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Review

Medicinal uses of honey: a review on its benefits to human health

Seema Rana[1], Meerambika Mishra[2]*, Dhananjay Yadav[3], Senthil Kumar Subramani[4], Charu Katare[1], GBKS Prasad[4]*

[1]Department of Food & Nutrition, Govt. K.R.G.PG Autonomous College, Kampu, Gwalior, India; [2]School of Life Sciences, Sambalpur University, Jyoti Vihar, Odisha, India; [3]Department of Medical Biotechnology, Yeungnam University, Gyeongsan, Republic of Korea - E-mail: dhanyadav16481@gmail.com; [4]School of Biochemistry, Jiwaji University, Gwalior, India

Summary. Honey often referred to as 'the drink of the gods', is naturally sweet and a substantially rich source of carbohydrates, amino acids and antioxidants. In spite of being rich in carbohydrates, honey has a low glycemic index and therefore effectively used as a dietary compliance by diabetics. The fructose content of honey has hepatoprotective capability, while the antioxidants present in it provide effective protection against oxidative damage. The therapeutic attribute of honey makes it the food of choice even in infants and diabetics. Honey is endowed with antioxidant, immune modulating, and wound healing, anti-inflammatory, therapeutic, nutritional, antimicrobial and antidiabetic qualities. The present review aims at discussing these capabilities of honey with special reference to its antidiabetic benefits under one dome.

Key words: honey, anti-diabetic, anti-hyperlipidemic, antioxidant, wound healing, antimicrobial

Introduction

Honey is a luxuriously rich, sweet, sticky, golden fluid made from the nectar of flowers. Its natural sweetness endowed with health benefits makes it an adept substitute for white sugar. Nectar, often referred to as 'the drink of the gods', is collected by hymenopteran honeybees and is gathered, modified and stored in the honeycomb to be used as food. Often used as a nutraceutical agent and an important component of herbal remedies, honey has been globally used both as medicine and also food since the past 2500 years. Its purity and efficacy can be gauged from its prevalent administration to infants and children at various stages of development (1).

Biochemical studies indicate the presence of about 400 compounds in honey, namely mixed sugars (glucose 31%, fructose 38%, and less than 5% sucrose), not more than 20% water, and 0.08% of certain acids with 0.18% of other minerals and numerous enzymes, phenolic acids, amino acids flavonoids, various proteins, etc. The composition of honey differs based on variations in pollen content weather conditions, micro-and macroclimate and honey processing methods (2, 3).

Disparity in its appearance and possibly taste is attributed to different biological origin of honey, however, the basic components imperative to its nutritional value, as glucose, fructose and 25 other oligosaccharides, largely remains unaltered. In spite of being rich in carbohydrates, its glycemic index ranges from 32 to 85, varying upon its source and hence 50-80 grams can be safely consumed per intake (4). Besides, honey also offers antimicrobial, antioxidant, pre-biotic, immunomodulating and nutritional effects (5). The medicinal properties of honey are attributed to its antioxidants, phenolic compounds, amino acids and vitamins content. Especially its antioxidative potential is fathomed by the composition pollen, propolis and wax as

* Seema Rana and Meerambika Mishra have equally contributed to this work.

they form the primal sources of phenolic compounds (6, 7). These compounds present in honey are grouped as simple phenols and polyphenols. While simple phenols in honey are basically phenolic acids, polyphenols are flavonoids (2, 8, 9).

Leptospermum scoparium belonging to the family Myrtaceae is the source of the Manuka honey which has well established therapeutic and antibacterial properties. Several researchers have professed the healing potential of Manuka honey in wounds, skin ulcers, fungal infections, diabetes, ophthalmic disorders peptic ulcers and other gastrointestinal track disorders (10, 11).

Nutrient composition of honey

The composition of honey varies based on disparities in climatic conditions, origin, the flowers used by the bees to collect nectar, weather conditions, processing methods and other macro- and micro-environmental factors which accentuate the therapeutic value of each kind of honey. Despite of such divergence, honey is largely composed of a complex of inverted sugars, other saccharides, enzymes, proteins, polyphenols, organic acids, 18 non-essential and non-essential amino acids, flavonoids, vitamins, minerals and maillard reaction products. The amount and inclusion of specific vitamins and minerals depend upon the origin. Preponderance of the dry weight of honey is composed of carbohydrates followed by water, protein in the form of amino acids (majorly proline and lysine) and enzymes (glucose oxidase, invertase, catalase etc.), vitamins (thiamine, riboflavin, niacin etc.), minerals (P, S, Ca, K etc. depending on origin) and certain trace (Cr, Ba, Ni etc.) and other volatile compounds (aldehydes, ketones, esters, alcohols, terpenes, acids, gluconic acid etc.). Honey varies in its perception, composition and qualities based on its botanical origin and processing methods. Studies have revealed origin based compositional variation among honey samples from some non-organic and organic honey from *Apis mellifera* when scrutinized based on their color, moisture content, water activity, hydroxymethylfurfural, diastase index, ash, total sugars, pH, acidity, reducing sugar, sucrose, viscosity and electrical conductivity (12).

Multiple samples from various places in Czech Republic, when analyzed using a spectrophotometer for the presence and amount of flavonols, total polyphenol, flavonoids, and 3',4'-dihydroxyflavones and other major antioxidants, showed ample disparity in their phenolic antioxidant proportion. These were identified by High-Performance Liquid Chromatography (HPLC) with a Diode-Array Detector (DAD) and Gas Chromatography-Mass Spectrometry (GC-MS). On an average , total flavonoids of 0.66 mg quercetin equivalents/100 g and 11.02 mg gallic acid equivalents/100 g, 3',4'-dihydroxyflavones and flavonols of 4.32 µg quercetin equivalents/100 g were found (13).

Methylglyoxal an exceedingly reactive antecedent in the creation of advanced glycation end products, was isolated and identified by HPLC from Manuka honey obtained from New Zealand. This fraction exhibited potent non-peroxide antibacterial activity. Methylglyoxal concentrations in non-manuka and manuka honey samples were directly identified and contrasted with values from standard o-phenylenediamine derivatisation which varied between 38 to 828 mg/kg (14).

As mentioned earlier, honey is a viscous concentrate of a plethora of sugars as fructose (38%) and glucose (31%), besides; it also contains many proteins, minerals, vitamins, enzymes, free amino acids flavonoids and polyphenols, quintessential for its biological functioning. Honey reduces blood glucose; serum fructosamine and glycosylated hemoglobin levels and wields antibacterial properties owing to its hydrogen peroxide and non-peroxide factors as methylglyoxal, flavonoids, and defensin-1 peptide (15).

Evaluation of carbohydrate concentration from 6 honey samples from Slovakia by ion-exchange chromatographic method with refractive index detection revealed the predominance of various sugars as fructose, glucose, saccharose and other ingredients in the honey. The kinetic study established that the time based change in the ratio of fructose/glucose was not noteworthy at temperature of 80°C (16). Another gas chromatography study conducted on the oligosaccharide content of seven monofloral willow honey revealed the presence of turanose, trehalose, palatinose, celobiose, raffinose, fructose sucrose, isomaltose, panose, maltose and glucose in it. The average values of

glucose and fructose was found to be between 32.92 to 38.88 and 35.27 to 42.29% respectively maintaing a fructose/glucose ratio of 0.78 to 1.10 (17).

Physio-chemical analysis of 38 natural honey samples procured from different regions of Argentina revealed mean values of minerals to be as phosphorous: 28.80 µg/g, iron as 3.91 µg/g, aluminum as 2.57 µg/g, manganese 0.33 µg/g, zinc 1.08 µg/g, copper 0.19 µg/g, calcium 56.35 µg/g, magnesium 23.38 µg/g, sodium 25.56 µg/g and potassium 482.75 µg/g. Moisture content of the honey samples were 16.24%, while pH was 3.85, free acidity 30.15mg/g, total acidity 31.65mg/g, reducing sugar 68.08%, sucrose 4.05%, diastase number 19.73, hidroximethylfurfural 8.98 mg/kg and ashes 0.11 % (18).

A study was conducted to evaluate the antioxidant potential of 4 different honey samples procured from different flowers (Coriander, Acacia, Palm and Sider) using DPPH free radical scavenging assay, superoxide anion generated in xanthine oxidase (XOD) system and low density lipoprotein (LDL) peroxidation assay. While the palm and sider honeys were found to have highest antioxidant potential in the DPPH assay, all the other ones showed similar antioxidant activity in XOD system analysis and LDL peroxidation assays. Eleven novel compounds were found upon GC/MS and HPLC analysis 90 other compounds, as aliphatic acids (thirty-seven compounds 54.73%, 8.72%, 22.87% and 64.10%) and phenolic acids (fifteen compounds 2.3%, 1.02%, 2.07% and 11.68%) were found to be prevalent (19). Honey is gaining more attention in recent times from medical scientists and researchers as a neutraceutical which exhibit various property such as antidiabetic, antihyperglycemic, antimicrobial, antioxidant and boosting immunity (Fig. 1).

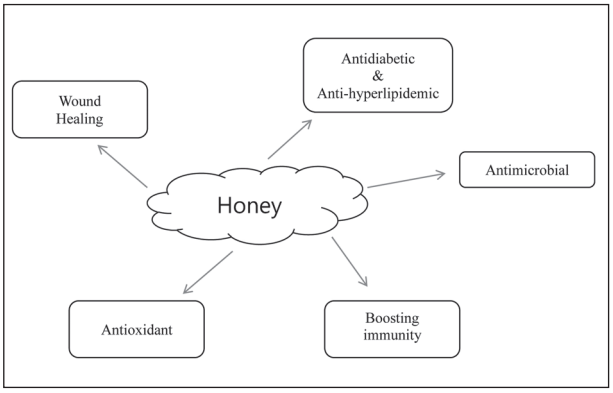

Figure 1. Applications of honey in health care

Therapeutic effects of honey

Antidiabetic and anti-hyperlipidemic proficiency of honey

Diabetes mellitus is a grave affliction that occurs by either defects in insulin secretion or its action, or both. The scarcity of insulin thus caused leads to hyperglycemia and disrupted carbohydrate, fat and protein metabolism (20, 21). Eventually secondary complications as tissue or vascular damage resulting retinopathy (22) cardiovascular complications (23), neuropathy (24), chronic kidney disease (25, 26). Diabetes is prevalent globally with numbers increasing exponentially with the passing time. The International Diabetes Federation (IDF) predicts the numbers to shoot up to 40.9 million in India and further rise to 69.9 million by 2025 (27). While diseases are looming threateningly in the face of globalization, oxidative stress associated with them are said to be the silent killer. The imbalance in the biochemical and oxidative stress markers lead to insufficient production of antioxidants in type 2 diabetic patients (28, 29). Therefore, it becomes imperative to additionally supplement the body with antioxidants from outside so as to fight the oxidative damage. Studies have effectively proved the antihypertensive, antibacterial, hepatoprotective, hypoglycemic, anti-inflammatory and antioxidant potential of honey (5, 30). The antioxidants in honey scavenge the free radicals pivotal in the diverse cascades of inflammation and also inhibit the formation of reactive oxygen species that is catalyzed by metal ions such as iron and copper which get caged by the flavonoids and other polyphenolic compounds present in honey (31).

The hypoglycemic potentiality of honey has also been ascertained in another study conducted on humans. A study comparing the glycemic index of two types of Iranian honey on healthy below 30 years aged individuals with mean BMI (body mass index) of 24.3±2.6 kg/m^2 found glycemic indices of thyme honey and clover honey to be 65.9 and 64.9 respectively however these are considerably lesser than that of glucose (214.4±53.0 mmol.min/l) (32). Another separate

investigation comparing the glycemic index of Malaysian and Australian honeys revealed that the glycemic index of these honey do marginally differ from each other (174±19 and 158±16 mmol×min/l, respectively), however, they are still significantly lower than that of glucose (33). It has also been seen to positively affect glycemic control, glucose and appetite managing hormones, body weight, food intake and oxidation of carbohydrate and energy expense (30).

Numerous reports have endorsed that honey is crucial in reducing cardinal biochemical markers associated with cardiovascular complications, hyperlipidemia and insulin resistance (34). It contains phenolic compounds and flavonoids which are antioxidants which scavenge free radicals, improve coronary vasodilatation, decrease clotting ability of the blood platelets thus preventing clot, and also prevents oxidation of LDL (35).

A comparative study found honey to be related with noteworthy lesser glycemic index against glucose or sucrose in healthy and type 1 diabetic individuals. The same study conducted on type 2 diabetics exhibited similar values for honey, glucose and sucrose. Honey when contrasted with dextrose showed momentously low rise in plasma glucose levels in diabetics, with a reduction of serum triglycerides, homocysteine and C reactive protein levels in healthy and hyperlipidemic subjects (36).

While sugar is considered poisonous for diabetics, artificial sweeteners too do not help the cause, however in order to improve the in general dietetic conformity of diabetics and to thwart their craving for sweets, some alternative is needed. Since honey tastes sweet but has hypoglycemic effect, as it increases insulin secretion to reduce blood glucose levels, its usage seems practical over saccharine or sucrose (36-38). Regular intake of honey dwindle the plasma prostaglandins, triglycerides and homocysteine levels while also boosting antioxidants, serum iron, serum lipid levels and blood indices in both healthy and hyperlipidemic subjects (38). In comparison to dextrose honey shows reduced plasma glucose levels in healthy individuals. It also contains fructose, minerals and antioxidants; fructose enhances hepatic glucose uptake and glycogen storage while also reducing glycemia and insulin levels. Increment in fructose intake from 3% to 20% of calories has been seen to raise the serum total cholesterol by 9% and LDL-C by 11 % (39). Hence, addition of honey to the diet would effectively circumvent hyperinsulinemia while also adding to the overall dietary compliance of diabetics (40).

A separate study case directed to unveil the effect of honey and sucrose on weight gain post long term usage, 2 month aged Sprague Dawley rats were given a powdered diet comprising of either sugar-free or 7.9% sucrose or 10% honey ad libitum for fifty-two weeks. The animals were weighed week and their food utilization was quantified once every two months. At the end of the study blood samples were obtained and quantified for blood sugar by glycosylated hemoglobin (HbA1c) and a fasting lipid profile. Dual energy x-ray absorptiometry analyses revealed body composition and bone mineral densities. The rats fed with sucrose showed noteworthy increase in weight and body fat those fed with honey or a sugar-free diet seemed healthy with reduced HbA1c levels and increased HDL-C levels. Honey consumption also provides readily absorbable calcium which strengthens the development of bone mass (41). Yaghoobi and co-workers have studied the influence of natural honey on total serum triglycerides, C-reactive protein, fasting blood glucose and BMI in obese subjects. The control group were administered a quotidian dose of 70 g of sucrose for 30 days while those in the experimental faction were given 70 g of natural honey for the equal time. Body weight, BMI, body fat weight, total cholesterol, LDL-C, HDL-C, triacylglycerol, fasting blood glucose and CRP were quantified before therapy and on the 3st day post therapy. Results indicated that the honey-administered group experienced a decline in body weight (1.3%) and body fat (1.1%), total cholesterol (3.3%), LDL-C (4.3%), triacylglycerol (19%), fasting blood glucose (4.2%), and CRP (3.3%), while a swell in HDL-C (3.3%) ($p<0.05$) level was seen in patients (42).

Antimicrobial competence of honey

Honey is also endowed with antimicrobial attributes effective against a large spectrum of multi-drug resistant, pathogenic and non-pathogenic bacteria, fungi and yeasts. This characteristic is owed to its high osmolarity, acidity, hydrogen peroxide, flavonoids, phe-

nolic acid, ascorbic acids and other non-peroxide phytochemicals (43). Honey is a super-saturated complex of sugars, thus possess a very low water activity which doesn't support microbial growth. *Staphylococcus aureus* has been reported to be extremely tolerant to low water activity even at 0.86; it has also been observed to be unaffected by the usage of concentrated sugar solutions on skin infections, however, is sensitive to the antibacterial constituents of honey (44). The antimicrobial competence of honey is also attributed to the presence of hydrogen peroxide, carotenoid-like substances, gluconic acids, amino acids, flavonoids, phenolic acids, non-peroxide components, natural acidity, high osmolarity, ascorbic acid, organic acids, neutral lipids, Maillard reaction products, benzoic acid, cinnamic acid and proteins (43, 45, 46). The broad spectrum antimicrobial action of honey has been confirmed against many organisms such as *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans, Rubella virus, Trichophyton mentagrophytes, Leishmania parasites, Bacillus anthracis, Campylobacter coli, Salmonella cholerae-suis, Campylobacter jejuni, Salmonella typhi, Salmonella typhimurium, Corynebacterium diphtheria, Serratia marcescens, Echinococcus parasite, Shigella sp., Enterococcus avium, Enterococcus faecalis, Streptococcus agalactiae, Enterococcus faecium, Streptococcus dysgalactiae, Enterococcus raffinosus, Streptococcus faecalis uberis, Epidermophyton floccosum Streptococcus mutans, Streptococcus pneumonia, Haemophilus influenza, Streptococcus pyogenes, Streptococcus uberis, Klebsiella pneumonia, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes var., Mycobacterium tuberculosis, Trichophyton tonsurans, Nocardia asteroids, Trichophyton rubrum, Proteus species and Vibrio choleriae* among others (47-52). A conclusive study on *Helicobacter pylori,* causative organism behind peptic ulcers has also been found to be sensitive towards the antibacterial action of honey. The antibacterial effect of honey on *Helicobacter pylori* could be due to the phytochemical content preferably than to hydrogen peroxide or osmolarity, even though an osmotic effect was shown to be fatal for *Helicobacter pylori*" (53, 54).

Immunity boosting capability of honey

Honey is said to have immunity boosting effects. Honey has been noted to maneuver monocytes to secrete cytokines as TNF-α, Interleukins 1 and 6 *invitro,* which act as messengers of the cell in inducing an immune response (55, 56). Additionally, honey poses as an excellent source of glucose and energy (substrate for glycolysis in oxygen deficient damaged tissues) for phagocytosing macrophages which produce hydrogen peroxide, thus eliminating infected cells or tissues. The high osmolarity and acidity of honey too adds to the cause as its water deficient acidic medium within the phagocytic vacuole doesn't support microbial growth (53). Another study undertaken to discover whether honey intake would have any effect on neutrophil phagocytosis, was carried out in young Sprague Dawley rats. The two months aged rats were catered a powdered diet with either sugar-free or 7.9% sucrose or 10% honey ad libitum for fifty-two weeks, following therapy the percentage of phagocytosing neutrophils and lymphocytes were counted by flow cytometry. The proportion of neutrophils that were involved in phagocytosis was analogous between sucrose- and honey given rats it was substantially less in sugar-free diet administered rats (79.2%, 74.7% and 51.7 %, respectively). The fraction of leukocytes turned lymphocytes fluctuated notably among the three setups, the maximum was in honey-given rats (53%, 40.1% and 29.5% for sucrose and sugar-free fed rats) (57). From the above mentioned studies the immune boosting potential of honey can be validated.

Antioxidant properties of honey

The antioxidant properties of honey are quite well endorsed. Flavonoids, amino acids, organic acids, enzymes as catalase, glucose oxidase, peroxidase, ascorbic acid, α-tocopherol carotenoids, proteins, maillard reaction products, minerals such as copper and iron, and over 150 polyphenolic constituents as catechins, ellagic acid, gallic acid, syringic acid, benzoic acid, ferulic acids, myricetin, chlorogenic acid, caffeic acid, hesperetin, coumaric acid, isoramnetin, chrysin, quercetin, galangin, luteolin, kaempferol and cinnamic acid derivatives are responsible for the antioxidative function of honey (5, 58-61). The antioxidant potential of honey is employed in a surfeit of applications as preventing enzymatic browning of fruit and vegetables (62), lipid peroxidation in meat (63), and inhibiting proliferation of food quality deteriorating organisms (64). Researchers have authenticated that honey is competent of reducing se-

rum prostaglandins levels while concurrently increasing nitric oxide (NO) in healthy individuals. A scientific investigation to appraise the influence of natural honey on prostaglandins, NO levels, blood indices and other biochemical parameters was done in an acquired immune deficiency syndrome (AIDS) affected 40 year old woman. The lady was administered with 80 g of natural honey, following which plasma and urinary prostaglandin F2 alpha and thromboxane B2 levels, plasma, urine and saliva content of NO-end product (total nitrite) and various other hematological tests were conducted prior to intake and 3 hours post consumption. All tests were repeated post 21 days of therapy and it was ascertained that consumption of natural honey substantially drops off prostaglandins levels and promotes NO end product, perks up hematological and biochemical parameters even in an immunocompromised, middle-aged patient with an established history of AIDS (65). Another research was directed to resolve whether the antidiabetic drugs glibenclamide and metformin, if used along with tualang honey would present supplementary fortification of the pancreas in streptozotocin induced diabetic rats against oxidative stress and spoil. The diabetes induced rats showed increased levels of lipid peroxidation, up-regulated activities of superoxide dismutase and glutathione peroxidase, concurrently catalase activity was considerably decreased upon administration of glibenclamide and metformin. Contrastingly, intake of glibenclamide, metformin with honey momentously up-regulated catalase activity and down-regulated glutathione peroxidase activity while lipid peroxidation were notably decreased (66). Thus honey acts an as elixir as it not only possess antioxidant activity but is also an extremely rich and healthy source of antioxidants for diabetics.

Wound healing facet of honey

Honey has been used since ages for its healing properties and now has been proved to exert antiseptic properties which offer miraculous healing in treating burns, infected surgical wounds, ophthalmic disorders, gastroenteritis, respiratory problems, oral health and ulcers. Its superfluous usage in infections can be attributed to its antimicrobial, antioxidant and antiseptic aptitude. Honey is said to vitalize angiogenesis, promotes the growth of fibroblasts and triggers formation of new epithelial cells, prevents cross contamination of tissues and formation of bacterial biofilms, so as to accentuate the process of wound healing and repair (67, 68). It creates a moist, acidic and hypertonic environment due to its high osmotic pressure; this pulls the protease rich lymph to the site of wound to remove dead or contaminated tissue or any foreign material which could potentially re-infect the wound and retard the healing process (10). The acidic environment created by the usage of honey in wound dressing increases the oxygen load of capillary haemoglobin, aerobic environment obstructs the growth of anaerobic bacteria which metabolize proteins to generate bad odour created due to formation of sulphur and ammonia (69). Even when the wound area is large honey is capable of reducing scarring and promotes new skin growth (70). Honey has been affirmed to be effective against MDR strains as MRSA, VRE and MDR and multi- drug resistant *Pseudomonas aeruginosa*, which are the most common and perilous pathogens infecting burn victims, wound infections and skin grafting patients (47, 71). Honey also possess diuretic potential and is thus used in the treatment of kidney inflammation and for stones. It has also been used to enhance oral hygiene and to avert gingivitis, dental plaque and periodontal diseases (72).

Beneficial effects of honey on food preparations

Since ancient ages food has been revered as the best and natural medicine which preserves and protects the sanctity of the body and its constituents. In diabetes the first line of defense is always life style modifications which chiefly include dietary amends. Low glycemic index foods also embellish the digestibility of the carbohydrate, thus augmenting colon carbohydrate retention, increased colonic fermentation and inflated short chain fatty acid manufacture. This has insinuations for systemic nitrogen and lipid metabolism, and other colonic reactions (73). The nutritional aptitude of honey has been well documented. Honey is a crucial source of antioxidants and carbohydrates which also has a low glycemic index thus making it an apt substitute of sugar or sucrose. A comparative study investigating the relative tolerance to honey and glucose of middle-aged, mild diabetics with familial history of diabetes exhibited were subjected to oral glucose tol-

erance test as well as honey tolerance test simultaneously. The glucose tolerance was found impaired in 18 subjects while 5 of the subjects were diagnosed mild diabetic. All subjects with impaired glucose tolerance displayed significantly lower levels of plasma glucose after honey consumption in impaired glucose tolerant individuals and considerably high degree of tolerance to honey in diabetics. It may thus be suggested that honey is an important sugar proxy for patients with impaired glucose tolerance or mild diabetes (74).

The potentiality of honey in increasing the shelf life of food was checked by substituting honey for sucrose in a cashew apple juice. Post180 days storage at a temperature of 28±2°C, the products (different concentrations of juice and honey) were evaluated based on their sensory perception and were found to maintain good taste. Apart from this, the product also had superior satisfactoriness, good color, flavor, microbiological quality and physicochemical stability. This could be a healthier option for the fruit drink market (75).

Research to establish the best "Candy" was out of varying concentrations of honey and carrot was carried out. Of all the other concentrations, the T1 (750 g honey+1,000 g carrot) candy was well accepted even after storage at room temperature (25-30°C) for 6 months. The honey based candy is an exceptional alternative to sucrose based ones both for children and diabetics as well (76). Rana and co-workers have verified the glycemic index of food products infused with various natural sweeteners on healthy and glucose impaired individuals. The mean Incremental Area Under the Curve (IAUC) of the food preparations were much lower than ($p=<0.01$) than that of glucose. And amidst all the natural sweeteners, the preparation made with honey has the lower glycemic index with contrast to rolls made with cane sugar and jaggery (77). These studies indicate that honey when used as a substitute for sucrose or artificial sweeteners is beneficial not only to healthy individuals but also to diabetics in reducing the burden of cardiovascular diseases (78).

Conclusion

Honey has been attributed with many nutritional and health benefits. While its low glycemic index makes it an equally sweet but exceptionally healthier alternative to sweeteners, its antimicrobial capability wreathes miracles in almost every aspect of infection and healing. Honey has been attributes for therapeutic from its anti-inflammatory and anti-oxidant properties as well as boosting of the immune system. Honey also increases the shelf life of food products and its addition to food also aggrandizes their nutritional value.

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Correspondence:
Dr. Dhananjay Yadav
Department of Medical Biotechnology,
Yeungnam University, Gyeongsan,
South Korea, 712-749
E-mail: dhanyadav16481@gmail.com

Prof. GBKS Prasad
School of Biochemistry, Jiwaji University,
Gwalior-474011, M.P. India
E-mail: gbksprasad@gmail.com