Honey
as Nutrient and Functional Food: A Review

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INTRODUCTION

As the only available sweetener honey was an important food for Homo sapiens since his very beginnings. Indeed, the relation between bees and Homo sapiens started as early as stone age [106]. In order to reach the sweet honey, man was ready to risk his life (Figure 1). Already the first written reference to honey, a Sumerian tablet writing, dating back to 2100-2000 BC, mentions honey's use as a drug and an ointment [105], see chapter 1 of the Bee Hexagon book on Honey and History. In most ancient cultures honey has been used for both nutritional purposes and for medicine [34, 105, 107, 183]. According to the bible, the wise Solomon has said: "Eat honey my son, because it is good" (Old Testament, proverb 24:13). The belief, that honey is a nutrient, drug and an ointment has been carried into our days. For a long time in human history it was the only known sweetener, until industrial sugar production began to replace it after 1800 [105]. In the long human history honey has been not only as a nutrient but also as a medicine [183]. A medicine branch, called apitherapy, has developed in recent years, offering treatments for many diseases by honey and the other bee products (see Chapter 7).

At present the annual world honey production is about 1.2 million tons, which is less than 1% of the total sugar production. Today, honey is one of the last untreated natural foods. The consumption of honey differs strongly from country to country. In the major honey producing and exporting countries China and Argentina the annual consumption is small: 0.1 to 0.2 kg per capita. It is higher in developed countries, where the home production does not always cover the market needs. In the European Union, which is both a major honey importer and producer, the annual consumption per capita varies from medium (0.3-0.4 kg) in Italy, France, Great Britain, Denmark, Portugal to high (1-1.8 kg) in Germany, Austria, Switzerland, Portugal, Hungary, Greece, while in overseas countries such as USA, Canada and Australia the average per capita consumption is 0.6 to 0.8 kg/year (see Honey Chapter on this homepage)

Different surveys on nutritional and health aspects of honey have been compiled [21, 35, 39, 159, 166, 252, 258]

.COMPOSITION AND NUTRITIONAL REQUIREMENTS

Carbohydrates

Main sugars are the monosaccharides fructose and glucose. Beyond the two monosaccharides, about 25 different oligosacharides have been detected, between them nutrition relevant ones such as panose, 1-kestose, 6-kestose, palatinose [118, 326]. The principal oligosaccharides in blossom honey are the disaccharides sucrose, maltose, trehalose and turanose. Honeydew honey compared to blossom honey contains higher amounts of oligosaccharides, and also trisaccharides such as melezitose and raffinose. During digestion the principal carbohydrates fructose and glucose are quickly transported into the blood and can be utilized for energy requirements of the human body. A daily dose of 20 g honey will cover about 3% of the required daily energy.

Proteins, enzymes and amino acids

Honey contains about 0.5% proteins, mainly enzymes and amino acids. Its contribution to human protein intake is marginal with respect to quantity (Table 2).

Three main honey enzymes are diastase (amylase), decomposing starch or glycogen into smaller sugar units, invertase (sucrase, glucosidase), decomposing sucrose into fructose and glucose, as well as glucose oxidase, producing hydrogen peroxide and gluconic acid from glucose. Since the saliva yields a sufficiently high activity of amylase and glucose oxidase, honey's contribution to sugar digestion is of minor importance. Honey glucose oxidase producing hydrogen peroxide, might exert an antibacterial effect in the oral cavity.

Table 1. **A. Main honey nutrients**, after [75]: B **Vitamins in honey**, according to [75, 100, 101, 115]

Ingredient		Amount	Recommended Daily Intake[1]		
		in 100 g	1-4 years old	4-15 years old	After 15 years old
Carbohydrates	kcal	300	1000-1100	1400-2700	2400-3100
Proteins	g	0.5	13-14	17-46	44-59
Fats	g	0	-	-	-
Minerals	mg				
Sodium (Na)		1.6-17	300	410-550	550
Calcium (Ca)		3-31	600	700-1200	1000-1200
Potassium (K)		40-3500	1000	1400-1900	2000
Magnesium (Mg)		0.7-13	80	120-310	300-400
Phosphorus (P)		2-15	500	600-1250	700-1250
Zinc (Zn)		0.05-2	3	5-9.5	7-10
Copper (Cu)		0.02-0.6	0.5-1	0.5-1	0.5-1
Iron (Fe)		0.03-4	8	8-15	10-15
Manganese (Mn)		0.02-2	1-1.5	1.5-5	2-5
Chromium (Cr)		0.01-0.3	0.02-0.06	0.02-0.1	0.03-1.5
Selenium (Se)		0.002-0.01	0.001-0.004	0.001-0.006	0.003-0.007
Vitamins		**mg/kg**			
Phyllochinon (K)		ca. 0.025	15	20-50	60-70
Thiamin (B_1)		0.02-0.9	0.6	0.8-1.4	1-1.3
Riboflavin (B_2)		0.01-0.9	0.7	0.9-1.6	1.2-1.5
Niacin[2] (B_3)		0.10-2.7 (170-355)*	7	10-18	13-17
Panthothenic acid (B_5)		0.02-1.9	4	4-6	6
Pyridoxin (B_6)		0.01-0.32	0.4	0.5-1.4	1.2-1.6
Folic acid (B_9)		0.01-0.7	0.2	0.3	0.4
Ascorbic acid (C)		0.1-2.5 (52-62)*	60	70-100	100

[2] Niacin equivalents: 1 mg nicotinamide = 1 mg niacin = 60 mg tryptophan (= niacin-precursor), *- according to Chua et al.[100] for Malaysian honey

Table 2 **Other trace elements in honey**, after [75]

Element	mg/100 g	Element	mg/100 g
Aluminium (Al)	0.01-2.4	Lead (Pb)*	0.001-0.03
Arsen (As)	0.014-0.026	Lithium (Li)	0.225-1.56
Barium (Ba)	0.01-0.08	Molybdenum (Mo)	0-0.004
Boron (B)	0.05-0.3	Nickel (Ni)	0-0.051
Bromine (Br)	0.4-1.3	Rubidium (Rb)	0.040-3.5
Cadmium (Cd)*	0-0.001	Silicium (Si)	0.05-24
Chlorine (Cl)	0.4-56	Strontium (Sr)	0.04-0.35
Cobalt (Co)	0.1-0.35	Sulfur (S)	0.7-26
Floride (F)	0.4-1.34	Vanadium (V)	0-0.013
Iodine (I)	10-100	Zirkonium (Zr)	0.05-0.08

*- elements regarded as toxic, can be partially of anthropological origin

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 (Table 2). It must be born in mind that different unifloral honeys contain different amounts of minerals [59]. A possible exception is the high content, measured in Malaysian honey[100].

Honey contains a number of other trace elements. From the nutritional point of view the minerals chrome, manganese and selenium are of nutritional importance, especially for children of the age of 1 to 15 year. The elements sulphur, boron, cobalt, fluorine, iodine, molybdenum and silicon can be important in human nutrition too, although there are no RDI values proposed for these elements (Table 2).

Honey contains 0.3-25 mg/kg choline and 0.06 to 5 mg/kg acetylcholine [166]. Choline is an essential for cardiovascular and brain function, and for cellular membrane composition and repair, while acetylcholine acts as a neurotransmitter.

Aroma compounds, taste-building compounds and polyphenols

There is a wide variety of honeys with different tastes and colours, depending on their botanical origin [108]. The sugars are the main taste-building compounds. Generally, honey with high fructose content (e.g. acacia) are sweet compared to those with high glucose concentration (e.g. rape). Beyond sugars the honey aroma depends on the quantity and quality of honey acids and amino acids. In the past decades some research on honey aroma compounds has been carried out and more than 500 different volatile compounds have been identified in different types of honey. Indeed, most aroma building compounds vary in the different types of honey depending on its botanical origin [76]. Honey flavour is an important quality for its application in food industry and also a selection criterion for consumer's choice.

Polyphenols are another important group of compounds with respect to appearance and functional properties. 56 to 500 mg/kg total polyphenols were found in different honey types, depending on the honey type [20, 154]. Polyphenols in honey are mainly flavonoids (e.g. quercetin, luteolin, kaempferol, apigenin, chrysin, galangin), phenolic acids and phenolic acid derivatives [343]. The flavonoid content can vary between 2 and 46 mg/kg of honey and was higher in samples produced during dry season with high temperatures [194]. The polyphenols are responsible for the antioxidant properties of honey.

ATHLETIC PERFORMANCE

The physiological action of gel and powdered forms of honey as a carbohydrate source for athlete performance, mainly cycling one, was studied recently under controlled conditions by Kreider and coworkers [127, 128, 202-204, 206]. Honey increases significantly the heart frequency and the blood glucose level during performance[207]. It did not promote physical or psychological signs of hypoglycemia in fasted subjects [204, 223], during resistance training [127] or following resistance training [126, 127]. In another trial the effect of low and high glycemic index carbohydrate gels and honey were tested on 64 km cycling performance [128, 207]. Both high (glucose) and low GI (honey) gels increased cycling performance, honey being slightly better than glucose. The carbohydrate profile and GI response of honey was identical to that of a popular sports gel[204, 302]. According to these authors honey is well tolerated and can be an effective carbohydrate source for athletic performance. Summarising the research on honey and sport nutrition it is recommended that the amount of honey should be adapted to the body weight and to the ingestion time before exercise [202]:

- 4 hours before exercise: ingest 4 g per kg body weight
- 1 hour before exercise: ingest 1 gram per kg body weight
- 10 minutes before exercise: ingest 0.5 g per kg body weight
- During exercises 30 to 60 g can be ingested during each hour of exercise.

After physical exercise or competition carbohydrates should be supplemented by protein for optimal recovery. Dry honey, combined with whey protein was found to be more effective than protein combinations with glucose or maltodextrin [202]. For optimal recovery athletes should consume about 1 g honey per kg body weight within 15 minutes and repeat this procedure for the next 4 to 6 hours. Combining of honey with protein (3:1) may help to inhibit protein catabolism after the exercise[202]. The results by Kreider and co-workers[127, 128, 202-205] should be confirmed by other researchers.

GLYCEMIC INDEX, GLUCOSE AND FRUCTOSE

Honey and Obesity

Due to its caloric content, it is expected that honey consumption causes obesity. However, there are reports that honey consumption triggers the release of apetite regulating hormones[215] It was shown that consumption of one tablespoon of honey in warm water 1-2 ours after dinner diminished the hunger feeling of obese individuals, who lost weight during the treatment within one month[196] Lemon juice with honey has a long tradition of use during fasting. During a 4 day fasting with 300 ml of lemon juice (half a lemon 290 ml water and a teaspoon of honey) led to a significant weight reduction of 2 kg and of free fat and total blood cholesterol[323]

Glycemic index and diabetes

Glycemic index

The impact of carbohydrates on human health is discussed controversially especially the understanding of how the carbohydrate content of a given food affects blood glucose levels. Today, the dietary significance of carbohydrates is often indicated in terms of the glycemic index (GI). Carbohydrates having a low GI induce a small increase of glucose in blood, while those with high GI induce a high blood glucose level. Fructose, besides glucose the main honey sugar, has a GI of 19, sucrose: 68. Theoretically high-fructose honeys like acacia, tupelo, chestnut, thyme, calluna should have a relatively lower GI. The only comprehensive data on honey GI is the one presented in table 3. It is based mainly on data of different Australian honeys [44, 147]. There was a significant negative correlation between fructose content and GI is probably due to the diverse fructose/glucose ratios of the various honey types testes. It is known that unifloral honeys have varying fructose content [147, 290]. Indeed, there is a significant negative correlation between honey GI and fructose concentration (Arcot & Brand-Miller, 2005). Some honeys, e.g. acacia and yellow box, with relatively high concentration of fructose, have a lower GI than other honey types (Table 3). A negative correlation between GI and fructose was established, while there was no significant correlation between GI and the other honey sugars. In a study with four North American honeys with different fructose content the resulting GI values were higher than those of the Australian study and varied between 69 and 74 [175]. In another US investigation the GI of a honey of an unidentified botanical origin was found to be 35[204]. Recently a study with German honeys revealed GI values lying between 49 and 89[63, 114] while one with Turkish monofloral ones from 2016 yielded values from 45 to 69[47] In these studies citrus, acacia, chestnut, linden and heather honey had low GI values between 49 and 55. A German rape honey had a GI of 64 while a German honeydew honey had the highest GI with 89, which was probably due to its high melezitose content.

In experiments with humans Ahmad et al showed that the honey induced glucose rise in blood is less pronounced that that after intake of artificial honey control and glucose[9].

The effect of ingestion of a 75 g sugar solution containing linden honey or fructose/glucose control on serum insulin and C-peptide values of healthy humans was examined. These parameters were significantly lower for honey. The mean serum glucose concentration was also lower for honey, but direct comparisons at the various times showed no significant differences between the honey and the control. However, the area under the concentration-time profile for glucose response was lower for the honey than the control[269]

The GI concept claims to predict the role of carbohydrates in the development of obesity[228], meaning that low GI honeys could 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, is introduced. It is calculated as the glycemic index multiplied with the carbohydrate content in a given portion, divided by 100. Values lower than 10 are considered low, 10 to 20 are intermediate ones and above 20 belong to the category "high". For an assumed honey portion of 25 g the glycemic load of most honeys is low and some are in the intermediate range (Table 3).

Diabetes

The GI concept was developed to provide a numeric classification of carbohydrate foods on the assumption that such data would be useful in situations in which glucose tolerance is impaired. Therefore food with low GI should provide benefits with respect to diabetes and to the reduction of coronary heart disease[182]. Thus, consumption of honeys with a low GI, e.g. acacia honey might have beneficial physiological effects and could be used by diabetes patients. The consumption of 50 to 80 g honey of unspecified type by healthy people or diabetes patients leads to smaller increases of blood insulin and glucose than the consumption of

the same amounts of glucose and of a sugar mixtures resembling to honey[19, 27, 181]. It was shown that consumption of honey had a favourable effect on diabetes patients, causing a significant decrease of plasma glucose[25, 27, 286].

Diabetes 2 type

This diabetes type is not dependent on insulin. Honey was well tolerated by patients with diabetes of unspecified type[58] and on diabetes type-2 patients[78, 193, 310]. According to a recent study, long term consumption of food with a high GI is a significant risk factor for type-2 diabetes[226], while relatively high amounts from 70 to 90 g honey were administered without any problems for the type 2 diabetes [8, 27], or even had favourable effects on such patients[27].

In a clinical trial published in 2016 150 g honey per patient was administered daily (n=20). Honey consumption resulted in more hyperglycemia in these patients, but without diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state (HHS). Longer-term honey consumption resulted also in weight reduction in all the patients, and control of the blood pressure in the patients, who had hypertension before the honey intervention. The median duration of the honey intervention, without anti-diabetic medicines was 1.09 years, with a range from 0.42 to 13.5 years. Ten of the 20 patients continued the honey intervention for more than 1 year, whereas the other 10 continued the intervention for one year or less. The only cause of the discontinuation of the honey intervention was persistent hyperglycemia. Despite persistent hyperglycemia in all the patients, and persistence of the dyslipidemia in the patients, who had dyslipidemia before the intervention, the macro-vascular complications, particularly the coronary heart disease (CHD), did not develop in any of them. On the contrary, the cardiovascular status improved in the patients, who had CHD before the intervention. However, micro-vascular complications developed in two patient volunteers, who continued the honey intervention, without medicines, for more than 8 years.[4]

It is important to study not only the short term effect but also the long term ones on diabetes 2 patients. The results of this study demonstrate that 8-week consumption of honey can provide beneficial effects on body weight and blood lipids of diabetic patients. On the other hand, haemoglobin A (1C) values increased, meaning that a cautious consumption of honey is recommended[51]

Diabetes 1 type

This type depends on insulin and is an autoimmune disease. Honey seems to be also well tolerated by type 1 diabetes patients. Honey caused a higher c-peptide increase than comparable amounts of sucrose or glucose[5]. The c-peptide is a mass of the insulin increase in blood. It has been also hypothesised that fructose might contribute to the positive effect of honey on diabetis[135]. Also, it was shown that honey (Gelam honey from Malaysia) induced differential expression of MAPK, NF-kappa B, IRS-1 (ser307), and Akt in HIT-T15 cells and exerts protective effects against diabetes-and hyperglycemia-induced oxidative stress by improving insulin content and insulin resistance[55].

On the other hand it was found that linden honey caused lower c-peptide increase than comparable amounts of a fructose/glucose mixture[269]. The contradiction between the two studies should be resolved.

Table 3. **Glycemic index (GI) and glycemic load (GL) for a serving (25 g) of honey**, after [44, 147]

	honey origin	Fructose g /100 g	GI	AC g/serving	GL (per serving)
Acacia (black lockust)*	Romania	43	32	21	7
Yellow box	Australia	46	35±4	18	6
Stringy bark	Australia	52	44±4	21	9
Red gum	Australia	35	46±3	18	8
Iron bark	Australia	34	48±3	15	7
Yapunya	Australia	42	52±5	17	9
Pure Australia	Australia		58±6	21	12
Commercial blend	Australia	38	62±3	18	11
Salvation June	Australia	32	64±5	15	10
Commercial blend	Australia	28	72±6	13	9
Honey of unspecified origin	Canada		87±8	21	18
average		55	55±5	18	10
Glucose			100		
Fructose			19		

AC = available carbohydrate

Fructose

Fructose is the main sugar in most honeys (Table 1). An over-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[132]. After reviewing clinical studies these authors found that fructose ingestion leads to a rise of de-novo lipogenesis, which finally has an unfavourable effect on energy regulation and on body weight.

In rat feeding experiments the hypertriglyceridemic effect observed after intake of fructose alone does not take place after feeding of honey fructose. Compared to rats fed with fructose, honey-fed rats had higher plasma α-tocopherol levels, higher α-tocopherol/triacylglycerol ratios, lower plasma NO_x 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 [89].

It was shown that in patients with hypertriglyceridemia, artificial honey increased TG, while honey decreased TG [16].

Recently it was found out that feeding rats by 10 % honey solution decreased the weight of the rats by decreasing their feeding frequency[68].

Feeding of honey or sugar to Wistar rats resulted both in increase of weight in comparison to controls. Sucrose fed fat cells were significantly larger than the honey fed ones.[304]

Honey ingestion by humans leads to a rise of blood fructose concentration: in one case (rape honey), this rise was lower than that achieved after fructose/glucose controls, in the other cases it was same as after the controls (acacia honey). Fructose metabolism may be inhibited by unidentified substances present in the rapeseed honey[268]

Fructose intolerance or incomplete absorption

It was shown that ingestion of 50 and 100 g honey by normal humans has a laxative effect due to incomplete fructose absorption[213, 214]. However these are quite large doses rarely ingested in normal honey consumption. On the other hand, in cases of fructose intolerance due to different disorders (fructosurea, hereditary fructose intolerance, metabolic deficiency) honey consumption is not recommended[330]

In the case of irritable bowel syndrome (IBS) high fructose foods, and also honey, are generally not recommended[117, 270] . However consumption of small quantities of glucose rich honeys should pose less problems or might be unproblematic.

Summarising the above research, honey has probably no or a weak effect on obesity compared to pure fructose. However, there is need of further tests with human nutrition studies, carried with a variety of unifloral honeys.

On the other hand caution is necessary when ingesting higher honey quantities or in cases of fructose intolerance of malabsorption.

INFANT NUTRITION

The application of honey in infant nutrition used to be a common recommendation during the last centuries and there are some interesting observations reported. Infants on a diet containing honey had better blood building and a higher weight increase compared to a diet without honey[149]. Honey was better tolerated by babies than sucrose [265] and compared to a water based placebo significantly reduced crying phases of infants [300]. Infants have a higher weight increase when fed by honey than by sucrose, and showed less throw up than the sucrose controls [260]. Compared to sucrose, ingestion of honey by infants resulted in an increase of haemoglobin content, better skin colour while no digestion problems were encountered[334, 344]. Infants exposed to a honey regimen had a better weight increase and during the regimen were less susceptible to diseases than infants fed normally or infants given blood building agents [149].

The positive effects of honey in infant diet are attributed to effects on the digestion process. One possible cause is the well established effect of oligosaccharides on *B. bifidus* [303]. When fed on a mixture of honey and milk infants showed a regularly steady weight gain and had an acidophilic microorganism flora rich in *B. bifidus*[169]. In an other experiment with honey and milk it was shown that the infants were suffering less frequently from diarrhoea, and their blood contained more haemoglobin compared to a diet based on sucrose

sweetened milk[334]. Feeding honey to infants improved calcium uptake into the blood, resulting in lighter and thinner faeces[65].

There is a health concern for infants regarding the presence of *Clostridium botulinum* in honey. Since the presence of this bacterium in natural foods is ubiquitous and honey is a non sterilized packaged food from natural origin the risk of a low contamination cannot be excluded. Spores of this bacterium can survive in honey, but they cannot build toxin. But in the stomach of infants younger than one year the bacteria spores from honey can survive, grow, and theoretically build the toxin. On the other hand humans older than 12 months can ingest honey without any risk. In some cases, infant botulism has been explained by ingestion of honey [104, 245, 266, 336]. In Germany about one case of infant botulism per year is reported [266]. As a result of the reported infant botulism cases some honey packers (e.g. the British Honey Importers and Packers Association) place a warning on the honey label that "honey should not be given to infants under 12 months of age". Recently, a scientific committee of the EU has examined the hazard of *Cl. botulinum* in honey. It has concluded, that no microbiological examinations of honey are necessary, as the incidence of *Cl. botulinum* is relatively low and tests will not prevent infant botulism. In the EU countries the health authorities have not issued a warning label on honey pots. Also, the counter-indication of honey in nourishing of infants in developing countries has been questioned [140].

For safety reasons honey should be given only to infants older than 1 year

FUNCTIONAL PROPERTIES

The functional properties of honey are tested in animals and cell cultures. They are discussed in detail in separate sections and are summarised in the following table:

Effect	Tested honey type
Antibacterial, antifungal and antiviral	Different honey types
Antioxidant and hepatoprotective	Different honey types
Anti-inflammatory	Different honey types
Anticancerogenic and antimutagenic	Different honey types
Radiation protection	Gelam and Tualang honey
Immunoactivating and immunosuppressive	Different honeys, often unspecified
Antiatherogenic	Different honeys, often unspecified
Probiotic and prebeiotic	Different honey types
Antinociceptive	Different honey types
Anti-neurogenerative	Different honey types
Anti-osteporosis	Tualang and honey of a unspecified floral origin
Improves the renal funciont	Honey of a unspecified floral origin
Improves the spatial memory of rats	Honeydew honey
Anxiolytic, antinociceptive, anticonvulsant and antidepressant	Different Nigerian honey of specified floral origin
Improves the fertility of rats	Tualang, Malaysia and Palestine honey

ANTIMICROBIAL PROPERTIES

The antimicrobial action of honey has been extensively reviewed in 1992 by Molan[255, 256] and in 2011 by Al-Waili et al. [17]. It has both a direct and an indirect action.

Indirect antimicrobial action

Honey can fight microbial infection by its immuno-activating, anti-inflammatory and prebiotic activity.

Direct antimicrobial action

illustration: Don Smith

Honey inhibits the growth of microorganisms and fungi. The antibacterial effect of honey, mostly against gram-positive bacteria, is very well documented [71, 253, 255, 257]. Both bacteriostatic and bactericidal effects have been reported, against many strains, many of which are pathogenic (Table 4).

In 1937 Dold et al. determined the antibacterial acivity as inhibine. The antibacterial assay carried out with *Staph. aureus* was senstitive to hydrogen peroxide. Researchers using this method found a good correlation between the capacity of honey to produce peroxide and the inhibine value. Honey glucose oxidase produces the antibacterial agent hydrogen peroxide [361], while another enzyme, catalase breaks it down[121]. Honey with a high catalase activity have a low antibacterial peroxide activity[70, 71]. White established a good correlation between the peroxide accumulation capacity and the antibacterial activity expressed as inhibine[123, 360]. Lavie was the first to postulate the existence of other antibacterial substances in honey[216].

Table 4 **Infections caused by bacteria that have found to be sensitive to honey** [253, 257]

Pathogen	Infection caused
Bacillus anthracis	anthrax
Corynebacterium diphtheriae	diphtheria
Escherichia coli	diarrhoea, septicaemia, urinary infections, wound infections
Haemophilus influenzae	ear infections, meningitus, respiratory infections, sinusitis
Klebsiella pneumoniae	pneumonia
Mycobacterium tuberculosis	tuberculosis
Proteus sp.	septicaemia, urinary infections
Pseudomonas aeruginosa	urinary infections, wound infections
Salmonella sp.	diarrhoea
Salmonella cholerae-suis	septicaemia
Salmonella typhi	typhoid
Salmonella typhimurium	wound infections
Serrata marcescens	septicaemia, wound infections
Shigella sp.	dysentery
Staphylococcus aureus	abscesses., boils, carbuncles, impetigo, wound infections
Streptococcus faecalis	urinary infections
Streptococcus mutans	dental carries
Streptococcus pneumoniae	ear infections, meningitis, pneumonia, sinusitis
Streptococcus pyogenes	ear infections, impetigo, puerperal fever, rheumatic fever, scarlet fever, sore throat, wound infections
Vibrio choleriae	cholera
Actin. pyogenes, Kleb. Pneum., Noc. asteroids, Staph. aureus, Streptoc. agal., dysgal.,	mastitis
Epiderm floccosum, Microsp. canis, M.. gypseum, Trichoph. rubrum, T. tonsurans, T. mentagr. var.	tinea
E coli, Salmonella, Shigella, Vibrio, Hel. pylori	peptic ulcer

Honey has been tested generally on individual bacteria, but it is able to inhibit a mixture of highly concentrated different human pathogen bacteria[29]

Different microbes present on the skin were also inhibited by the action of honey[244]

Different antibacterials to optimise action and reduce chances for developing bacterial resistance

It was reported that depending on the antibacterial test it is possible to differentiate between the peroxide and non peroxide antibacterial action. Using this test different types of antibacterial substances have been determined, the chemical identity of which remains to be determined. The substances have different chemical characteristics: acidic, basic or neutral and that the main non-peroxide antibacterial activity is acidic[71].

Studies with Malaysian Tualang honey showed also, that the main non-peroxide antibacterial activity is acidic[198]. Interestingly, honey acts best against bacteria in acidic medium. This is important from therapeutic point of view as the wound medium is also acidic[26]

Truchado et al, using another antibacterial test measured also mainly non-peroxide antibacterial activity[346]. Thus, depending on the antibacterial test different types of antibacterial activity can be determined. Summarising, antimicrobial effect of honey is due to different substances and depends on the botanical origin of honey [71, 253, 255, 257]. There are non-peroxide antibacterial substances with different chemical origin, e.g. and compounds with different chemical properties:

1. Phenolics and flavonoids, present in honey are also likely candidates, as many of them have been shown to have antibacterial activity [32, 109, 139, 192, 232, 262, 357], but in one study there was no correlation between honey phenolics and antibacterial action[346]. In a study with Cuban unifloral honeys honeys with higher phenolic content tended to have a higher antibacterial activity[37]

2. The high sugar concentration of honey[267], and also the low honey pH[367] can be responsible for the antibacterial activity.

3. Undetermined components of the water and methanolic extract of chestnut honey inhibit pathogenic bacteria like *Erwinia carotovora*, *Yersinia enterocolitica*, and *Aeromonas hydrophila* interfering in the quorum signal (QS) system of bacteria. The bacterial QS system is thought to determine the virulence of bacteria. The substances are thought to belong to the carbohydrate fraction of honey [345].

4. Carbohydrate break-down Maillard products, present in Canadian honey[83, 87] and probably also in any honey, have an antibacterial activity. These substances are also present in fresh honey.

5. Antibacterial aromatic acids [307] and 10-HDA, the main royal jelly acid with antibacterial properties[176] have also been found in honey.

6. An antibacterial honey protein as defensin-1, which originates in royal jelly, was also found in honey[210].

7. Honey bacteria produce antibiotic-like antifungal peptide compounds, e.g. bacillomycin F [219, 220]

8. The strong antibacterial activity of Manuka honey is due to the presence of the antibacterial substance methylglyoxal[240].

9. Lysozyme[221]

10. MRJP1-containing glycoproteins[88]

Summarising, following antibacterial factors are responsible for the antibacterial action

- **Osmotic effect of sugars**
- **pH and honey acids**
- **Hydrogen peroxide**
- **Others**: **phenolics, carbohydrates, Maillard products, proteins, antibiotic-like peptides methylglyoxal, and other non-determined substances**

Contrary to the non-peroxide activity, the peroxide one can be destroyed by heat, by light and by storage [71] (Table 6). The antibacterial activity of light blossom honey was more influenced by these different factors that of the dark honeydew honey. Thus, for optimum antibacterial activity, honey should be stored in a cool, dark place and should be consumed when fresh.

Some of the antimicrobial activity originates from the bees (the peroxide producing enzymes, the honey acids, carbohydrates, defensin-1, antibiotic-like compouns) while some of it originate of it from the plants (methylglyoxal, polyphenols) while a third part might be created during honey storage (Maillard products).

Many of the honey antimicrobials are in fact produced by honey probiotic bacteria, present in present honey[277].

Influence of processing and storage

In two papers the influence of honey conditioning and storage on antibacterial activity was tested:

Table 5. **Influence of heat, light and storage on the antibacterial activity of honey against *Staph. aureus*** after [70, 73]

	Non-peroxide activity		Peroxide activity	
Storage: 15 months at rt	light	dark	light	dark
Blossom honey	76	86	19	48
Honeydew honey	78	80	63	70
Heat: 15 min 70°C				
Blossom honey	86		8	
Honeydew honey	94		78	

antibacterial activity in % of the untreated controls, rt – room temperature 20-25 °C

In a paper from India in 2016 the effect of filtration and processing (heating at 77 °C for 30 minutes) in 3 different honeys was tested in different bacterial strains. The MIC values increased from 6.25 % (unprocessed honey) to 25 % (filtered honey) and 50 % (processed honey) [328]

Only fresh and unheated honey has optimum antibacterial activity. Early research showed that the peroxide activity is destroyed by heat and by storage in the light [122, 358, 359]. On the other hand it was shown that the non-peroxide activity is less susceptible to heat and light[70, 73, 157]. On the other hand, Maillard products which are produced upon heating and storage of honey have also antibacterial activity[83, 87]. The results are difficult to interpret as it is not clear which type of antibacterial activity has been tested in many studies. However, taken a whole there is an overall decrease of all activity upon storage, less if stored in the dark.

For optimum activity store unheated honey in a dark cool place.

Mechanism of antimicrobial action: bactericidal or bacteriostatic?

In most of the reports on honey antibacterial action no distinction has been made between the two. Most experiments report on stop of bacterial growth after a certain time. The higher the concentration the longer is the period of growth inhibition. Complete inhibition of growth is important for controlling infections[255]

The bactericidal action of honey seems to be dependent on the time of honey action. The time for bactericidal action depends on the bacteria type and vary from several to 40 hours. The concentration of honey also plays a role. Honey concentrations varying from 5 to 50 % have been found to be bactericidal. Generally, the higher the concentration, the faster the bactericidal action can take place [255].

Antiviral, fungicide, anti-parasite activity and neamaticidal activity

Antiviral activity: it was reported that honey has been shown to inhibit in vitro the *Rubella* virus [372] and *Herpes* virus[28, 163], *P. sativum, N. sativa, Z. multiflora and Z. mauritiana* honeys from Iran have anti- HIV-1 activity as tested by PCR, due to methylglyoxal[57]

High inhibitory activity against the influenza virus of various sources was reported for Manuka honey[355] due to methylglyoxal[95]

Anti-parasite activity

It was reported that honey inhibited the growth of three species of the *Leishmania* parasite [373] Honey extract exhibited anthelmintic activity[297] Pakistan honey was found to exibit antiparasitic activity against the model nematode Caenorhabditis elegans [49]

Neamticidal activity of honey against the model nematode *Caenorhabditis elegans* is reported[309]

Honey has **fungicide** acitivity, but not many funghi species have been tested. It has antifungal activity against dermatophytes, that can cause human mycoses (Tinea). Such mycoses is a common disease in humans. Honey has been shown to have a fungicide activity agains dermatopytes from the genera *Epidermophyton, Microsporum* and *Thrichophyton*, all species that can affect humans [257].

Recently honey samples from different floral sources were evaluated for their ability to inhibit the growth of 40 yeast strains (*Candida albicans, C. krusei, C. glabrata and Trichosoporon spp*.). Rhododendron and multifloral honeys have generally more inhibitory effect than eucalyptus and orange honeys (P < 0.05) [200]. Different unifloral honey from Slovakia also showed antifungal activity against *Penicillium crustosum, P. expansum, P. griseofulvum, P. raistrickii and P. verrucosum* , mostly at concentration higher than 10% [186]. Further studies are now required to demonstrate if this antifungal activity has any clinical application.

A mixture of honey and yoghurt was successfully tested to control vulvovvaginal candidasis of pregnant women[2]

The fungicide effect of honey against *Candida albicans* is due to the effect of honey flavonoids [90]. The fungicide effect of honey against *Candida albicans* is due to the effect of honey flavonoids [90]. On the other hand bacteria strain BH072 with a antifungal peptide was isolated in honey[374]

Different Iranian honeys have antifungal activity Candida, Aspergillus Species and Trichophyton Rubrum[191]

Invasive aspergillosis has become an increasing problem in immunocompromised patients in recent years. Due to increased antimicrobial resistance, natural agents with medicinal and immunomodulatory effects have gained more attention. Aspergilus infected mice fed with honey have a longer survival than controls[274]

Why is honey successful in antivirulence therapy?
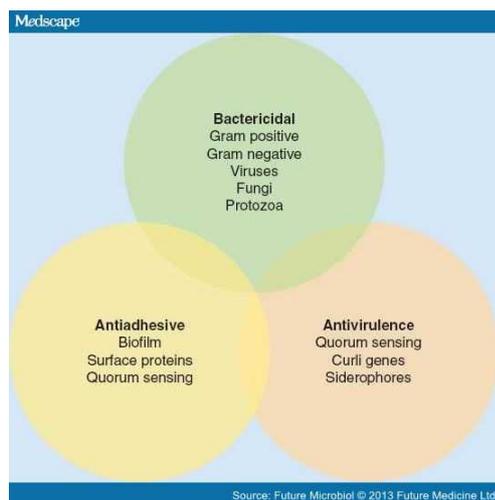
The review of Maddocks and Jenkins 2013

The review [230] addresses the issue: It is becoming increasingly apparent that honey impacts on the virulence of bacterial pathogens in addition to affecting cellular structure and metabolism. This is an attractive attribute for an antimicrobial, and studies investigating novel ways of treating bacterial infection are beginning to focus on antivirulence treatments rather than traditional bactericidal or bacteriostatic remedies. Honey inhibits quorum sensing and virulence. Honey reduces the capacity of pathogenic microorganisms to obtain iron from their host is detrimental to both colonization and subsequent progression of infection. Moreover these mechanisms demonstrate that honey functions via two independent mechanisms, being both bactericidal and antivirulent making it an attractive antimicrobial whose multifaceted action is not likely to promote resistance. In summary: the multiple effects of honey can be assigned to individual subgroups, but collectively exert a combined effect against numerous different types of microorganism (see figure above) Honey can be used together with antibiotics in a synergistice way in order to increase antibiotic action.

The review of Carter et al. 2016

This review is about Manuka honey [92] as the antimicrobial properties of this type of honey is most widely researched (see there all original references, here only the conclusions are given). In this review arguments for using honey as an antimicrobial action for wide use in hospitals are collected.

As there are equally potent antimicrobial honeys (see below antibacterial properties of monofloral honeys), probably the conclusions of this review which made mostly for manuka honey, are probably valid for all potent antimicrobial honeys.

Ultrastructural studies of bacterial cells and communities treated by honey

oney can profoundly alter the size and shape of bacterial cells, although the extent of this varies in different bacterial species. S. aureus cultures treated with manuka honey had more cells with completed septa compared to those treated with artificial honey, suggesting cells entered but failed to complete the division

stage of the cell cycle, although externally these cells appeared normal by scanning electron microscopy (SEM) More recently, phase-contrast imaging following treatment with a sub-lethal dose of manuka honey found cells of S. aureus and Bacillus subtilis were significantly smaller and were more likely to have condensed DNA than those growing without honey. It is difficult to directly compare these studies as they used different amounts of honey and treatment times, but overall the results suggest an uncoupling of growth and cell division, which is often seen in response to nutritional and environmental stresses.

Honey treatment has been reported to cause cultures of the Gram negative species E. coli and P. aeruginosa to have both abnormally shorter and longer cells. This apparent degeneration of the P. aeruginosa cell was supported by quantitative PCR analysis that showed a 10-fold down-regulation in honey-treated cells of oprF, which encodes an outer-membrane porin that is important for structural stability.

'Omics analyses assess the whole-cell response to inhibition by honey

The ability to assess whole cell outputs has revolutionized the study of drug-pathogen interactions and has particular value for complex natural products like honey where effects on multiple processes are likely. Microarray and proteomic studies of bacteria exposed to honey suggested an induction of stress-related processes and suppression of protein synthesis. While overall this is fairly typical of a response to inhibitory agents, honey produced a unique "signature" of differential expression that included many proteins with hypothetical or unknown functions, suggesting a novel mode of action. Specific genes or proteins found to be down-regulated in 'omics analyses of S. aureus and E. coli O157/H7 have functions relating to virulence, quorum sensing and biofilm formation, and in P. aeruginosa there was a down-regulation of proteins involved in flagellation. These phenotypes are critical for pathogens to establish and produce invasive infection and indicate that as well as inhibiting growth, honey can reduce the pathogenic potential of infecting bacteria.

Interactions between honey and conventional antibiotics

As well as use as a sole agent, there is scope for using honey to augment treatment with conventional antibiotics. This may have particular value when combined with systemic agents that can be delivered to a wound bed via blood circulation while honey is applied topically. Combined treatments can also lower the therapeutic dose of antimicrobial agents and prevent the development of resistance, and in some cases can result in drug synergy, where the combined activity is greater than the sum of the individual activities of each drug partner. Different studies show a successful synergetic action of manuka honey and different antibiotics.

Indirect antimicrobial action

Honey has **immuno-activating activity** and **prebiotic** activity (see below) and thus can act as an indirect activator of the organism defence system against microbes.

ANTIOXIDANT ACTION AND OTHER ACTIONS LINKED TO IT
In vitro measured antioxidant activity

The term "oxidative stress" describes the lack of equilibrium in the organism between the production of free radicals and the antioxidant protective activity. The protection against oxidation is thought to prevent some chronic diseases. The oxidative modification of the lipoproteins is considered to be an important factor for the pathogenesis of arteriosclerosis.

Honey has been found to contain significant antioxidant activity [1, 20, 33, 61, 69, 85, 110, 143, 148, 155, 155, 172, 272, 287] the antioxidants being glucose oxidase, catalase, ascorbic acid, flavonoids, phenolic acids, carotenoid derivatives, organic acids, Maillard reaction products, amino acids, proteins. Recent results show that high-molecular-mass melanoidins found in honey are also potent antioxidants [84, 86] These and other Maillard products seem to be the dominant antioxidants [87].

Different methods have been applied and also antioxidant activity units determined. The different methods for the determination of the antioxidant activity have been reviewed [36].

Honey seems to potentiate the antioxidant action of herbs, thus making it an ideal sweetener of herb infusions [285]

The impact of heat on the antioxidant capacity of clover and buckwheat honey during storage was analysed recently. Processing clover honey did not significantly impact antioxidant capacity. Storage during 6 months reduced the antioxidant capacity of honeys by about 30%, with no impact of storage temperature or

container type detected at the end point of the storage period. Another work also reports a decrease of phenolic content and the antioxidant capacity of acacia honey after one year of storage of honey at room temperature[315]

In another study both antioxidant activity and brown pigment formation increased with heat treatment and time [348]. This can be explained by the formation of the antioxidants HMF and similar Maillard products.

On the other hand other works report no change of antioxidant capacity of processed and raw honeys after storage [354]. In another work honey heating at high temperatures does not seem to influence the antioxidant activity of honey[314]

If honey is fermented to mead it loses some of its antioxidant activity, this loss is less pronounced in acacia and linden honey[116].

Summarising the results it seems that heating of honey at high temperatures does not seem to influence the antioxidant properties of honey, while storage can lead to both decrease and increase of acitivity. Further research is necessary to clarify the conflicting results.

Antioxidant effect in vivo

The antioxidant activity of honey was not influenced after digestion[275]

There is a significant correlation between the antioxidant activity, the phenolic content of honey and the inhibition of the in vitro lipoprotein oxidation of human serum. It was found that honey intake caused a higher antioxidative effect in blood than the intake of black tea, although its in vitro effect measured as ORAC activity was five times smaller than that of black tea [156].

Generally, the darker the honey, the higher its phenolic content and its antioxidant power. [64, 138, 155, 238, 292, 312, 352]. Further, in a lipid peroxidation model system buckwheat honey showed a similar antioxidant activity as 1 mM α-tocopherol [272]. Also, the influences of honey ingestion on the antioxidative capacity of plasma was also tested [24, 317]. In the first study the trial persons were given maize syrup or buckwheat honeys with a different antioxidant capacity in a dose of 1.5 g/kg body weight. In comparison to the sugar control honey caused an increase of both the antioxidant and the reducing serum capacity [317]. In the second study humans received a diet supplemented with a daily honey consumption of 1.2 g/kg body weight. Honey increased the body antioxidant agents: blood vitamin C concentration by 47%, β-carotene by 3%, uric acid by 12%, and glutathione reductase by 7% [24]. It should be borne in mind that the antioxidant activity depends on the botanical origin of honey and has remarkable variations in honey from different sources [20, 54, 148, 155, 208, 352].

The antioxidant activity of honey is probably the reason of the protective effect of honey against damage and oxidative stress induced by CS in rat testis[250]

Manuka honey protects middle-aged rats from oxidative damage. Ingested honey resulted in different antioxidant effects: the level of DNA damage was reduced, as well as the malondialdehyde level and the glutathione peroxidase activity in the liver of both the young and middle-aged groups. The glutathione peroxidase activity was increased in the erythrocytes and the catalase activity was reduced in the liver and erythrocytes of both young and middle-aged rats given supplementation[185]

Links to other diseases

In a review by Erejuwa et al. the antioxidant properties of honey are reviewed and honey is praised as a "novel antioxidant". This review presents findings that indicate honey may ameliorate oxidative stress in the gastrointestinal tract (GIT), liver, pancreas, kidney, reproductive organs and plasma/serum. Besides, the review highlights data that demonstrate the synergistic antioxidant effect of honey and antidiabetic drugs in the pancreas, kidney and serum of diabetic rats. This is strengthened by the finding that honey potentiates the antioxidant effects of herbs[285] These data suggest that honey, administered alone or in combination with conventional therapy, might be a novel antioxidant in the management of chronic diseases commonly associated with oxidative stress. In view of the fact that the majority of these data emanate from animal studies, there is an urgent need to investigate this antioxidant effect of honey in human subjects with chronic or degenerative diseases. The authors go on to suggest that honey might be the better antioxidant than accepted antioxidants such as vitamin C and E, as the latter act also as oxidants [136]

Hepatoprotective effects

Generally, antioxidant and hepatoprotective properties correlate well with each other, as decreasing harmful radicals will protect the liver from them.

The amelioration of oxidative stress, as a result of honey administration, was accompanied by significant reductions in the size of enlarged hepatocytes and edema, restoration of bile canal iculidilatation and reduced number of apoptotic cells[197]. Similar hepatoprotective effect of honey was also reported in rats with obstruction of the common bile duct[137].

In rats with N-ethylmaleimide (NEM)-induced liver injury, honey supplementation significantly restored the levels of hepatic glutathione, ameliorated the (NEM)-induced congestion and mononuclear cell infiltration in the liver[201]. These findings, generally, suggest that amelioration of oxidative stress in the liver may contribute to the hepatoprotective effect of honey.

Honey was an effective hepatoprotective agent against paracetamol-induced liver damage in rats[151]

Honey significantly improved the high-fat-diet-induced hepatic injury, steatosis, fibrosis, oxidative stress, and inflammation in rats. Honey also inhibited the overexpression of TXNIP and the activation of NLRP3 inflammasome. These effects were replicated in BRL-3A cell line which showed that the down-regulation of TXNIP or inhibition of NLRP3 contributed to the suppression of NLRP3 inflammasome activation, inflammation, and re-balanced lipid metabolism[366]

Anti-inflammatory effects

Inflammation in the body is often caused by free radicals. Thus antioxidant and anti-inflammatory effects of honey are probably linked to each other. Indeed, the anti-inflammatory action of honey is well documented (see above).

Radioprotective effects

Gelam honey from Malaysia modulates the expression of antioxidant enzymes at gene and protein levels in irradiated HDFs indicating its potential as a radioprotectant agent[12] Tualang honey protects keratinocytes from ultraviolet radiation-induced inflammation and DNA damage[11]

Honey, oxidative stress, hypertension and diabetes

Oxidative stress is implicated in the pathogenesis and/or complications of hypertension and/or diabetes mellitus. A combination of these disorders increases the risk of developing cardiovascular events. This study investigated the effects of streptozotocin (60 mg/kg; ip)-induced diabetes on blood pressure, oxidative stress and effects of honey on these parameters in the kidneys of streptozotocin-induced diabetic Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR). Diabetic WKY and SHR were randomized into four groups and received distilled water (0.5 mL) and tualang honey (1.0 g/kg) orally once daily for three weeks. Control SHR had reduced malondialdehyde (MDA) and increased systolic blood pressure (SBP), catalase (CAT) activity, and total antioxidant status (TAS). SBP, activities of glutathione peroxidase (GPx) and glutathione reductase (GR) were elevated while TAS was reduced in diabetic WKY. In contrast, SBP, TAS, activities of GPx and GR were reduced in diabetic SHR. Antioxidant (tualang honey) treatment further reduced SBP in diabetic SHR but not in diabetic WKY. It also increased TAS, GSH, reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio, activities of GPx and GR in diabetic SHR. These data suggest that differences in types, severity, and complications of diseases as well as strains may influence responses to blood pressure and oxidative stress[134]

Antioxidant scavenging activity is linked to the prevention of many chronic and age dependent pathological conditions like cancer, diabetes, atherosclerosis, cataract and other chronic pathological conditions [40, 136].

ANTI-INFLAMMATORY EFFECTS

Anti-inflammatory effects of honey in humans were studied by Al Waili and Boni [30] after ingestion of 70 g honey. The mean plasma concentration of thromboxane B(2) was reduced by 7%, 34%, and 35%, that of PGE(2) by 14%, 10%, and 19% at 1, 2, and 3 hours, respectively, after honey ingestion. The level of PGF(2α) was decreased by 31% at 2 hours and by 14% at 3 hours after honey ingestion. At day 15, plasma concentrations of thromboxane B(2), PGE(2) and PGF(2α) were decreased by 48%, 63% and 50%, respectively.

Ingestion of honey had a positive effect in an experimental model of inflammatory bowel disease in rats [67]. Honey administration is as effective as prednisolone treatment in an inflammatory model of colitis. The postulated mechanism of action is by preventing the formation of free radicals released from the inflamed tissues. The reduction of inflammation could be due to the antibacterial effect of honey or to a direct antiinflammatory effect. A support of the latter hypothesis was shown in animal studies, where antiinflammatory effects of honey were observed in wounds with no bacterial infection [295]. Experiments with honey to reduce artificial inflammation of rabbits point out that the antifinlammtory effect might be due to improved blood parameters such as reduced infiltration of neutrophils and decreased myeloperoxidase activity[190].

Gelam honey from Malaysia attenuates Carrageenan-induced rat paw inflammation via NF-kappa B pathway[170], attenuates the oxidative stress-induced inflammatory pathways in pancreatic hamster cellsan[308] and ovalbumin-induced airway inflammation in a mice model of allergic asthma[320]

New Zealand rewarewa, manuka and kanuka honey samples exhibited potent, dose-dependent reduction of human neutrophil superoxide production in vitro. This inhibitory activity did not correlate with levels of known phenolic-based free radical scavengers. Furthermore, the active honeys did not scavenge superoxide generated in a cell-free xanthine/xanthine oxidase assay. In C57BL/6J mice, topical application of manuka and rewarewa honey samples with the highest in vitro activity suppressed arachidonic acid-induced ear oedema, and rewarewa honey suppressed both oedema and leukocyte (monocyte and neutrophil) infiltration. Together, these findings demonstrate that some indigenous NZ honeys exhibit clinically relevant anti-inflammatory activity[222]

Gelam honey from Malaysia attenuates Carrageenan-induced rat paw inflammation via NF-kappa B pathway[170]

Honey flavonoids significantly inhibited the release of pro-inflammatory cytokines such as TNF-alpha and IL-1 beta. The expressions of iNOS and the production of reactive oxygen intermediates (ROS) were also significantly inhibited. Accordingly, the present study demonstrates that HFE is a potent inhibitor of microglial activation and thus a potential preventive therapeutic agent for neurodegenerative diseases involving neuroinflammation[91]

Tualang honey protects keratinocytes from ultraviolet radiation-induced inflammation and DNA damage [11]

Ingestion of honey by rats showed that honey has analgesic and anti-inflammatory effects by the involvement of autonomic receptors[283]

Analgesic action

Pain soothing action can come into being by direct anti-inflammatory action and by action on the brain. The analgesic action of honey has been shown to be due to the anti-inflammatory action (see above) but also to a action on the brain via the opioid system, due possibly to honey flavonoids[371]

Inflammation in specific parts of the human body is thought to be a major cause of chronic diseases, especially of cardiovascular diseases [363]. Thus, the positive effect of honey on cardiovascular health can be explained by the ant-inflammatory activity of honey.

ANTIMUTAGENIC AND ANTITUMOR EFFECTS

Antimutagenic effects

Mutagenic substances act directly or indirectly by promoting mutations of genetic structure. During the roasting and frying of food heterocyclic amines are built, 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 via the Ames assay and compared to that of a sugar analogue and to individually tested simple sugars. All honeys exhibited significant inhibition of Trp-p-1 mutagenicity. Glucose and fructose were found to be similar antimutagenic as honey and were more antimutagenic than maltose and sucrose [353].

Stingless bee honeys from west Amazonian Ecuador showed anti-mutagenic activity assayed with Saccharomyces cerevisiae D7 strain, inhibiting back mutation over the entire tested concentration range[160]

Antitumor effects

A 2012 review summarises the anticancerogenic properties of a number of honey flavonoids[6]

The anticancerogenic effects of honey have been recently reviewed[14, 133, 278]. These effects of honey have been thoroughly investigated in certain cancers such as breast, liver and colorectal cancer cell lines. In contrast, limited but promising data are available for other forms of cancers including prostate, bladder, endometrial, kidney, skin, cervical, oral and bone cancer cells.

Breast cancer

Breast cancer is the most frequent cause of death in women. Anticancer activity is targeted to regulate the estrogen signal pathway.

Tsiapara et al. investigated the influence of Greek honey extracts (thyme, pine and fir honey) on the oestrogenic activity and cell viability of breast MCF-7 cancer cells. The authors found that the honey samples exhibited a biphasic activity in MCF-7 cells depending on the concentration—an antiestrogenic effect at low concentrations and an estrogenic effect at high concentrations. In the presence of estradiol, thyme and pine honey extractswere found to antagonize estrogen activity, while fir honey extract enhanced estrogen activity in MCF-7 cells. The study also reported variations on the effects of the three honey extracts on cell viability. While the study found no effect of thyme and pine honey on MCF-7 cells, fir honey enhanced the viability of MCF-7 cells. These dual effects of honey extracts are mostly likely due to their high contents of phenolic compounds such as kaempferol and quercetin. The authors concluded that modulation of oestrogen activity was linked to the rich phenolic content of Greek honeys and suggested that a thyme honey-enriched diet may prevent cancer related processes in breast, cancer[347].

Tualang and Manuka honeys also exert an antitumor activity against breast cancer lines[144],[145, 187]

Several studies have also confirmed the antimetastic, antiproliferative and anticancer effects of honey on breast tumor or cancer in rodents[180, 280],[281]

The above cited studies suggest that honey exhibits anticancer effect as evident by its antiestrogen activity and potential in inducing mitochondrial membrane depolarization and apoptosis in breast cancer cells.

Colorectal cancer

This is the third commonest cancer in the world and also second or third leading cause of cancer death.

In different studies the anti-liver cancer studies in cell studies and mice models[279],[281],[178],[179],[356],[145]

Details of some of the cited studies:

The antimetastatic effect of honey and its possible mode of antitumor action was studied by applying honey in spontaneous mammary carcinoma, in methylcholanthrene-induced fibrosarcoma of CBA mouse and in anaplastic colon adenocarcinoma of Y59 rats [279]. A statistically significant antimetastatic 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, the authors postulate that honey given orally before tumour cell inoculation may have an impact on tumour spreading.

In another work 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. A pronounced antimetastatic effect was observed when honey was applied before tumour-cell inoculation (peroral 2 g kg⁻¹ for mice or 1 g kg⁻¹ for rats, once a day for 10 consecutive days) [281].

The anti-proliferative effect of honey in colon cancer cells was explained by its antioxidant and anti-inflammatory properties [178].

Honey exerted antiproliferative potential against the HCT-15 and HT-29 colon cancer cells as assessed by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. Flow cytometric analysis showed the increasing accumulation of hypodiploid nuclei in the sub-G(1) phase of cell cycle indicating apoptosis. Honey transduced the apoptotic signal via initial depletion of intracellular non protein thiols, consequently reducing the mitochondrial membrane potential (MMP) and increasing the reactive oxygen species (ROS) generation. An increasing earlier lipid layer break was observed in the treated cells compared to the control. Honey induced apoptosis was accompanied by up-regulating the p53 and modulating the expression of pro and anti-apoptotic proteins. Further apoptosis induction was substantiated using DNA fragmentation assay and YO-PRO-1 staining. Results showed honey as a plausible candidate for induction of apoptosis through ROS and mitochondria-dependent mechanisms in colon cancer cells. This will promote honey as a potential chemotherapeutic agent against colon cancer[179].

Gelam and Nenas monofloral honeys inhibit proliferation of HT 29 colon cancer cells by inducing DNA damage and apoptosis[356]

Manuka honey has antiproliferative activity of manuka honey on three different cancer cell lines, murine melanoma (B16.F1) and colorectal carcinoma (CT26) as well as human breast cancer (MCF-7) cells in vitro[145]

Liver cancer

In different studies the anti-liver cancer studies in cell studies and mice models has been demonstrated[50, 131, 161, 164, 184]

Other cancers

Honey ingestion by rats induced antitumor and pronounced antimetastatic effects. The experimental evaluation of antitumor properties of honey was carried out using five strains of rat and mice tumors. Honey potentiated the antitumor activity of 5-fluorouracil and cyclophosphamide[158]

In another study the antitumour effect of bee honey against **bladder cancer** was examined in vitro and in vivo in mice [332]. According to these results honey is an effective agent for inhibiting in vitro the growth of different bladder cancer cell lines (T24, RT4, 253J and MBT-2). It is also effective when administered intralesionally or orally in the MBT-2 bladder cancer implantation mice models.

Three Spanish honeys induced apoptosis in a concentration and time dependent-manner, in addition, honeys with the higher phenolic content, heather and polyfloral, were the most effective to induce apoptosis in HL-60 cells. However, honeys did not generate reactive oxygen species (ROS) and N-acetyl-L-cysteine (NAC) could not block honeys-induced apoptosis in HL-60 cells, a human peripheral **blood promyelocytic leukemia** cell line. These data support that honeys induced apoptosis in HL-60 cells through a ROS-independent cell death pathway, indicating that the antiproliferative and apoptotic effects of honey varied according to the floral origin and the phenolic content[263]

Tsiapara et al. investigated the influence of Greek honey extracts (thyme, pine and fir honey) on the oestrogenic activity and cell viability of breast (MCF-7), **endometrial** (Ishikawa) and **prostate** (PC-3) cancer cells. Thyme honey reduced the viability of Ishikawa and PC-3 cells, whereas fir honey stimulated the viability of MCF-7 cells. The authors concluded that modulation of oestrogen activity was linked to the rich phenolic content of Greek honeys[347], especially to the action of protocatechuic and p-hydroxybenzoic acids[329]

The antiproliferative activity, apoptosis, and the antitumor effects of honey on **human renal cancer** cell lines (ACHN) were studied. Honey decreased the cell viability in the malignant cells in a concentration-and time-dependent manner. Honey induced apoptosis of the ACHN cells in a concentration-dependent manner. It is concluded that honey may cause cell death in the ACHN cells by inducing apoptosis [311]

HMF, a compound found in heated honey has been found to possess antitumor properties[249]. Thus, overheated honeys could potentially compensate the loss of quality by winning anti-cancer properties.

Jungle honey, collected from tree blossom by wild honeybees that live in the tropical forest of Nigeria) enhanced immune functions and antitumour activity in mice[150].

Tualang honey from Malaysia has: antiproliferative activity on OSCC and HOS cell lines, exerting early apoptosis effects[153] and antitumor effects in experimental breast cancer in rats[187]. This honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and **cervical cancer cell** lines (uterine cancer)[144] and inhibits also primary human keloid fibroblasts[333]

Polish honey exhibited **anti-brain tumor activity**, measured by the inhibition of glioblastoma multiforme U87MG[264]

Manuka honey has antiproliferative activity of manuka honey on three different cancer cell lines, **murine melanoma** (B16.F1) and colorectal carcinoma (CT26) as well as human breast cancer (MCF-7) cells in vitro[145]

Honey inhibits **mouth cancer cells** (oral squamous cell carcinoma) and **bone cancer cells** [153]

Mechanism of action

Two recent rewiews [14, 133] discuss the possible mechanisms of action in detail. Summarising, following effects lead to the anticancer activity of honey: These include, but are not limited to: cell cycle arrest (antiproliferation), activation of mitochondrial pathway, induction of mitochondrial outer membrane permeabilization, induction of apoptosis, inhibition of Tumor Necrosis Factor (TNF), modulation of oxidative stress, anti-inflammatory action, immuno-modulation, modulation of insulin signaling and inhibition of angiogenesis, anti-mutagenic effects

IMMUNOMODULATING, IMMUNOACTIVATING AND IMMUNOSUPPRESSIVE PROPERTIES

Immnomodulating properties

Immunomodulation is the adaptive response of the response of the immune system to a stimulus and can be both a immunosuppressive and immunoactiveting response.

Honey is an immunomodulator. The immunomodulating responses of honey in relation to its application in skin disorders is reviewed in 2016[243]. Honey has also immunomodulating properties in wound healing, where it can both activate and inhibit immune response by triggering the production of cytokinines. The immunomodulatory activity of honey is highly complex because of the involvement of multiple quantitatively variable compounds among honeys of different origins. The identification of these individual compounds and their contributions to wound healing is crucial for a better understanding of the mechanisms behind honey-mediated healing of chronic wounds[234]

Immuno-activating properties

The effect of honey on the antibody production against thymus-dependent antigen sheep red blood cells and thymus-independent antigen (*Escherichia coli*) in mice was studied [31]. According to this study oral honey stimulates antibody production during primary and secondary immune responses against thymus-dependent and thymus-independent antigens.

It has been reported that honey stimulates T-lymphocytes in cell culture to multiply, and activates neutrophils [7]

In a study with humans receiving a diet supplemented with a daily honey consumption for two weeks of 1.2 g/kg body weight ingestion of honey following effects were observed: Increase of serum iron by 20% and decrease of plasma ferritin by 11%, an 50 % increase of monocytes and slight increases of lymphocyte and eosinophil percentages, reduction in serum of immunoglobulin E (34%) aspartate transaminase (22%) and alanine transaminase (18%), lactic acid dehydrogenase (41%), fasting sugar (5%) and creatine kinase and finally an increase in blood of copper (33%) and slight elevations of zinc and magnesium, hemoglobin and packed cell volume [24]

Honey increase proliferation of B- and T-lymphocytes and neutrophils in vitro[7].

Nigerose, a sugar present in honey [118, 326], has immunoprotective activity[271].

In another study with rats, feeding of honey caused an increase of lymphocytes in comparison with the sucrose fed controls[97].

Apalbumine 1, the dominant royal jelly in honey with immunostimulating properties, is present in honey[66]

Immuno-supressive propeties

In animal experiments honey showed an immunosuppressive activity [120]. In experiments with isolated leukocytes honey inhibited phagocytic myeloperoxidase activity [248].

These findings is in line with the common belief that ingestion of honey can relieve pollen hypersensitivity. Immuno suppression plays also a positive role in autoimmune diseases.

Honey causes both an enhancement of the immune response and an immuno-supression. The immunoactivating effects are in line with the common belief that honey improves human reaction to viral infections. Honey may be also trigger immunoactivating activity by its stimulatory effects on lymphocytes and also by its probiotic effects (see above).
On the other hand the immunosuppressive activity of honey is probably due to ts anti-inflammatory effect. These effects are in line with the belief that honey ingestion will decrease allergic reactions like hay fever.

CARDIOVASCULAR HEALTH

Feeding of honey or sugar to Wistar rats resulted both in increase of weight in comparison to controls. Sucrose fed fat cells were significantly larger than the honey fed ones. Compared to the controls (no sugars) sucrose feeding increased blood pressure, but not the honey fed rats[304].

Ahmad et al. tested the effect of honey on bovine thrombin -induced oxidative burst in human blood phagocytes. Honey treatment of phagocytes activated by bovine thrombin showed effective suppression of oxidative respiratory burst. It can be assumed that this suppressive activity of honey could be beneficial in the interruption of the pathological progress of cardiovascular disease and may play a cardioprotective role[10]

Ingestion of honey by healthy humans has an effect on blood homostasis by inhibiting platelet aggregation. The anticoagulant effect of could be due to several subsnances present in honey: hydrogen peroxide, a platelet aggregation inhibitor, to honey flavonoids or sugars[13] or to by the influence on platelet function caused by honey induced LDL oxidation[165].

Compared with fructose-fed rats, honey-fed rats had a higher plasma α-tocopherol level, and an α-tocopherol/triacylglycerol ratio, as well as a lower plasma nitrate levels and susceptibility of the heart to lipid peroxidation[89]

Greek honey exerts strong antioxidant activity on both human LDL, in accordance to previous studies with honeys of other origin5, and on serum total lipoprotein oxidation in vitro. The exact quantity of honey which can be consumed daily for major antioxidant protection, needs to be estimated[236].

In experiments with rats Tualang honey confered cardioprotective effects on ISO-induced oxidative stress by contributing to endogenous antioxidant enzyme activity via inhibition of lipid peroxidation[195].

Honey ingestion improves experimental heart weaknesses as extrasystoles, arrhythmia and tachicardia of rats[299]

DIGESTION, PREBIOTIC AND PROBIOTIC EFFECTS

Effects on digestion

Consumption of manuka honey only mildly affects substrate metabolism of the mice gut microbiota[306]

Natural honey diminished the starch digestibility in vitro compared to simulated honey (0% phenolics), an effect due to honey phenolics [284]

In the case of irritable bowel syndrome (IBS) high fructose foods, and also honey, are generally not recommended[117, 270]. However it should be researched if honeys rich in glucose might be used by IBS patients.

Prebiotic effects

Important honey effects on human digestion have been linked to honey oligosaccharides. These honey constituents has a prebiotic effect, similar to that of fructooligosaccharides [313, 369]. The oligosaccharide panose was the most active oligosaccharide. These compounds exert the prebiotic effect in a synergistic mode of action, rather to one of individual components, leading to an increase of bifidobacteria and lactobacilli [349]. According to an in vitro study on five bifidobacteria strains honey has a growth promoting effect similar to that of fructose and glucose oligosaccharides[188]. Unifloral honeys of sour-wood, alfalfa and sage origin honey stimulated also the growth of five human intestinal bifidobacteria [325]. In another study honey increases both in vivo (small and large intestines of rats) and in vitro the building of *Lactobacillus acidophilus* and *Lactobacillus plantarum*, while sucrose failed to produce any effect[319].

Honey showed prebiotic activity towards 3 Lactobacillus species isolated from human faeces[338]

It is not clear whether all types of honey exibit prebiotic effects and whether some honeys have a stronger prebiotic effect. Sour-wood, alfalfa and sage[188] and also clover honey[188] have been shown to have prebiotic activity.

The prebiotic activity of chestnut honey was found to be higher than that of acacia honey[227].

Oligosaccharides from honeydew honey have prebiotic activity[313].

Theoretically honeydew honeys, containing more oligosaccharides should have a stronger prebiotic activity than blossom honeys. There is need of more research on prebiotic activity of unifloral honeys.

When added to yoghurt honey improves the viability of *Probiotic* bifidus[41] and *Lactobacillus* bacteria[52]

Honey was successfully used to improve the probiotic properties of the Indian yoghurt product lassi[321]

However the influence of the oligosaccharide content is questioned. Sage, alfalfa and sourwood honey, which vary in their oligosaccharide contents, were compared with sucrose, high fructose corn syrup and inulin in their ability to support growth, activity and viability of lactic acid bacteria and bifidobacteria typically used in yoghurt manufacturing. Growth and the end products of fermentation (lactic and acetic acids) were determined. Growth and acid production by organisms studied in the presence of different sweeteners were dependent on the specific organism investigated; however, it was not influenced by sweetener type, oligosaccharide content or the floral source of the honeys. All the sweeteners studied supported the growth, activity and viability of the organisms studied[294]

Lactic acid bacteria (LAB) isolated from honey can restore commensal microbiomes and prevent infections, it does not have a detrimental effect when applied in a single dose on humans[239]

Probiotic effects

It has been shown in a study by a Swedish research group that fresh honey has probiotic *Bifidus* and *Lactobacilus* bacteria. However these bacteria are viable only in fresh honey, about 2-3 months old [276]

In a 2014 study this research was continued. A unique lactic acid bacterial (LAB) microbiota was discovered which is in symbiosis with honeybees and present in large amounts in fresh honey across the world. The LAB symbionts are the source to the unknown factors contributing to many of honey's properties. The LAB was very active against severe wound pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and vancomycin-resistant Enterococcus (VRE) among others. The mechanisms of action are partly shown by elucidating the production of active compounds such as proteins, fatty acids, anaesthetics, organic acids, volatiles and hydrogen peroxide. This and other symbionts produce a myriad of active compounds that remain in variable amounts in mature honey[277]

Gluconobacter oxydans isolated from Indian honey was found to possess probiotic properties with siderophorogenic potential[56]

HONEY AND THE BRAIN

The neurological effects of honey have been reviewed in 2014[298]: According to the original references cited in the review honey has following effects:

1. The normal diet of two-month-old rats was supplemented with honey, and their brain function was assessed over a one-year period. Honey-fed rats showed significantly less anxiety and better spatial memory throughout all stages compared with the control group of rats. More importantly, the spatial

memory of honey-fed rats, as assessed by object recognition tasks, was significantly greater during later month

2. Honey decreased the number of degenerated neuronal cells in the hippocampal CA1 region, a region that is known to be highly susceptible to oxidative insult.

3. Rats were fed with different concentrations of honey (10, 20 and 40%) at a dose of 0.5 mL/100 g. Significant dose-dependent increases in exploratory activities in a hole board test and in locomotor, rearing and grooming activities in an open-field test were found in the honey-fed test groups rats compared with the control group rats. These findings indicate that the consumption of honey mitigates anxiety and exerts an excitatory effect on the central nervous system, especially at the highest nonsedative dose.

4. Glial cells may also respond to honey therapy because honey shows a neuroprotective effect in the cerebral focal-induced ischemia model in rats.

Honey ingestion improves anxiety and the spatial memory of rats[98] and also improves memory performance and hippocampal morphology in stressed ovariectomized rats[23] and of noise stressed rats. It also caused an anti-depressant effect as shown by the inhibition of MAO[368].

Tualang honey ingested by stressed ovariectomised (OVX) rats by hypothalamic-pituitary-adrenal axis enhanced the brain-derived neurotrophic factor BDNF concentration[22]. This honey type also enhanced hippocampal pyramidal count and spatial memory performance of adult male rats[189]. It also improved spatial learning and memory performance during cerebral hypoperfusion-induced neurodegeneration[316]

Research with different Nigerian honeys was carried out. The results showed that honey significantly ($p < 0.05$) decreased locomotion and rearing behaviors in NIB and amphetamine-induced locomotor activity when compared to the control group. Exploratory behavior was significantly increased in both holeboard and elevated plus maze but had no significant effect on spatial working memory. Honey sample from Umudike has significant hypnotic and anticonvulsant effects. The antinociceptive models (hot plate and tail flick tests) showed that the honey samples significantly increased the pain reaction time and naloxone blocked these central antinociceptive effects. The force swimming test showed that only the Idanre (ID) honey sample had antidepressant effect. In conclusion, some of these honey samples have central inhibitory property, anxiolytic, antinociceptive, anticonvulsant and antidepressant effects, thus may be used as nutraceutic. It can also be inferred that some of these effects are probably mediated through dopaminergic and opioidergic systems[15].

Other effects

Antinociceptive activity

The antinociceptive (pain-soothing) effect is thought to be triggered by quinoline alkaloids. These quinoline alkaloids are present in exceptionally high concentration in chestnut honey, while they were present in much lesser quantities in honeydew, acacia, thyme, lavender, dandelion, sulla, thymus, sunflower and linden honeys[60, 62].

Antiacetylcholinesterase activity

Antiacetylcholinesterase activity is thought to be linked with the prevention of neurodegenerative diseases such as Alzheimer. Several Brazilian honeys have significant antiacetylcholinesterase activity, which depended on the floral source[224]

Honey improving renal function

Experiments with rats showed that honey ingestion improves their renal function[18]

Honey for good fertility

Tualang honey from Malaysia was found to have a beneficial effect on menopausal rats by preventing uterine atrophy, increased bonde density and suppression of increase of body weight[370] and ameliorates restraint stress-induced impaired pregnancy outcomes in female rats[162]

Malaysan honey had a positive effect of testicular function in rats[233]. A study with Palestine honey showed an increased spermatogenesis in rats[3].

Against osteoporosis

Honey improves on the short term Ca absorption in rat bones in a positive dose response fashion, but this effect disappears on the long term[45] It was shown in a review article that Tualang honey can be used as an alternative treatment of postmenopausal osteoporosis of women[130]

Honey as a protective factor against chronic diseases

The information compiled above shows numerous biological and functional effects of honey. Honey influences significantly the major factors contributing to chronic diseases in humans: inhibition of tissue oxidation and formation of damaging radicals, positive influence on heart disease risk factors, anticancerogenic properties, antibacterial activity, overweight

Biological effect	Protection of chronic diseases
Antioxidative effects	All chronic diseases
Antiinflammatory effect	All chronic diseases
Anticancerogenic, antimutagenic properties	Cancer
Antimicrobial effects	Microbial infections, gut diseases
Antimicrobial effects, prebiotic effects	Gut diseases
Hepatoprotective effects	Liver diseases
Immunomodulating effects	Microbial infections, diseases of the immune system
Appetite diminisher	Obesity
Calory donator	Energy supply to fight chronic diseases
Neuroprotective, memory enhancing	Chronic brain diseases

NUTRITIONAL AND FUNCTIONAL PROPERTIES OF UNIFLORAL HONEYS

Due to different proportions of the possible sources, nectar and/or honeydew coming from a great variety of plants, no honey is completely the same as another one. This variability could be a handicap, given the market requirement for a consistent product, but when properly managed, it also could represent an opportunity for enhancing honey by offering to the consumer a number of typical products with special characteristics, according to the particular botanical origin. Indeed, unifloral honeys are regarded as a more valuable class of honey, and botanical denominations are widely employed on the European market, often achieving higher prices than honey blends. Unifloral honeys have higher prices than blend honeys. In countries like France, Italy and Spain 30 to 50 % of the marketed honey is unifloral. In non-European countries, with the exception of the Manuka New Zealand honey, unifloral honeys have a smaller importance. Information on European unifloral honeys is compiled in the special Apidologie Issue 35 from 2004. In Europe there are more than 100 plant species that can give origin to unifloral honey, most of them having only a local importance [289].

While the characterisation of microscopical, physical and physical properties of unifloral honeys is well advanced, the nutritional and health enhancing properties of unifloral honeys is quite a new field of research.

The composition of honey depends on its botanical origin, regarding the main nutrients, the carbohydrates, and also the minor ones Persano and Piro[290].

Glycemic Index and fructose

The variation of the Glycemic Index (GI) varies according to the botanical origin of honey is described earlier in this chapter.

Vitamins

Table 6: **Average concentration of water-soluble vitamins in Sardinian monofloral honeys** mg/kg +/- SD, after [101]

	B$_2$	B$_3$	B$_5$	B$_9$	C	Sum
Eucalyptus (n = 5)	<1.458	<2.262	<3.686	5.6 ± 0.4	3.2 ± 0.7	<16.2
Sulla (n = 3)	<0.417	5 ± 1	5.2 ± 0.7	<0.383	1.3 ± 0.8	<12
Citrus (n = 3)	2.2 ± 0.2	26 ± 2	<5.613	<0.383	2 ± 2	<36
Asphodel (n = 3)	3.7 ± 0.3	5.8 ± 0.1	16 ± 6	<1.1	2 ± 2	<28
Acacia (n = 2)	<0.25	5 ± 1	<1.75	<0.325	1.2 ± 0.2	<8.5
Lavender (n = 2)	4 ± 1	<3.125	<0.58	<1.575	2.2 ± 0.4	<11.5
Thistle (n = 3)	<4.16	8.6 ± 0.8	<1.75	<1.447	2.3 ± 0.3	<18.3
Strawberry-tree (n = 3)	<0.87	<4.633	<10.11	<0.39	4 ± 1	<20
Heather (n = 1)	<0.25	5.92 ± 0.01	<0.58	<0.50	2.7 ± 0.9	<10.0
Rosemary (n = 1)	<0.25	<0.75	<0.58	1.7 ± 0.2	1.5 ± 0.2	<4.8
Linden (n = 1)	<0.25	7.0 ± 0.3	<0.58	1.28 ± 0.05	<0.10	<9.2
Multifloral (n = 1)	1.1 ± 0.5	8 ± 1	<0.58	1.8 ± 0.3	<0.10	<11.6

Antioxidant properties

The antioxidant activity of honey has been reviewed above. The antioxidant properties of honey depend on the botanical origin of honey, the darker the honey the higher its antioxidative power [1, 1, 38, 64, 94, 102, 146, 148, 155, 199, 208, 209, 238, 261, 261, 288, 291, 292, 305, 352] This effect seems to be due to honey polyphenols (see section on antioxidant properties above). Exceptions are some relatively lighter honeys like arbutus honey from southern Europe,[38] and sourwood honey from Malaysia[261], ferula honey from Sicily[48] and willow herb from Finland[171]

Following dark honey types have especially high antioxidant power:

- Buckwheat *(Fagopyrum sp.)*
- Black cumin (Carum bulbocastanum)
- Chinese milk vetch *(Astragalus adsurgens)*
- Gelam *(Malaleuca cajuputi powell)*
- Heather (Caluna vulgaris, Erica umbellata)
- Honeydew (all types of honeydew honeys)
- Manuka (*Leptospermum Scoparium*
- Strawberry tree honey (Arbutus menziesii)
- Sweet chestnut *(Castanea sativa)*
- Tualang (*Koompassia excelsa*)

Antibacterial properties

The antimicrobial effect of honey is due to different substances and depends on the botanical origin of honey [71, 225, 253, 255, 257]

The antibacterial properties of honey have been reviewed above. The dependence of the antibacterial activity on the botanical origin is less clear cut than the antioxidant properties of honey. This can be explained by two facts. On one hand, there are different antibacterial factors: hydrogen peroxide, different honey components, most of all acids, and also phenolics, on the other a part of the antibacterial substances are added by the bees[71].

The hydrogen peroxide in honey is produced by glucose oxidase and destroyed by catalase. The resultant between the two enzymes will determine the peroxide accumulation capacity of honey.

According to White and Dustmann the peroxide accumulation capacity of honey depends on the botanical origin of honey. Generally, dark honeys have a higher activity[123, 360].

The non-peroxide, antibacterial activity depends also on the botanical source of honey [71, 346], but there was no clear cut correlation between honey colour and non-peroxide activity. Taormina et al found that darker honeys (buckwheat, blueberry) have a significant non-peroxide activity[337]

Manuka is considered the honey with the strongest antibacterial properties [257], but there is increasing evidence that other unifloral honeys, most of them with a dark colour have a similarly high antibacterial potency (table 7).

Table 7. **Antibacterial potency of unifloral honeys**

Honey type	Antibacterial potency, type of antibacterial activity	Reference
Dark colour		
Buckwheat	high potency, undetermined type	[254]
Blueberry	high potency, undetermined type	[82]
Chestnut	average to high, both peroxide and non-peroxide	[71, 255, 346, 364]
Cotton	high, undetermined, peroxide	[255, 361]
Fennel	High, peroxide	[42]
Gelam	High, peroxide and non-peroxide	[251]
Heather	low to high, undetermined type	[71, 255]
Honeydew, dark, both coniferous and non coniferous	high: both peroxide and non peroxide	[71 81, 123, 235, 255] [42]
Jarrah	high: peroxide and non peroxide	[173]
Kanuka	High: non peroxide	[168, 365]
Linen vine (Cuba)	high, undetermined type	[37]
Manuka	high: peroxide and non-peroxide	[71, 255]
Marri (red gum)	high: peroxide and non peroxide	[173]
Medlar	high: non-peroxide	[341]
Tualang	high: peroxide and non peroxide	[198, 335]
Intermediate colour		
Eucalyptus,	low to high: peroxide and non peroxide	[71, 81, 346, 362]
Linden,	low to high: peroxide and non peroxide	[255, 346]
Revanil	high: peroxide and non peroxide	[211]
Thyme	low to high: peroxide and non-peroxide	[81, 93]
Tupello	average: peroxide	[361]
Ulmo (Chile)	**high**: probably peroxide	[322]
Light colour		
Acacia	low-average: undetermined, non-peroxide	[71, 346]
Christmas vine (Cuba)	low, undetermined type	[37]
Borage	low-medium	[81, 259]
Clover	Average, undetermined, peroxide,	[81, 94, 255, 361]
Willow herb (Finland)	**high**, undetermined	[171]
Lavender	medium: undetermined or non-peroxide	[71, 346, 362]
Lucerne	low: undetermined and peroxide	[346, 361]
Rosemary	low to high, undetermined, non-peroxide	[362 172],
Orange	low-average: peroxide and non-peroxide	[71, 346, 361]
Rape	low to high: peroxide and non peroxide	[53, 71, 81, 255]
Rhododendron	low to high, undetermined or non-peroxide	[71, 346]
Sunflower	low-average: undetermined or non-peroxide	[71, 346]
Taraxacum	low-high: undetermined, non-peroxide	[71, 346]

Summary		
High activity	**Intermediate activity**	**Low activity**
blueberry, buckwheat, chestnut, cotton, fire-weed, gelam, heather, jarrah, honeydew, linen vine, manuka, red gum, revanil, tualang, ulmo	eucalyptus, clover, lavender, linden, rape, rhododendron, rosemary, thyme, tupello	acacia, Christmas vine, borage, , lucerne, orange

Imunostimulating effects

Apalbumine 1, the dominant royal jelly in honey with immunostimulating properties, is present in unifloforal honeys in different quantities. The quantity of apalbumine decreases in the following order: Chestnut > dandelion > Rape, Linden, Acacia [66]

Prebiotic properties

It is not clear whether all types of honey exibit prebiotic effects and whether some honeys have a stronger prebiotic effect. Sour-wood, alfalfa, sage and clover honeys[188] have been shown to have prebiotic activity.

It was shown that the prebiotic activity of chestnut honey is bigger than that of acacia honey[227].

Oligosaccharides from honeydew honey have prebiotic activity[313]. Theoretically honeydew honeys, containing more oligosaccharides should have a stronger prebiotic activity than blossom honeys. There is need of more research on prebiotic activity of unifloral honeys.

Mineral content

The mineral composition of honey depends on the botanical origin of honey[59, 74, 231, 301, 342]

Variation of honey mineral content, after[59]
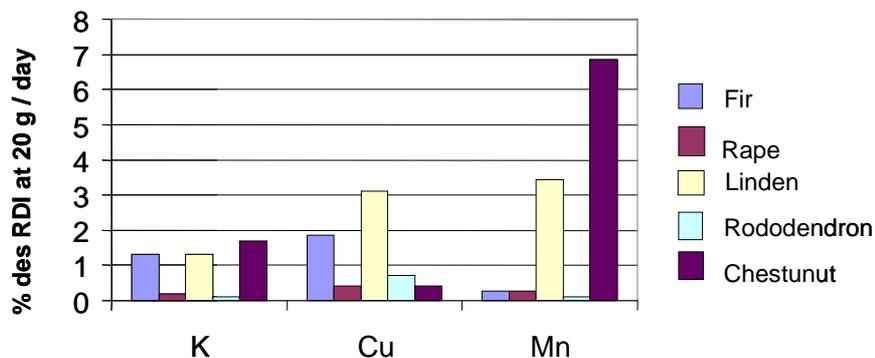
Lavandula stoechas, Citrus spp. and Echium plantagineum honeys collected in Portugal were determined by fluorometry after reaction with 2.3-diaminonaphthalene. The selenium levels of the honey samples studied were low, ranging from <1.0 to 2.91 µg/100 g fresh weight. The honeys from Erica spp., C sativa and E. plantagineum presented the highest selenium values from all the honeys studied (median values 1.69, 1.51 and 1.51 µg /100 g fresh weight), and the honeys from Eucalyptus spp., L stoechas and Citrus spp. presented the lowest values (median values 1.33, 1.28 and 1.20 µg /100 g fresh weight). The selenium content of Erica spp., was significantly higher than that observed for the Eucalyptus spp., L. stoechas and Citrus spp. and the selenium level of the Eucalyptus spp., was also significantly lower than that observed C. sativa and E. plantagineum honeys[103].

Gastroprotective properties

The content of nitrate (NO_3) in honey is thought to be the causative action of the gastroprotective action of honey. Dark honeys like honeydew and sweet chestnut had considerably higher concentration than light honeys (acacia, orange blossom, lavender, sunflower, arbutus) [62]

HONEY PRODUCED BY DIFFERENT HONEYBEES

Apis mellifera honey

Most studied honeys are those produced by *Apis mellifera*, which is spread all over the world. In Europe there are different local honeybee *Apis mellifera* subspecies, but there are very few studies comparing the biological properties of the different species as there are generally no differences in the honeys produced by these bees. In a study in Scilly the honeys produced by the local black bees *Apis mellifera ssp. Sicula* had about 10 times higher content of polyphenolics and higher antibacterial activity than the same honey species produced by other *Apis mellifera* bees[340].

Honey of different Asian honeybees

In Asia some of the honey is produced by local bee species: *Apis cerana*, *Apis dorsata, Apis florae and Apis laboriosa*. In one study in all these honeys both peroxide and non-peroxide antibacterial activity was encountered, Apis florea honey having the highest activity. However it is not clear whether the differences encountered are due to the bee or to the honey plant species[152]. Tualang honey from Malasia, produced by *Apis dorsata* has an exceptionally high antibacterial activity, comparable to that of Manuka honey [237, 273, 335]

Stingless bee honey

Honey from different stingless bees has considerable antibacterial activity[77, 113, 174, 246, 293, 339], in some honeys being comparable to the one of Manuka honey[77, 293, 339]. Stingless bee honey from Ghana had a higher antibiotic activity than 8 synthetic antibiotics[212]. Honey from the Brazilian stingless bee Plebeija spp. had a higher antioxidant activity than the honey gather in comparable hives nearby by the africanized bee *A.Melifera* [119] The antibacterial activity of honeys from 5different Brazilian stingless bees is different[247].

QUANTITY AND TIME OF HONEY INGESTION

From nutrition point of view honey is a sugar. For sweeteners a maximum of 40 to 50 g per day is generally accepted. Taking into consideration that other sugars are also ingested a quantity of 20 g daily can be recommended. However it should be remembered, that for health enhancing and medical purposes higher amounts, 50 to 80 g of honey per day are recommended (see Chapter 8 on honey and medicine). But such high intake should be limited to a certain period of time.

HONEY USES

Food industry
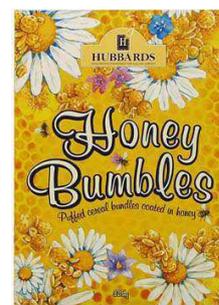
Due to its various favourable properties honey is used as an additive to a variety of food and beverages (see Table 5). The application of honey as a food additive is based on its manifold properties. The antibacterial effect of honey (see part II) counteracts microbial spoilage of food, e.g. of meat [272]. The antioxidant effect of honey prevents oxidation of food during storage. Honey acts against lipid oxidation of meat [241, 272] and is thus a efficient meat additive for preventing oxidation spoilage, e.g. to poultry [43] or to meat and muscle of

unspecified origin [272]. Effects of honey against enzymatic browning of fruits and vegetables [96], soft drinks [217] light raisin [242], apple slices [282] have been reported. Honey enzymes have a clearing effect in fruit juices and fruit drinks manufacturing [218, 282]. Other physical and sensory properties make honey a good candidate for an additive to a wide variety of food: good sensory and rheological properties, superior microwave reactivity than synthetic sugars etc. More information on honey application in food is available through the American National Honey Board (http://www.nhb.org/foodtech/index.html).

Honey enhances the growth of dairy starter cultures in milk and milk products. Especially species with week growth rates in milk such as bifidobacteria are usually fortified by growth enhancers or by honey. The growth rate of two bifidobacteria Bf-1 and Bf-6 in milk can be stimulated by the addition of honey to milk [350]. The effect of honey was more pronounced than the one caused by common growth enhancers based on other oligosaccharides. Thus, honey can be used as a prebiotic additive to probiotic milk products.

Honey added to non fat dry milk has a favourable influence on some other "good bacteria" [99] The milk was incubated with *Streptococcus thermophilus*, Lactobacillus acidophilus, *Lactobacillus delbrueckii* subsp. *bulgaricus*, or *Bifidobacterium bifidum*. Honey supported the growth of all strains. The authors conclude that various oligosaccharides found in honey may be responsible for the enhanced lactic acid production by bifidobacteria.

Due to its antioxidant activity the addition of honey to patties seems to prevent formation of heterocyclic aromatic amine and overall mutagenicity in fried ground-beef patties [324].

Acacia honey did not affect the survival of the microbial flora of yoghurt during a 6 week refrigerated storage period [351]. Also, honey had no effect on pH and lactic acid levels of the final products. In addition, at a rate of approximately 3.0% (w/v), it highly improves the sensory quality of the product without having a detrimental effect on characteristic lactic acid bacteria. Another study with sunflower honey showed that addition of honey (2,4 and 6 %) increased the values of *Streptococcus thermophilus* and *Lactobacillus delbrueckii subsp. bulgaricus* values, optimum sweetness was at 4 % honey[318].

Another main application of honey in food industry is in baking, cereal and the confectionary industry. A review on these applications is summarised in a PhD study [331]. Proposed advantages of honey additions to baked goods are moisture retention, good texture, improved baking, flavour and sensory properties.

Acacia and chestnut honey had a stimulatory effect on the growth of Lactobacillus casei Lc-01 in cow's and goat's milk[327]

An overview of the different application of honey in food industry is given in the table below. A wide variety of the application research on different application of honey as a food additive has been commissioned by the American National Honey Board. (www.honey.com) All the mentioned applications showcase a detailed description of the research carried out, together with comprehensive explanations of the honey use.

Honey applications in the food industry

Use	Explanation
Sweetener for: sport beverages, non-alcoholic fruit beverages, ice tea, yoghurt drinks, chocolate milk beverages; fermented beverages; vinegar, vegetable juices; in mead production	supplies different natural honey flavours and colours; honey sugars are fermentable and give alcoholic drinks unique flavours; prevents browning due to antioxidative properties
Additive to poultry and other meat, to fruit and vegetable processing	Antioxidant and preservative (anti-bacterial) properties, reduces browning, improves sensory properties
Additive to microwave foods: cakes, muffins, cookies, glazes	Superior microwave reactivity and water activity managements than synthetic sugars
Additive to flour bagels, cereals, chicken marinades, French fries, bread, pasta, extruded snacks, corn chips, potato chips	Improves sensory properties, adds/retains moisture due to hygroscopic properties; improves browning due to reducing sugars;
Additive to frozen ice cream and dough	Better stability and sensory properties
Additive to fruit spreads, peanut butter, nut spread,	Better storability and sensory properties
Additive to salsas and sauces	Neutralises sour and burn intensity
Additive to fried or roasted beef, poultry	Reduces the formation of heterocyclic aromatic amines and their mutagenic effects
Dried honey	Convenient as consistent in texture, flavour and colour,

Honey in cosmetics

Since old times honey was used in cosmetics. Queen Cleopatra took a bath of honey and milk for her beauty. Today honey is also contained in many cosmetic products. It is a component of the water soluble part of cosmetic emulsions as a humidifier for the cosmetics product and for the skin. Generally, honey cosmetics is suitable for all skin types. Honey is hygroscopic, antibacterial and fungicide, and its ingredients nurture the skin. It is mildly acetic and contributes to strengthening the upper acetic protective skin layer (pH of the skin is 5.5).

Honey cosmetic products

Shampoo, Hairbalm and purifying lotion with honey

A hand cream and sun cream with honey

Mask is the best form that complies with the consistency of honey. It nourishes the skin and keeps it moisturized. Regular use of them keeps skin juvenile and retards wrinkle formation. To mix the ingredients you can use mixer. They are left for about ½ an hour, then removed using a gauze and warm water and then washed.

Simple recipes for honey cosmetics taken from different Internet sources

Face Masks

Cleopatra mask
Honey 1 teaspoonful
Milk 1 tablespoonful
Egg white of 1 egg

Egg yolk mask
Honey 1 teaspoonful
Glycerin 1 teaspoonful
Egg yolk of 1 egg

Fairness Mask
Honey 10 g
Distilled water 155 ml + alcohol 70% 30 ml
Borax 4 g
Bergamot oil 3 drops + orange oil 2drops

Hand Care

Emulsion for hands
Honey 2 teaspoonful
Almond oil 1 teaspoonful
Perfume few drops
Massage your hands, leave for a while and wash if you need.

Honey mask
Place a cloth in warm water and apply to your face to open the pores. Smear on honey, and leave on for 15 to 30 minutes. Rinse off with warm water, then use cold water to close the pores.
Use once a week.

Egg white mask
Honey 1 teaspoonful
Glycerin 1 teaspoonful
Egg White of 1 egg

Quick mask
Honey 100 g
Alcohol 25 ml
Water 25 ml

Paste for hands
Honey 10 g
Wheat flour 6 g
Water 4 g
Massage your hands

Honey Bath
Add 200-250 g of honey to the bathing water.
If used once in a while (e.g. every 2 weeks), it will keep on a good turger of the cells and nourishes the skin.

1/2 cup sea salt
2 tablespoons baking soda
1 cup boiling water
1 cup honey
2 cups milk
10 drops of vanilla oil
dissolve sea salt and baking soda in bathwater, dissolve honey in boiling water and add milk, add milk-honey mixture and vanilla oil to bathwater, swirl water to blend all ingredients

Cracked Lips
Honey 10 g
Lemon juice 10 g
To be used concomitantly with lip moisturizer containing Panthenol.
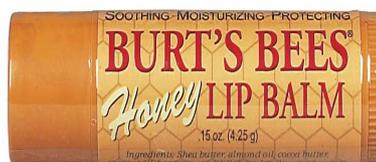
Further reading for this section: [111]

ALLERGY, POTENTIAL HEALTH HAZARDS AND COUNTERINDICATIONS

Allergy

Up to 5 % of the population is suffering from allergies. Compared to other foods allergy to honey seems relatively uncommon. Recently honey allergy was reviewed[124]. In epidemiological studies with normal people the allergy incidence is very low. In one study in Turkey with 4331 students no honey allergy could be detected, while in another Turkish study with 3810 patients searching consultation in an allergy clinic the honey allergy incidence was 1.8 %.

The incidence of honey allergy, reported in a group of 173 food allergy patients was 2.3% as reported by [125]. In this study with allergic patients the allergy honey allergy is explained by the presence of honey components of bee origin or by dandelion and *Compositae* pollen.

Allergies reported can involve reactions varying from cough to anaphylaxis [167].

It was also reported that patients allergic to pollen are rarely allergic to honey, although there is one reported case of honey pollen allergy[80].

Potential health hazards

Toxic compounds in honey

Honey as any other natural food can be contaminated from the environment, e.g. heavy metals, pesticides, antibiotics etc. Generally, the contamination levels found in Europe do not present a health hazard. [72].

A few plants 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[112]. Honey containing *R. ponticum* is called mad honey and is found in some regions of Turkey. Ingestion of this type of honey is not lethal, it causes some complaints such as dizziness, nausea-vomiting, sweating, weakness, blurred vision, convulsions and loss of consciousness, extremity paresthesia, excessive perspiration and salivation[79]

Toxicity of honey from other plants has also been reported: Datura plants (from Mexico and Hungary), belladonna flowers and Hyoscamus niger plants (from Hungary), Serjania lethalis (from Brazil), Gelsemium sempervirens (from the American Southwest), Kalmia latifolia, Tripetalia paniculata and Ledum palustre[177]

Substances of the other toxin group, pyrazolidine alkaloids, are found in different honey types and the potential intoxication by these substances is reviewed by [129]

Cases of honey poisoning have been reported very rarely in the literature and concern mostly individuals from the following regions: Caucasus, Turkey, New Zealand, Australia, Japan, Nepal, South Africa and different countries in North and South America. The symptoms encountered after honey poisoning are vomiting, headache, stomach ache, unconsciousness, delirium, nausea and sight weakness. In general those poisonous plants are known to the local beekeepers, thus honey, which can 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 from the market only and not from individual beekeepers.

Clostridium botulinum

There is a health concern for infants regarding the presence of *Clostridium* (*Cl.*) *botulinum* in honey. Since the presence of this bacterium in natural foods is ubiquitous and honey is a non sterilized packaged food from natural origin the risk of a low contamination level cannot be excluded. Spores of this bacterium can survive in honey, but they cannot build toxin. Thus, in the stomach of infants younger than one year the bacteria spores from honey can survive and theoretically build the toxin, while children older than 12 months can ingest honey without any risk. In some cases, infant botulism has been attributed to ingestion of honey [104, 336]. In Germany one case of infant botulism per year is reported [266]. As a result of the reported infant botulism cases some honey packers (e.g. the British Honey Importers and Packers Association) place a warning on the honey label that "honey should not be given to infants under 12 months of age".

In 2002 a scientific committee of the EU examined the hazard of *Cl. botulinum* in honey It has concluded that microbiological examinations of honey are necessary for controlling the spore concentration in honey, as the incidence of *Cl. botulinum* is relatively low and sporadic and as such tests will not prevent infant botulism. Thus, in the EU countries the health authorities have not issued a regulation for placing a warning label on honey jars[141].

Counter Indications

People with fructose intolerance should generally abstain from honey consumption or consume honey rich in glucose.

HEALTH CLAIMS FOR HONEY

According to the EU Regulation 1924/2006 [142] different health claims can be made: The claims are classified using the Passclaim project classification of the International Life Science Institute (ILSI) [46], wherever possible In the Passclaim project the claims are classified into the following subject areas:

1. Diet-related cardiovascular disease
2. Bone health and osteoporosis
3. Physical performance and fitness
4. Body weight regulation, insulin sensitivity and diabetes risk
5. Diet-related cancer
6. Mental state and performance
7. Gut health, digestion and immunity

Honey health claims

Quantity and time of honey ingestion

The health enhancing effects in human adults, described in this report were mostly achieved after ingestion of 50 to 80 g of honey per day.

The health claims of honey which are reported below are valid for intakes of following amounts of honey:

- *Adults: after ingestion of 50 to 80 g per day by adults,*
- *General (adults or infants): 0.8 g to 1.2 g honey per g human weight*

The health effects reported in the different publications reported above were measured mostly after 2 to 3 weeks of daily honey ingestion. Practical apitherapists suggest a daily honey ingestion for 1.5 to 2 months [229, 296].

The main honey health claims for honey are

Physical performance and fitness

Honey is high carbohydrate food and its ingestion increases performance and fitness

Ingestion of honey increases performance and fitness

Gut health and digestion
Long term ingestion of honey can improve gut and gastroenterological health

Immunity

L*ong term ingestion of honey can improve the immunological reaction towards infections*

Specific nutritional effects

Nutrition of infants

- *Honey should not be given to infants less than one year old*
- *Honey can be recommended as food for infants older than one year..*

Nutrition of Diabetes II patients

There evidence that honey can be used as a sweetener by humans with diabetes II. Any honey can be used for this purpose, the most suitable honey is acacia honey (Robinia pseudoacacia), as it has the lowest GI.

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