohydrates comprising mainly of fructose and glucose. Both of these monosaccharides are readily absorbed in gastrointestinal tract as they do not need to be hydrolyzed by enzymes. It has been reported that fructose reduces hyperglycemia in diabetes induced mice (Kwon et al., 2008), healthy subjects as well as diabetic patients (Erejuwa et al., 2012). Yet another hypothesis regarding the positive effect of honey on anti-diabetic people is the presence of palatinose (isomaltulose), an oligosaccharide of fructose. Palatinose is reported to delay digestion and absorption of glucose resulting in reduced glycemia (Kashimura and Nagai, 2007). It is found that glucose acts in synergy to increase the absorption of fructose (Jones et al., 2011), thereby enhancing the food intake-lowering effects of fructose (Thibault, 1994).

Liver has a role in pathophysiology and control of glycemia. Fructose activates the hepatic glucose phosphorylation via activation of glucokinase (Van Schaftingen and Davies, 1991). It also suppresses the enzyme phosphorylase thereby inhibiting glycogenolysis (Youn et al., 1987). The synergistic effect of fructose and glucose play an important role in modulating the enzymes involved in metabolism of glycogen and glucose in liver (Regan et al., 1980; Shiota et al., 2005). Honey supplementation has been reported to have protective effect against alloxan, streptozotocin (STZ) (Erejuwa et

al., 2012), carbon-tetrachloride (Al-Waili, 2003) and trichlorofon induced (Eraslan et al., 2010) liver damage. In a comparative study of natural honey with D-glucose in healthy human individuals it was found that at the end of a time span of 60 minutes, natural honey increased blood glucose level to a lesser extent (20%) as compared to D-glucose (52%) and this value further reduced to 9.25% at the end 180 minutes (Ahmad et al., 2008).

In type 1 diabetic patients, supplementation of honey produces lower glycemic and peak increment indices as compared to that of sucrose (Abdulrhman et al., 2011). Similar effect was observed when honey was supplemented to children suffering from type 1 diabetes mellitus (Abdulrhman et al., 2011). Administration of honey to STZ-induced diabetic rats showed reduction in fructosamine levels in blood and this effect increased when honey was given in combination with the anti-diabetic drugs metformin and glibenclamide (Erejuwa et al., 2011). But when this same study was carried out in humans, no significant increase in fructosamine was observed and interestingly, increased levels of glycosylated haemoglobin was demonstrated (Bahrami et al., 2009). Considering the fact that very high dose of honey was administered in patients who participated in this study, this may also justify the high serum levels of glycosylated haemoglobin in them.

Honey supplementation in diabetic patients showed increased level of insulin concentration (Aronoff et al., 2004), and reduced insulin resistance (Katsilambros et al., 1988). Same results were obtained when STZ-induced diabetic rats were supplemented with honey where improvement in pancreatic islets was also observed (Erejuwa et al., 2011). However, it is worth mentioning that despite a range of studies reporting the beneficial effects of honey on conditions of glycemia, some studies are available that indicate no significant beneficial effect of honey on hyperglycemia and type 2 diabetes (Bornet et al., 1985; Katsilambros et al., 1988).

Wound healing property of honey

Many studies in literature report the beneficial effects of honey in treatment and cleaning of wound (Bulman, 1955) and its potential to halt wounds necrosis (Efem, 1993). Honey acts by forming a protective barrier over the wounds thereby preventing further infection (Bergman et al., 1983). In a study on treatment of deep dermal burns made on Yorkshire pigs, topical application of honey was done on the wounds. In case of honey application, epithelialisation was achieved in 21 days as compared to 28 days when administered with

sulfadiazine. Less inflammation was also observed in all pigs which were treated with honey (Postmes et al., 1997). The time taken for complete repair of wound (superficial burns) created by red hot pins was much less when honey was applied to it as compared to sucrose of same composition (Burlando, 1978).

In another study, full thickness wounds were created on the back of buffalo calves and dressed either with honey or nitrofurazone along with appropriate control. Complete healing and scar formation occurred much faster in case of honey application (Kumar et al., 1993). Similar kind of experiment was repeated with additional artificial infection created by injecting *Staphylococcus aureus* two days prior to 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 (Gupta et al., 1992).

In another study, topical application of honey was compared with boiled potato peel by applying both to wounds in human patients. All subjects demonstrated a better wound healing time which was within 7 days when treated with honey (Subrahmanyam, 1996).

Role of honey in Gastric ailments

High sugar content of honey promotes sodium and water absorption from the bowel. Both clinical and animal studies indicate that use of honey can result in reduced gastric acid secretion. In a study comprising of 600 gastric ulcer patients treated with oral administration of honey, 80% recovery rate was observed (Kandil et al., 1987).

Alcoholic oxidation was found to be increased when honey solution was administered in stomach of rats prior to administration of ethanol at the rate of 0.5g/kg body weight. Honey provided protection against effects of alcohol and oral administration of honey before alcohol consumption reverses the change in pH effect induced by it (Ali, 1991). Fructose however also has been reported to reduce the alcohol intoxication and affect increase in the fall of rate of blood ethanol levels (Brown et al., 1972) and hence a synergistic effect is likely to exist when used together. A beneficial effect of honey against gastritis, duodenitis and duodenal ulcers has also been reported where in, patients were administered 30 ml of honey before meals three times a day (Salem, 1982).

Oral rehydration products are now available in market which are used to treat diarrhoea. These formulations are mixtures of various sugars and electrolytes that help in movement of water across the gastrointestinal (GI) tract.

In order to find out the role of honey in GI tract water absorption, rehydration solution was prepared using honey as source of carbohydrates and the electrolyte concentration was kept as it is in commercial preparations. Children (8-12 yrs) and suffering from gastroenteritis were divided into two groups; one received conventional rehydration solution while other, the rehydration syrup containing honey. It was observed that in case of bacterial gastroenteritis, honey-containing rehydration solution was more effective than conventional ones (58 versus 93 hours) in reducing the disease condition (Haffejee and Moosa, 1985).

In yet another study, honey was administered to rats suffering from acetylsalicylic acid- induced gastric ulcers and effects were compared with *Nigella sativa* extract and cimetidine. Natural honey showed healing effects in 15 out of 18 rats compared to 14/18 and 17/18 in cases of *Nigella sativa* and cimetidine respectively (Bukhari et al., 2011).

Dental health and honey

In a randomized, double blind, placebo controlled trial using Manuka honey to treat plaque gingivitis, significant reduction in plaque scores and bleeding were observed when honey was administered in the form of chewing gum for 10 minutes, three time a day (English et al, 2004). Oral application of honey in patients after surgical removal of impacted third molar significantly reduced the post surgical pain and edema (Elbagoury and Fayed, 1985). A mixture of honey and mustard oil (equal v/v) had positive effects for inhibiting growth of microorganisms within human root canal specimens at a concentration of 12.5% as compared to conventional medicine comprising of camphorated paramonochloro-phenol at 25% concentration. Honey was also found to be an effective and viable alternative for endodontic medication (Sobhi and Manzoor, 2004).

Honey and ophthalmology

It has been reported that honey is used to treat eye-discharging pus. Some doctors from India have been using honey to treat bacterial corneal ulcers. Honey has also been reported to treat inflammation of eye lids, cornea and condition of conjunctivitis. It has been demonstrated to cure keratitis and blepharitis when applied undiluted or as a solution (20-50% honey mixed with water) to lower eyelids (Emarah, 1982).

Honey and dermatology

Topical application of a mixture of honey, bees wax and olive oil every day for at least four weeks has been shown to be helpful in the treatment of psoriasis vulgaris and dermatitis. The same mixture was also found to cure dandruff problems in human subjects (Al-Waili, 2001). Conditions of eborrheic dermatitis can also be treated by the application of mixture of tree oil, cinnamic acid and honey due to its antifungal activity against the pathogenic *Malassezia* species (Gupta et al., 2004).

Safety reports of honey

Honey produced from flowers of oleanders, rhododendrons, mountain laurels, sheep laurel, and azaleas may cause honey-induced intoxication. Symptoms include dizziness, weakness, excessive perspiration, nausea, and vomiting. Less commonly, low blood pressure, shock, heart rhythm irregularities, and convulsions may occur, with rare cases resulting in death. Honey intoxication is more likely when using "natural" unprocessed honey and those from farmers who may have a small number of hives. Commercial processing with pooling of honey from numerous sources, is thought to dilute any toxins that might be present in any of them (Snowdon and Cliver, 1996). Honey being a natural product, the presence of *Botulinum* endospores has also been reported. However, when honey is consumed by adults, the well established digestive systems destroy the spores but consumption of honey by infants may contract botulism if the sample is infected.

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