APITHERAPY - *HEALTH* *AND HEALING FROM THE* *BEES*

Dr. Kemal ÇElIK-Animal Science Dept.

Dr. H.Fatih ASGUN- *Cardiovascular Surgery Dept.*

Çanakkale Onsekiz Mart University

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What is Apiteraphy?

Apitherapy or "**Bee therapy**" (from the Latin *apis* which means bee) is the medicinal use of products made by honeybees. Products of the Honeybee include **honey, pollen, beeswax, propolis, royal jelly** and **bee venom**. Some of the conditions treated are: multiple sclerosis, arthritis, wounds, pain, gout, shingles, burns, tendonitis and infections. Great philosophers and physicians, such as Aristotle and Hippocrates were fascinated by the industrious bees. They captured them in hives, studying their complex communities and harvesting the honey for their own consumption. One long-standing use of honey (recorded from as early as 2500 BC and still used today) is in the treatment of wounds and burns to the skin. The ancient Egyptians used honey in very many different medicines, but one particular document gives instruction for placing honey directly onto the affected part of the body and wrapping it round with cloth as a dressing. This was used for open wounds, cut, burns or ulcers and this would help the would to dry out and heal satisfactorily as the honey would form a barrier to prevent further infection. The wound would also heal with the minimum of scarring. A number of properties inherent to honey might contribute to its ability to fight infection and promote healing. Its high sugar content allows it to draw infection and fluid from wounds by a process called 'osmosis' Honey prevents bacterial growth through its acidic pH and through the work of an enzyme that produces small amounts of hydrogen peroxide. Its ability to keep the area around a wound moist and protected promotes fast healing and prevents scarring. Honey also contains components from the specific plants used by the bees in their production, and it is speculated that some of these components might further add to the antibacterial and wound-healing effects of honey. The process of pasteurization, used to sterilize commercial honeys, destroys the enzyme involved in the production of hydrogen peroxide, rendering these honeys less antibacterial, and deficient of any medicinal benefit.

Figure 1. The apitherapy is widespread today

Why we may need an Apiteraphy ?

There are many reasons for that: Each of us has been, is or can be ill some day, our family members or friends can be in the same situation and may need our generous help;

· to prevent diseases is much easier than to treat them;

· the classical treatments, based only on chemical treatments have usually too many side-effects; ·the bee products have an extraordinary richness in **nutrients** and "soft" active compounds which can protect our health efficiently against over 500 diseases; the beekeepers have the second highest longevity among all professions; they are usually strong and generous with their friends all their life; why?

Because they regularly receive their bees "treatment" (good, natural food and stimuli). Probably the most important thing related to Apitherapy is that this multi-millenarian natural healing method can increase your general knowledge and can help you to help other people in need.

General Importance of Bee and Bee Products for Humans

Bees and beekeeping contribute to peoples' livelihoods in almost every country on earth. Honey and the other products obtained from bees have long been known by every society. The diversity in bee species, their uses and in beekeeping practices varies greatly between regions. In many parts of the world, significant volumes of honey are today still obtained by plundering wild colonies of bees, while elsewhere beekeeping is practised by highly skilled people. Beekeeping is an ancient tradition, and honey bees have been kept in Europe for several millennia. Bees are critically important in the environment, sustaining biodiversity by providing essential pollination for a wide range of crops and wild plants. They contribute to human wealth and wellbeing directly through the production of honey and other food and feed supplies such as: pollen, wax for food processing, propolis in food technology, and royal jelly as a dietary supplement and ingredient in food.

The Food and Agriculture Organization of the United Nations (FAO) estimates that of the 100 crop species that provide 90% of food worldwide, 71 are pollinated by bees. The majority of crops grown in the European Union depend on insect pollination. Beyond the essential value of pollination to maintaining biodiversity, the global annual monetary value of pollination has been estimated at hundreds of billions of euros. Aristotle callled honey the nectar of the gods. Throughout history, ra honey, bee pollen, propolis, and royal jelly have been valued as both food and medicine. Science now confirms this ancient wisdom.

Bee Products Characteristics

Bee Pollen characteristics

Bee pollen is the male seed of a flower blossom which has been gathered by the bees and to which special elements from the bees has been added. The honeybee collects pollen and mixes it with its own digestive enzymes. One pollen granule contains from one hundred thousand to five million pollen spores each capable of reproducing its entire species. Bee pollen is often referred to as nature's most complete food. Human consumption of bee pollen is praised in the Bible, other religious books, and ancient Chinese and Egyptian texts. It has long been prescribed by traditional health practitioners - including the fathers of Western medicine Hippocrates, Pliny the Elder, and Pythagoras - for its healing properties. More than 40 research studies document the therapeutic efficacy and safety of bee pollen. Clinical tests show that orally ingested bee pollen particles are rapidly and easily absorbed-

they pass directly from the stomach into the blood stream. Within two hours after ingestion, bee pollen is found in the blood, in cerebral spinal fluids, and in the urine. Bee pollen rejuvenates your body, stimulates organs and glands, enhances vitality, and brings about a longer life span. Bee pollen's ability to consistently and noticeably increase energy levels makes it a favorite substance among many world class athletes and those interested in sustaining and enhancing quality performance. Bee pollen contains most of the known nutrients, including all of those necessary for human survival. When compared to any other food, it contains a higher percentage of all necessary nutrients. Bee pollen is approximately 25% complete protein containing at least 18 amino acids. In addition, bee pollen provides more than a dozen vitamins, 28 minerals, 11 enzymes or co-enzymes, 14 beneficial fatty acids, 11 carbohydrates, and is rich in minerals, the full spectrum of vitamins, and hormones. It is low in calories. Several nutrients in bee pollen, such as proteins, beneficial fats, vitamins B, C, D, E, and beta-carotene, calcium, magnesium, selenium, nucleic acids, lecithin, and cysteine, are scientifically well documented for their ability to strengthen immunity, counteract the effects of radiation and chemical toxins (which are the two most severe stressors to your immune system, and generate optimal health and vitality. Bee pollen provides anti-oxidants that scavenge free radicals caused by exposure to radiation, chemical pollutants, and other intense physical or emotional stressors. Radiation and chemical pollutants are known as the two most severe stressors to your immune system. According to the Centers for Disease Control and the Environmental Protection Agency, the two premier health monitoring organizations in the world, this year you will be exposed to over 200 different forms of radioactive toxins and over 60,000 different chemical toxins. Toxins by definition stress your immune system, harm other parts of your body, and cause a wide range of common health problems. All forms of radiation, and most chemical pollutants, also produce cumulative side-effects. Any substance that effectively protects your body from the side-effects of exposure to radiation or chemical pollutants is considered a strong immune stimulant and generator of health. Exposure to radiation and/or chemical pollutants adversely decreases a number of vital body substances. These include antibodies and other white blood cells (your immune response), red blood cells, and nutrients in blood and mother's milk, such as protein and the antioxidant vitamins C and E.
Bee pollen is documented to counteract the effects that radiation and chemical pollutants have on these important barometers of health. Equally important, bee pollen has been proven clinically to generate health.

Fig.3 Bee pollen

Table 1. The average composition of dried pollen

	Bee-collected		Hand-collected
	%[a]	%[b]	%[b]
Water (air-dried-pollen)	7	11	10
Crude protein	20	21	20
Ash	3	3	4
Ether extracts (crude fat)	5	5	5
Carbohydrate			
Reducing sugars	36	26	3
Non-reducing sugars	1	3	8
Starch	-	3	8
Undetermined	28	29	43

Table 2. Minor components of bee collected pollen (Crane, 1990)

Flavonoids	At least 8 (flavonoid pattern is characteristic for each pollen type)
Carotenoids	At least 11
Vitamins	C, E, B complex (including, Niacin, Biotin, Pantothenic acid, Riboflavin (B_2), and Pyridoxine (B_6)).
Minerals	Principal minerals: K, Na, Ca, Mg, P, S. Trace elements: A1, B, C1, Cu, I, Fe, Mn, Ni, Si, Ti and Zn
Terpenes	
Free animo acids	All
Nucleic acids and nucleosides	DNA, RNA and others
Enzymes	More than 100
Growth regulators	Auxins, brassins, gibberellines, kinins and growth inhibitors

Table 3. Non-scientific claims and reports of benefits, cures or improvements derived from the use or consumption of bee-collected pollen (Sharma and Singh, 1980)

Improvements	**Cures of benefits**
Athletic preformance	Cancer in animals
Digestive assimilation	Colds
Rejuvenation	Acne
General vitality	Male sterility[a]
Skin vitality	Anaemia[b]
Appetite[b]	High blood pressure[b]
Haemoglobin content[b]	Nervous and endocrine disorders[b]
Sexual prowess	Ulcers
Performances (of a race horse)	

Bee Venom Characteristics

Among the many species of insects, only very few have the capability of defending themselves with a sting and venom injection during stinging. All insects that can sting are members of the order Hymenoptera, which includes ants, wasps and bees. Since the sting is believed to have evolved from the egg-laying apparatus of the ancestral, hymenopteran species, only females can sting. The sting is always at or near the abdominal end, rather than the head. Therefore the pain inflicted by a honeybee, defending its colony, is not caused by a bite, as is frequently said, but by a sting. There are many other poisonous insects which secrete venom. They usually cover their body with it, spray it, create wounds and secrete it into the wound, or inject it via mouthparts or a sting. In some cases, the venom is used for defense of the individual or, in the case of social insects, the colony. But venom is also used in killing prey (as with some wasps or spiders) or for immobilizing and preserving prey (for their own or their developing offspring's consumption). Honeybee venom is produced by two glands associated with the sting apparatus of worker bees. Its production increases during the first two weeks of the adult worker's life and reaches a maximum when the worker bee becomes involved in hive defence and foraging. It diminishes as the bee gets older. The queen bee's production of venom is highest on emergence, probably because it must be prepared for immediate battles with other queens. When a bee stings, it does not normally inject all of the 0.15 to 0.3 mg of venom held in a full venom sac. Only when it stings an animal with skin as tough as ours will it lose its sting - and with it the whole sting apparatus, including the venom sac, muscles and the nerve centre These nerves and muscles however keep injecting venom for a while, or until the venom sac is empty. The loss of such a considerable portion of its body is almost always fatal to the bee. The median lethal dose (**LD_{50}**) for an adult human is 2.8 mg of venom per kg of body weight, i.e. a person weighing 60 kg has a *50%* chance of surviving injections totalling 168 mg of bee venom (Schumacher et al., 1989). Assuming each bee injects all its venom and no stings are quickly removed at a maximum of 0.3 mg venom per sting, 600 stings could well be lethal for such a person. For a child weighing 10 kg, as little as 90 stings could be fatal. Therefore, quick removal of the stings is important. However, most human deaths result from one or few bee stings due to allergic reactions, heart failure or suffocation from swelling around the neck or the mouth. Used in small doses however, bee venom can be of benefit in trcating a large number of ailments. This therapeutic value was already known to many ancient civilizations. Today, the only uses of bee venom are in human and veterinary medicine.

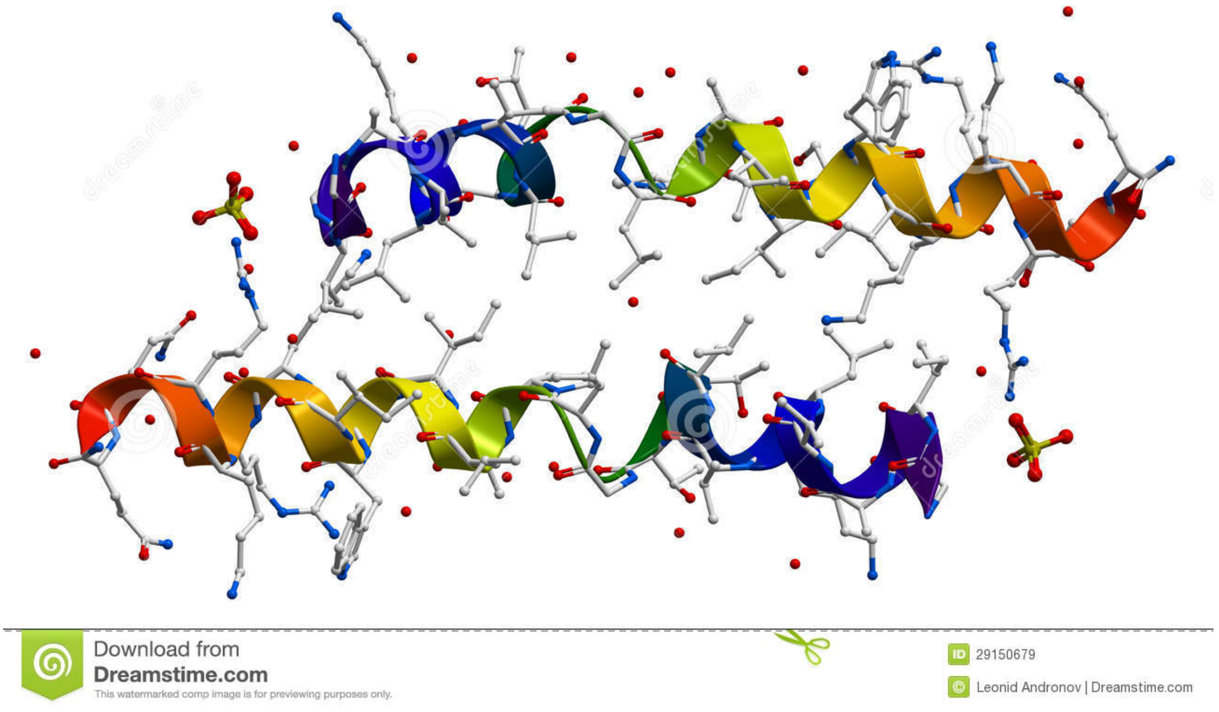
Physical characteristics of venom

Honeybee venom is a clear, odourless, watery liquid. When coming into contact with mucous membranes or eyes, it causes considerable burning and irritation. Dried venom takes on a light yellow colour and some commercial preparations are brown, thought to be due to oxidation of some of the venom proteins. Venom contains a number of very volatile compounds which are easily lost during collection.

The composition of venom

A large number of studies have been carried out on the composition of honeybee venom. Much of the basic identification of compounds, their isolation and the study of their pharmacological effects was done in the 1950's and 1960's. There are some comprehensive summaries in Piek (1986) which cover the morphology of the venom apparatus, the collection of venom, the pharmacological effects of bee venom and allergies to the Hymenoptera venom of bees, wasps and ants. 88% of venom is water. The glucose, fructose and phospholipid contents of venom are similar to those in bee's blood (Crane, 1990). At least 18 pharmacologically active components have been described, including various enzymes, peptides and amines. Table 4. lists the major components as summarized from Dotimas and Hider (1987) and Shipolini (1984). No further discussion of the detailed chemistry and various effects of individual components will be attempted here. Schmidt (1992) presents a comprehensive account of allergies to honeybee and other Hymenoptera venoms. Crane (1990), Dotimas and Hider (1987) and Banks and Shipolini (1986) give a very good overview of its composition, effects, harvesting and use. Venom from other Apis species is similar, but even the venoms from the various races within each species are slightly different from each other. The toxicity of Apis cerana venom has been reported to be twice as high as that of *A. Mellifera* (Benton and Morse, 1968).

Figure 3. Melittin, the principal component of bee venom*



* http://www.dreamstime.com/royalty-free-stock-images-melittin-principal-component-bee-venom-image29150679

Table 4. Composition of venom from honeybee worker

Class of molecules	Component	% of dry venom[a]	% of dry venom[b]
Enzymes	*Phospholipase A_2*	*10-12*	*10-12*
	Hyaluronidase	*1-3*	*1.5-2.0*
	Acid Phosphomonoesterase		*1.0*
	Lysophospholipase		*1.0*
	a -glucosidase		*0.6*
Other proteins and peptides	Melittin	50	40-50
	Pamine	1-3	3
	Mast Cell Degranulating Peptide (MCD)	1-2	2
	Secapin	0.5-2.0	0.5
	Procamine	1-2	1.4
	Adolapin		1.0
	Protease inhibitor	0.1	0.8
	Tertiapin	13-15	0.1
	Small peptides (with less than 5 amino acids)		
Physiologically active amines	Histamine	0.5-2.0	0.5-1.6
	Dopamine	0.2-1.0	0.13-1.0
	Noradrenaline	0.1-0.5	0.1-0.7
Amino Acids	t -aminobutyric acid	0.5	0.4
	a -amino acids	1	
Sugars	Glucose & fructose	2	
Phospholipids		5	
Volatile compounds		4-8	

The physiological effects of venom

Unconfirmed circumstantial evidence

Bee venom has long been used in traditional medicine for the treatment of various kinds of rheumatism. Although venoms of the different honeybee species differ slightly, there have been reports of successful rheumatism treatment with Apis dorsata venom by Sharma and

Singh (1983) and with A. cerana venom by Krell (1992, unpublished). The list of benefits to human beings as well as to animals is very long. Most of the reports of cures are of individual cases, though several unrelated patients have experienced the improvement or cure of similar ailments. Bee venom treatments are often accompanied by changes in life style, nutrition or other which may account for part, if not most of the benefits from treatments. Reported clinical tests were often conducted in countries with less rigorous methods than the standard Western, double-blind placebo tests. Despite these considerations, many patients did report positive results and many of the successful treatments occurred after established medical or surgical procedures had failed. However, there is a very real resistance in Western medical circles either to accept these results or to test bee venom treatments according to Western medical standards. The diseases and problems which have been reported by patients or doctors as improved or healed with bee venom therapy are listed below (Table 5). This does not constituent an endorsement or recommendation for the treatments. Stinging should never be tried unless there is immediate access to emergency treatment in case of an allergic reaction.

Figure 4. Bee Venom and HIV*

More than 34 million people worldwide are living with the human immunodeficiency virus (HIV), but research recently conducted at the Washington University School of Medicine in St. Louis **has shown that bee venom, and its main active component, melittin, carried via nanoparticles, is able to destroy unhealthy cells and tumors caused by viruses like HIV.** Melittin is a potent toxin in bee venom, which can poke holes in the protective envelope which surrounds HIV, as well as numerous other viruses. Thankfully and surprisingly, this toxin doesn't harm healthy cells, only the ones infected with the virus.

* http://www.trueactivist.com/new-study-bee-venom-found-to-destroy-hiv/

Table 5. List of diseases and health problems improved or healed according to anecdotal reports

Humans		
Arthritis, many types	Multiple sclerosis	Premenstrual syndrome
Epilepsy	Bursitis	Ligament injuries
Mastis	Some types of cancer	Sore throat
Chronic pain	Migraine	General immuno-stimulant
Decreases blood viscosity and coagulability	Dilates capillaries and arteries	Decreases blood cholesterol level
Neruoses	Rhinosinusitis	Endoarteriosis
Therosclerosis	Polyneuritis	Radicultitis
Infectious spondylitis	Neuralgia	Endoarthritis
Infect. Polyarthritis	Malaria	Intercostal myalgia
Myositis	Tropical ulcers	Slowly healing wounds
Thrombophiletritis	Cancer, temporary	Keratoconjunctivitis
Iritis	Iridocytis	Asthma

Scientific evidence

During the last seven decades, over 1700 scientific publications on the composition and various effects of bee venom in animals and humans have been published. An overwhelming proportion comes from Eastern Europe and Asia. Most of them concentrate on demonstrating the site specific, physiological effects of individual components such as membrane destruction, toxicity, or the stimulation or blocking of enzyme reactions. This has largely increased our understanding of the processes occurring after a sting, the physiological effects of isolated venom compounds and the substances responsible for most of the allergic reactions. It has contributed little to verifying the increasing claims of different therapeutic values attributed to honeybee venom, however. A study with whole bee venom on dogs (Vick and Brooks, 1972) and rats (Dunn, 1984) showed that melittin and apamine produce increased plasma cortisol. Together with various other arguments, this suggests that many of the curative effects of bee venom may work through stimulation of the body's enzyme and immune system, in a way similar to the common drug cortisone. Cortisone has been used in the treatment of many ailments, but it is also known to have strong, undesirable side-effects. Melittin also appears to have toxic side effects as do some of the other individual compounds in venom. When whole venom is applied however, no side-effects have been shown, other than in allergic patients (Broadman, 1962 and Weeks, 1992 personal communication).

The anti-inflammatory effects of bee venom are perhaps the best studied and the various mechanisms have been repeatedly described in scientific literature (Rekka and Kourounakis, 1990; Kim, 1989 and others). The neurotoxic venom compounds have shown a potential benefit for epileptic patients (Ziai, 1990). The protective value of bee venom and melittin against the lethal or damaging effects of x-rays has been investigated (Shipman and Cole, 1967 and Ginsberg et al., 1968). Though these and many other results are encouraging, no clinical studies have been carried out to verify the effectiveness using tests accepted by the Western medical establishment. Nevertheless, more and more physicians and healers are experimenting with this benign treatment after they have tested the patient's allergic reactions to bee venom. Recently, after long efforts by the American Apitherapy Society and its members, some interest has been shown by national institutions in several Western European countries and the USA for clinical and large scale tests of bee venom therapy.

A good summary of the scientific studies, with further references can be found in Banks and Shipolini (1986) and Schmidt (1992). Summaries of some of the major specific effects of the various venom compounds that are shorter and more easily understood, can be found in Mraz (1983), Dotimas and Hider (1987), Crane (1990) and Schmidt and Buchmann (1992). The American Apitherapy Society keeps records of scientific as well as anecdotal information on the use of bee venom. It is also probably the best source of information on any subject related to apitherapy.

The use of venom today

No uses for venom, other than medical ones are known to the author. The only legally accepted medical use of bee venom in Western European and North American countries is for desensitizing people who are hypersensitive (allergic) to bee venom. Since the early 1980's, pure bee venom has been used for desensitization. The use of whole body extracts has been largely discontinued after a double-blind test proved the higher efficiency of pure venom (Hunt et al., 1978). In Eastern Europe and in many Asian countries bee venom has been used in official medical treatment of a large variety of ailments for a considerable length of time.

The use of pure venom injections and well placed bee stings is increasing in Western countries as an alternative to heavy (and soinetimes ineffective) drug use, which is often associated with numerous side-effects. This is particularly so for arthritis and other rheumatoid inflammations. Application methods for venom include natural bee stings, subcutaneous injections, electrophoresis, ointments, inhalations and tablets (Sharma and Singh, 1983). Since bee venom has both a local and a systemic effect, correct placement of injections, or stings and the dosage are very important. Therefore, bee venom therapy must be properly learned. Still, relief of some ailments can be obtained by simply applying a sting or two to the affected area, i.e. to some painful, immobile arthritic joints. A society for api-acupuncture was formed in 1980 in Japan. In the following years, many reports of experiences and successes in api-acupuncture appeared (in Japanese) in Honeybee Science (e.g. Ohta, 1983 and Sagawa, 1983). In the Republic of China, bee venom therapy is combined with a knowledge of acupuncture by many hospitals and physicians. In the West, the American Apitherapy Society (AAS) is collecting case histories and information on bee venom therapy, together with medical uses of other bee products. There may be other national organizations, particularly in Eastern Europe and Asia. IBRA and Apimondia also have a wide collection of reference materials.

Venom products

Bee venom may be sold as whole bee extract, pure lidquid venom or an injectable solution, but in either form the market is extremely limited. Most venom is sold in a dry crystalline form. Since venom does not need to be processed, it can be prepared wherever bee venom therapy finds sufficient support. Production in small quantities is easy, as long as stringent sanitary controls and aseptic working conditions can be provided. The beekeeper has to work under extremely clean conditions, since most of the venom preparations will later be used for injections into humans or animals. For injections, the venom can be mixed at the time of injection with injectable fluids, such as distilled (sterile) water, saline solutions and certain oils, or it may be taken from prepared ampoules. Ampoules with set doses of ready-to-inject venom should only be prepared by certified pharmaceutical laboratories, because of the need to maintain stringent aseptic conditions and to measure the dosages very precisely. There are creams available which include bee venom (e.g. Forapin and Apicosan in Germany. Apivene in France and Immenin in Austria) which are used for external application on arthritic joints (BeeWell, 1993 and Sharma and Singh 1983) but neither the ingredients nor their proportions are known to the author. Tablets can be impregnated with quantities of bee venom, but Sharma and Singh (1983) recommended the removal of toxic proteins, such as Melittin and the use of colours to indicate different dosages. The tablets should be placed under the tongue, but no indication is given to the effect or usefulness of such a preparation.

Some specialized laboratories may be able to separate and purify different venom compounds and sell them to scientific and pharmaceutical laboratories. Phospholipase A_2 and highly active peptides are among some of the proteins purified from bee venom for scientific suppliers or laboratories (Schmidt and Buchmann, 1992). Entry to this limited market requires a highly sophisticated laboratory and very well-trained technicians and chemists. No further use or inclusion of venom in other products is presently known to the author. Though not directly related, bee sting emergency kits can be sold in some countries, particularly to people who are allergic. They also should be at hand for any beekeeper working with Africanized honeybees and at training centres, police and fire departments, in areas with Africanized honeybees. In the USA, they are now available only against a prescription. Such a kit (e.g. Anakit by Hollister Stier, USA) should contain at least:

1) One syringe with a premeasured content of epinephrine (adrenaline) or atropine, for immediate intramuscular injection - usually 0. 3m1 of a diluted solution of epinephrine (1: 1000) in saline solution. There are special, easy-to-use, syringes available from bee supply houses or through pharmacies, which can even be used through clothing (Epipen by Centre Laboratories, USA).

2. anti-histamine tablets. 3. tourniquet. 4. instructions about when, where and how to use the syringe and anti-histamine tablets; when not to use epinephrine, and where to seek medical

help. Epinephrine injections should be given only in extreme emergencies when no other medical help is available. The sting emergency kit has a limited shelf-life and should be kept refrigerated when not in use.

Caution

Collecting bee venom requires careful work with the highest degree of cleanliness, since the venom will be injected directly without further processing or sterilization. Protection of the collector against the disturbed bees and highly irritative dry venom is very important, too. Since people up to several hundred meters away might get stung by the highly irritated bees, further precautions at the time of collection in the apiary must be considered. When handling dry venom, laboratory gowns, gloves and face masks should be worn to avoid getting venom dust into the eyes and lungs. All equipment should be carefully washed afterwards. Contact between other people and contaminated material should be avoided People who do not regularly handle bees, who only get stung occasionally or are exposed occasionally to venom dust, run the risk of developing allergies. Using bee stings for self-treatment of various diseases can be risky, because allcrgies to bee venom can be developed quickly even after long periods of use. An emergency kit or quick access to an emergency service should always be available. No other side-effects have been reported, but regular supervision, check-ups and controls should be continued with competent doctors trained in apitherapy. Since severe allergic reactions are possible, bee venom should not be casually included in any health or medicinal products. Products containing bee venom need labels stating the contents and warning people of possible allergic reactions.

Honey Characteristics

Honey is the most important primary product of beekeeping both from a quantitative and an economic point of view. It was also the first bee product used by humankind in ancient times. The history of the use of honey is parallel to the history of man and in virtually every culture evidence can be found of its use as a food source and as a symbol employed in religious, magic and therapeutic ceremonies (Cartland, 1970; Crane, 1980; Zwaeneprel, 1984) an appreciation and reverence it owes among other reasons to its unique position until very recently, as the only concentrated form of sugar available to man in most parts of the world. The same cultural richness has produced an equally colourful variety of uses of honey in other products. "Honey is the natural sweet substance produced by honeybees from the nectar of blossoms or from the secretion of living parts of plants or excretions of plant sucking insects on the living parts of plants, which honeybees collect, transform and combine with specific substances of their own, store and leave in the honey comb to ripen and mature. This is the general definition of honey in the Codex Alimentarius (1989) in which all commercially required characteristics of the product are described. The interested reader is also referred to other texts such as "Honey, a comprehensive survey" (Crane, 1975). Honey in this bulletin, will refer to the honey produced by *Apis mellifera* unless otherwise specified. There are other honeybee species which make honey, and other bees and even wasps which store different kinds of honeys as their food reserves.

Physical characteristics of honey

Viscosity

Freshly extracted honey is a viscous liquid. Its viscosity depends on a large variety of substances and therefore varies with its composition and particularly with its water content. Viscosity is an important technical parameter during honey processing, because it reduces honey flow during extraction, pumping, settling, filtration, mixing and bottling. Raising the temperature of honey lowers its viscosity a phenomenon widely exploited during industrial honey processing. Some honeys, however, show different characteristics in regard to viscosity: Heather (*Calluna vulgaris*) Manuka (*Leptospermum scoparium*) and *Carvia callosa* are described as thixotrophic which means they are gel-like (extremely viscous) when standing still and turn liquid when agitated or stirred. By contrast a number of Eucalyptus honeys show the opposite characteristics. Their viscosity increases with agitation.

Density

Another physical characteristic of practical importance is density. Honey density, expressed as specific gravity is greater than water density, but it also depends on the water content of the honey. Because of the variation in density it is sometimes possible to observe distinct stratification of honey in large storage tanks. The high water content (less dense) honey settles above the denser, drier honey. Such inconvenient separation can be avoided by more thorough mixing.

Table 6. True specific gravity of honeys with different water content

Water content (%)	Specific gravity at 20°C	Water content (%)	Specific gravity at 20°C	Water content (%)	Specific gravity at 20°C
13.0	1.4457	16.0	1.4295	19.0	1.4101
14.0	1.4404	17.0	1.4237	20.0	1.4027
15.0	1.4350	18.0	1.4171	21.0	1.3950

Hygroscopicity

The strongly hygroscopic character of honey is important both in processing and for final use. In end products containing honey this tendency to absorb and hold moisture is often a desired effect such as, for example, in pastry and bread. During processing or storage however, the same hygroscopicity can become problematic, causing difficulties in preservation and storage due to excessive water content. From Table 6 it can be readily seen that normal honey with a water content of 18,3 % or less will absorb moisture from the air at a relative humidity of above 60%.

Surface tension

It is the low surface tension of honey that makes it an excellent humectant in cosmetic products The surface tension varies with the origin of the honey and is probably due to colloidal substances. Together with high viscosity, it is responsible for the foaming characteristics of honey.

Thermal properties

For the design of honey processing plants its thermal properties have to be taken into account. The heat absorbing capacity, i.e. specific heat, varies from *0.56* to 0.73 cal/g/^{0}C according to its composition and state of crystallization. The thermal conductivity varies from 118 to 143 x 10-~ cal/cm^{2}/sec/^{0}C (White, 1975a). One can therefore calculate the amount of heat, cooling and mixing necessary to treat a certain amount of honey, i.e. before and after filtration or pasteurization. The relatively low heat conductivity, combined with high viscosity leads to rapid overheating from point-heat sources and thus the need for careful stirring and for heating only in water baths.

Colour

Colour in liquid honey varies from clear and colourless (like water) to dark amber or black The various honey colours are basically all nuances of yellow amber, like different dilutions or concentrations of caramelized sugar, which has been used traditionally as a colour standard. More modern methods for measuring honey colour are described below. Colour varies with botanical origin, age and storage conditions, but transparency or clarity depends on the amount of suspended particles such as pollen. Less common honey colours are bright yellow (sunflower) reddish undertones (chestnut) greyish (eucalyptus) and greenish (honeydew). Once crystallized, honey turns lighter in colour because the glucose crystals are white. Some of the honeys reportedly "as white as milk" in some parts of East Africa are finely crystallized honeys which are almost water white, i.e. colourless, in their liquid state. The most important aspect of honey colour lies in its value for marketing and determination of its end use. Darker honeys are more often for industrial use, while lighter honeys are marketed for direct consumption. In many countries with a large honey market, consumer preferences are determined by the colour of honey (as an indication of a preferred flavour) and thus, next to general quality determinations, colour is the single most important factor determining import and wholesale prices. Honey colour is frequently given in millimetres on a Pfund scale (an optical density reading generally used in international honey trade).

Crystallization

Crystallization is another important characteristic for honey marketing, though not for price determination. In temperate climates most honeys crystallize at normal storage temperatures. This is due to the fact that honey is an oversaturated sugar solution, i.e. it contains more sugar than can remain in solution. Many consumers still think that if honey has crystallized it has gone bad or has been adulterated with sugar. The crystallization results from the formation of monohydrate glucose crystals, which vary in number, shape, dimension and quality with the honey composition and storage conditions. The lower the water and the higher the glucose content of honey, the faster the crystallization. Temperature is important, since above 25° and below 5°C virtually no crystallization occurs. Around 14°C is the optimum temperature for fast crystallization, but also the presence of solid particles (e.g. pollen grains) and slow stirring result in quicker crystallization. Usually, slow crystallization produces bigger and more irregular crystals. During crystallization water is freed. Consequently, the water content of the liquid phase increases and with it the risk of fermentation. Thus, partially crystallized honey may present preservation problems, which is why controlled and complete crystallization is often induced deliberately. In addition, partially crystallized or reliquified honey is not an attractive presentation for retail shelves.

The composition of honey

The average composition of all honeys, is shown in table 7.

Sugars account for 95 to 99% of honey dry matter. The majority of these are the simple sugars fructose and glucose which represent *85-95%* of total sugars. Generally, fructose is more abundant than glucose. This predominance of simple sugars and particularly the high percentage of fructose are responsible for most of the physical and nutritional characteristics of honey. Small quantities of other sugars are also present, such as disaccharides (sucrose, maltose and isomaltose) and a few trisaccharides and oligosaccharides. Though quantitatively of minor importance, their presence can provide information about adulteration and the botanical origin of the honey.

Water is quantitatively the second most important component of honey. Its content is critical, since it affects the storage of honey. Only honeys with less than 18% water can be stored with little to no risk of fermentation. The final water content depends on a number of environmental factors during production such as weather and humidity inside the hive, but also on nectar conditions and treatment of honey during extraction and storage. It can be reduced before or after extraction by special techniques. Among the minor constituents **organic acids** are the most important and of these gluconic acid, which is a by-product of enzymatic digestion of glucose, predominates. The organic acids are responsible for the acidity of honey and contribute largely to its characteristic taste. Minerals are present in very small quantities, potassium being the most abundant. Dark honeys, particularly honeydew honeys are the richest in minerals. Other trace elements include **nitrogenous compounds** among which the enzymes originate from salivary secretions of the worker honeybees. They have an important role in the formation of the honey. Their commercial importance is not related to human nutrition, but to their fragility and uniqueness. Thus their reduction or absence in adulterated, overheated or excessively stored honeys serves as an indicator of freshness. The main enzymes in honey are invertase (saccharase) **diastase (amylase)** and **glucose oxidase**. Traces of other proteins, enzymes or amino acids as well as water soluble vitamins are thought to result from pollen contamination in honey. Virtually absent in newly produced honey, **hydroxvmethylfurfural** (HMF) is a byproduct of fructose decay, formed during storage or during heating. Thus, its presence is considered the main indicator of honey deterioration. Even though some of the substances responsible for honey colour and flavour have been identified. the majority are still unknown. It is more than likely that honeys from different botanical origins contain different aromatic and other substances which contribute to the specific colours and flavours and thus allow to distinguish one honey from another. Similarly, it is very likely that, depending on their botanical origin, honeys contain traces of pharmacologically active substances. Some of them have been identified, such as those responsible for the toxicity of certain honeys, but for the majority of possible substances, scientific verification requires further studies.

Figure 6. Honey; an important drug

Table 7. Average composition honeys

Component (% except pH and diastase valute)	Average	Standard deviation	Range
Water	<>17.2	1.5	13.4 - 22.9
Fructose	38.2	2.1	27.2 - 44.3
Glucose	31.3	3.0	22.0 - 40.7
Sucrose	1.3	0.9	0.2 - 7.6
Maltose (reducing disaccharides calculated as maltose)	7.3	2.1	2.7 - 16.0
Higher sugars	1.5	1.0	0.1 - 8.5
Free acids (as gluconic acid)	0.43	0.16	0.13 - 092
Lactone (as glucolactone)	0.14	0.07	0.0 - 0.37
Total acid (as gluconic acid)	0.57	0.20	0.17 - 1.17
Ash	0.169	0.15	0.020 - 1.028
Nitrogen	0.041	0.026	0.000 - 0.133
pH	3.91	-	3.42 - 6.10
Diastase value	20.8	9.8	2.1 - 61.2

The physiological effects of honey

Unconfirmed circumstantial evidence

For thousands of years honey was the only source of concentrated sugar. uniqueness, scarcity and desirability connected it to divinity very early in human history thus ascribing to it symbolic, magic and therapeutic significance. Much of the myth many of the traditional medicinal uses have continued until today. Few of these medicinal benefits have seen scientific confirmation and they are not always exclusive to honey. The majority are due to the high sugar content and therefore can also be found in other sweet substances with high sugar contents. It was not by accident that sugar, when first introduced to Europe, was considered a medicine for many diseases and was used with caution. The major properties and effects commonly attributed to honey (Donadieu, 1983) are briefly described below, but there are hundreds of different local uses in various countries, according to the specific cultures and traditions, and it is impossible to mention all of them. The Koran also mentions several uses for honey and other bee products (El Banby, 1987).

Nutritional benefits

Honey is said to facilitate better physical performance and resistance to fatigue, particularly for repeated effort; it also promotes higher mental efficiency. It is therefore used by both the healthy and the sick for any kind of weakness, particularly in the case of digestive or assimilative problems. Improved growth of non-breast fed newborn infants, improved calcium fixation in bones and curing anaemia and anorexia may all be attributed to some nutritional benefit or stimulation from eating honey.

Benefits to the digestive apparatus

Honey is said to improve food assimilation and to be useful for chronic and infective intestinal problems such as constipation, duodenal ulcers and liver disturbances. Salem (1981) and Haffejee and Moosa (1985) have reported successful treatment of various gastrointestinal disorders.

Benefits to the respiratory system

In temperate climates and places with considerable temperature fluctuations, honey is a well known remedy for colds and mouth, throat or bronchial irritations and infections. The benefits, apart from antibacterial effects, are assumed to relate to the soothing and relaxing effect of fructose.

Benefits to skin and wound healing

Honey is used in moisturizing and nourishing cosmetic creams, but also in pharmaceutical preparations applied directly on open wounds, sores, bed sores, ulcers, varicose ulcers and burns. It helps against infections, promotes tissue regeneration, and reduces scarring also in its pure, unprocessed form (Hutton, 1966; Manjo, 1975; Armon, 1980 and Dumronglert, 1983). If applied immediately, honey reduces blistering of burns and speeds regeneration of new tissue. Many case histories are reported in the literature for human as well as veterinary medicine (sores, open wounds and teat lesions in cows). A cream, applied three times per day and prepared from equal parts of honey, rye flour and olive oil, has been successfully used on many sores and open wounds -even gangrenous wounds in horses. Lucke (1935) successfully tested a honey and cod liver oil mixture suspended in a simple non-reactive cream base on open wounds in humans, but he gave no details on proportions.

Benefit to eye disorders

Clinical cases or traditional claims that honey reduces and cures eye cataracts, cures conjunctivitis and various afflictions of the cornea if applied directly into the eye, are known from Europe, Asia, and Central America. This is said to be more true for Meliponid and Trigonid honeys from South and Central America and India. There are also case histories of ceratitis rosacea and corneal ulcers, healed with pure honey or a 3 % sulphidine ointment in which Vaseline was replaced by honey.

Medicine-like benefit

Frequently, specific benefits of unifloral honeys are reported, based on the traditional assumption that honey made from the nectar of a medicinal plant has the same or similar beneficial activity as the one recognized for the whole plant or some parts of it. Even if no transfer of active ingredients is involved, mechanisms similar to homeopathic potentiation are possible. Empirically effective therapies such as Bach flower therapy and aroma-therapy suggest that there can be much more to the medicinal value of honey than chemical analysis and quantification reveals. These claims are not supported by orthodox scientific evidence.

Diabetes

Frequently, claims are voiced that honey is good for diabetics. This is unlikely to find confirmation because of its high sugar content. However, it is better than products made with cane sugar, as a study by Katsilambros et al.,(1988) has shown. It revealed that insulin levels were lower when compared to the uptake of equal caloric values of other foods, but blood sugar level was equal or higher than in the other compared products shortly after eating. In healthy individuals, the consumption of honey produced lower blood sugar readings than the consumption of the same quantity of sucrose.

Ayurvedic medicine

Traditional, but well-studied medicinal systems as the ayurvedic medicine of India, use honey predominantly as a vehicle for faster absorption of various drugs such as herbal extracts. Secondarily, it is also thought to support the treatment of several more specific ailments, particularly those related to respiratory irritations and infections, mouth sores and eye cataracts. It also serves as a general tonic for newborn infants, the young and the elderly, the convalescent and hard working farmers (Nananiaya, 1992, personal communication). In general, no distinction is being made between honey from *Apis mellifera A. cerana or A. dorsata.*

Other benefits

Honey is said to normalize kidney function, reduce fevers and help insomnia. It is also supposed to help recovery from alcohol intoxication and protect the liver; effects also ascribed to fructose syrups. Heart, circulation and liver ailments and convalescent patients in general improved after injection with solutions of 20 and 40% honey in water.

Scientific evidence

According to scientific evidence it would be better to consider honey as a food, rather than a medicine. Most of the benefits described above, at least for internal use, can most likely be ascribed to nutritional effects of some kind. On the other hand, our scientific understanding of cause and effect, typically only confirmed if a single compound measurably affects a well defined symptom, is far too limited to explain possibly more complex and subtle, particularly synergistic interactions.

Energy source

As food, honey is mainly composed of the simple sugars fructose and glucose, which form the basis of almost all indications on how, when and why to use it. The main consideration is the fact that honey provides immediately available calories, from which it derives its energy value for healthy and sick people: quick access to energy without requiring lengthy or complicated digestive action. The same direct absorption also carries a risk of pathological sugar metabolism, such as diabetes and obesity.

Non-energetic nutrients

Often honey is recommended because of its content of other nutrients like vitamins and minerals, but their quantity is so low that it is unrealistic to think they can provide any significant supplement in a deficient diet. Similar arguments are made for the nutritional and health benefits from most other bee products, particularly pollen and royal jelly. Although their beneficial characteristics have been shown in numerous cases, they cannot be based on simple numeric values, i.e. X amount of substance Y. Yet, it is well known that the quality and availability of a nutrient is important for its usefulness to the body. Micronutrients in unprocessed honey can be assumed to be of the highest quality possible. Thus from a nutritional point of view, a synergistic balancing effect or one that unlocks the availability of other nutrients already present, is one of the more plausible yet untested hypotheses.

Topical applications

Topical applications under controlled conditions have shown accelerated wound healing in animals (Bergman et al., 1983, El Banby et al. 1989) and of experimental burn wounds in rats (Burlando, 1978) but also of various types of wounds, including post-operative ones in humans (Cavanagh et al., 1970; Kandil et al., 1987a, b and 1989; Effem, 1988 and Green, 1988). Similar, yet not equal, effects are obtained with the application of purified sucrose and special polysaccharide powders (Chirife et al., 1982). External as well as internal wounds from operations become bacteriologically sterile within a few days and dry out. The simultaneous stimulation of tissue regeneration by honey reduces scarring and healing times. In addition, dressings applied with honey do not stick to the wounds or delicate new skins. In many tropical field hospitals, where antibiotics and other medicines are scarce, honey has been employed successfully for a long time.

Table 8. Nutrients in honey in relation to human requirements (Crane, 1980)

Nutrient	Unit	Average amount in 100 g honey	Recommended daily intake
Energy equivalent	K.Cal	304	2800
<u>Vitamins</u>			
A	I.U.	-	5000
B1 (Thiamin)	mg.	0.004 - 0.006	1.5
B2 (Riboflavin)	mg.	0.002- 0.06	1.7
Nicotinic acid (niacin)	mg.	0.11.- 0.36	20
B6 (Pyridoxine)	mg.	0.008 - 0.32	2.0
Pantothenic acid	mg.	0.02 - 0.11	10
Bc (Folic acid)	mg.	-	0.4
B12 (Cyanocobaltamine)	mg.	-	6
C (Ascorbic acid)	□g	2.2 - 2.4	60
D	mg.	-	400
E (Tocopherol)	I.U.	-	30
H (Biotin)	I.U.	-	0.3
<u>Minerals</u>	mg.		
Calcium	mg.	4 - 30	1000
Chlorine	mg.	2 - 20	
Copper	mg.	0.01 - 0.1	2.0
Iodine	mg.	-	0.15
Iron	mg.	1. - 3.4	18
Magnesium	mg.	0.7 - 13	400
Phosphorous	mg.	2 - 60	1000

Potassium	mg.	10 - 470	-
Sodium	mg.	0.6 - 40	-
Zinc	mg.	0.2 0.5	15

Antibacterial activity

Antibacterial activity is the easiest to test and is probably the most studied biological activity of honey. In normal honey it is attributed to high sugar concentration and acidity (pH range 3.5 to 5.0). Yet, since also diluted honey has shown antibacterial activity, the active ingredient was attributed to an elusive substance generically termed "inhibin". Much of this activity was later attributed to hydrogen peroxide (H_20_2) an enzymatic by-product during the formation of gluconic acid from glucose. The responsible enzyme, glucose oxidase is basically inactive in concentrated normal honey. Thus, in honey solutions (diluted honey) with the right pH, antibacterial activity is largely due to the presence of hydrogen peroxide. The biological significance of such a mechanism arises from the requirement to protect immature honey (with high moisture content) inside the colony until higher sugar concentrations are achieved. Both mechanisms can partially explain the sterilizing effect of honey on wounds and some of its efficacy against cold infections, but it does not explain its beneficial effect on burn wounds (Heggers, et al., 1987) and faster wound healing with less scarred tissue. Subralimanyam (1993) has experienced 100% acceptance of skin grafts after storage in honey for up to 12 weeks. Antibacterial activity varies greatly between different types of honey (Dustmann, 1979; Revathy and Banerji, 1980; Jeddar et al., 1985 and Molan et al., 1988). In addition to glucose oxidase, honey seems to contain other mostly unknown substances with antibacterial effects, among which are polyphenols. These other factors have been identified in a few cases (Toth et al., 1987; Bogdanov, 1989 and Molan et al., 1989) but as a whole there are few scientific studies on the various claims of the beneficial effects of honey. However, it has been well demonstrated that most of the antibacterial activities of honey are lost after heating or prolonged exposure to sunlight (Dustmann, 1979).

Information sources on honey therapy

Mladenov (1972) published a book (in Rumanian) on honey therapy in Rumania and there are several articles on honey therapy in Apimondia (1976) as well as in Crane (1975 and 1990). The American Apitherapy Society collects case histories and scientific information on all therapeutical uses of bee products.

Honey as an ingredient in medicine-like products

The medicinal use of honey is probably its most widely known use, but such uses do not require special preparations. If not used straight, it is mixed at home with other liquids such as hot milk, teas or other infusions, wine and other alcoholic beverages. The pharmacopoeias of many countries describe a honey-based preparation which can be prepared by pharmacists (honey rose water) which is used for topical application in infected throats and various ulcers of the mouth. More common is the use of honey in herbal and other traditional extracts. If the extract is presented in the form of a syrup, the preparations need to be sterilized with heat before or after the addition of the active ingredients, or a preservative like potassium sorbate or alcohol needs to be added. Sometimes fermented honey syrups are used as a base. These fermented syrups are made by adding yeasts to a mix that contains a much higher ratio of sugar to water (1:1) than is used for honey wines, mead or beer (see next section). Plant extracts are added after fermentation and clarification.

The addition of honey to herbal extracts and also prior to fermentation (as described above) is commonly practised in ayurvedic medicine as mentioned in 2.4.1. Traditional African medicinal extracts are also mixed with honey and probably not only because they are easier to take that way. In Europe, many traditional formulations are also known and some were even recommended by Hippocrates. Honey is also a fundamental ingredient in some medicinal wines and vinegars. In one case herbs are crushed and immersed for 10 to 30 days in the wine, to which some alcohol may be added in order to improve the extraction and preservation. The liquid obtained needs to be filtered and pasteurized; honey is then added.

Propolis Characteristics

Propolis is a mixture of various amounts of beeswax and resins collected by the honeybee from plants, particularly from flowers and leaf buds. Since it is difficult to observe bees on their foraging trips the exact sources of the resins are usually not known. Bees have been observed scraping the protective resins of flower and leaf buds with their mandibles and then carrying them to the hive like pollen pellets on their hind legs. It can be assumed that in the process of collecting and modelling the resins, they are mixed with some saliva and other secretions of the bees as well as with wax. These resins are used by worker bees to line the inside of nest cavities and all brood combs, repair combs, seal small cracks in the hive, reduce the size of hive entrances seal off inside the hive any dead animals or insects which are too large to be carried out and perhaps most important of all, to mix small quantities of propolis with wax to seal brood cells. These uses are significant because they take advantage of the antibacterial and antifungal effects of propolis in protecting the colony against diseases. Propolis has been shown to kill the bee's most ardent bacterial foe, *Bacillus* larvae - the cause of American Foul Brood (Mlagan and Sulimanovic, 1982; Meresta and Meresta, 1988). The use of propolis thus reduces the chance of infection in the developing brood and the growth of decomposing bacteria in dead animal tissue.

The composition of propolis depends on the type of plants accessible to the bees. Propolis changes in colour, odour and probably medicinal characteristics, according to source and the season of the year. Moreover, some bees and some colonies are more avid collectors-generally to the dismay of the beekeeper, since propolis is a very sticky substance which, in abundance, can make it difficult to remove frames from the boxes. Foraging for propolis is only known with the Western honeybee *Apis mellifera*. The Asian species of Apis do not collect propolis. Only Meliponine or stingless bees are known to collect similarly sticky resinous substances, for sealing hives and constructing honey and pollen pots for storage. In this bulletin, however, propoli shall refer only to resins collected by honeybees, since almost all of the research has been done on it. There may well be similar traditional uses for resins collected by Meliponids. In the natural distribution ranges of *Apis mellifera*, a multitude of traditional uses are known for this versatile substance. The Greeks and Romans already knew that propolis would heal skin abscesses and through the centuries its use in medicine has received varying attention. The ancient Egyptians knew about the benefits of propolis and in Africa it is still used today, as a medicine, an adhesive for tuning drums, sealing cracked water containers or canoes and dozens of other uses. It has been incorporated in special varnishes such as those used by Stradivarius for his violins (Jolly, 1978).

Physical characteristics of propolis

The colour of propolis ranges from yellow to dark brown depending on the origin of the resins. But, even transparent propolis has been reported by Coggshall and Morse (1984). At temperatures of 250 to 45 ^{0}C propolis is a soft, pliable and very sticky substance. At less than 150 C, and particularly when frozen or at near freezing, it becomes hard and brittle. It will remain brittle after such treatment even at higher temperatures. Above 45 ^{0}C it will become increasingly sticky and gummy. Typically propolis will become liquid at 60 to 70^{0}C, but for some samples the melting point may be as high as 100^{0}C. The most common solvents used for commercial extraction are ethanol (ethyl alcohol) ether, glycol and water. For chemical analysis a large variety of solvents may be used in order to extract the various fractions. Many of the bactericidal components are soluble in water or alcohol.

The composition of propolis

In one recent analysis of propolis from England, 150 compounds were identified in only one sample (Greenaway, et al., 1990), but in total more than 180 have been isolated so far. It appears that with every new analysis, new compounds are found. Propolis resins are collected from a large variety of trees and shrubs. Each region and colony seems to have its own preferred resin sources, which results in the large variation of colour, odour and composition. Comparisons with tree resins in Europe suggest that, wherever Populus species are present, honeybees preferably collect the resins from leaf buds of these trees.A Cuban study suggests that the plant resins collected are at least partially metabolized by bees (Cuellar et al., 1990). The presence of sugars (Greenaway et al., 1987) also suggests some metabolization by bees, i.e. as a result of adding saliva during both scraping and chewing. A list of the major classes of chemicals occurring in propolis is given below with references to some recent reviews and analyses from different countries. The major compounds are resins composed of flavonoids and phenolic acids or their esters, which often form up to 50% of all ingredients. The variation in beeswax content also influences the chemical analysis. In addition it must be said that most studies do not attempt to determine all components, but limit themselves to a class of chemicals or a method of extraction. The selection of the studies presented here is based on the most recent publications with preference given to the most complete studies or to studies from countries where these are the only references.

Figure 6. Propolis is a vegetable mastic made by honeybees from resins collected on the bark and buds of certain trees and balsamic plants

The physiological effects of propolis

Unconfirmed circumstantial evidence

The following uses of propolis or its extracts have been found in literature, but without substantiating evidence or reference to scientific studies: anti-asthmatic treatment in mouth sprays, support of pulmonary system, anti-rheumatic (Donadieu, 1979), inhibition of melanoma and carcinoma tumour cells, tissue regeneration, strengthening of capillaries, anti-diabetic activity, phytoinhibitor, inhibiting plant and seed germination in general and potato and leaf salad seed germination (Bianchi, 1991) in particular.

Composition of Propolis

The composition of propolis varies from hive to hive, from district to district, and from season to season. Normally, it is dark brown in color, but it can be found in green, red, black, and white hues, depending on the sources of resin found in the particular hive area. Honey bees are opportunists, gathering what they need from available sources, and detailed analyses show that the chemical composition of propolis varies considerably from region to region, along with the vegetation. In northern temperate climates, for example, bees collect resins from trees, such as poplars and conifers (the biological role of resin in trees is to seal wounds and defend against bacteria, fungi and insects). "Typical" northern temperate propolis has approximately 50 constituents, primarily resins and vegetable balsams (50%),waxes (30%), essential oils (10%), and pollen (5%). Propolis also contains persistent lipophilic acaricides, a natural pesticide that deters mite infestations. In neotropical regions, in addition to a large variety of trees, bees may also gather resin from flowers in the genera *Clusia* and *Dalechampia*, which are the only known plant genera that produce floral resins to attract pollinators. *Clusia* resin contains polyprenylated benzophenones. In some areas of Chile, propolis contains viscidone, a terpene from *Baccharis* shrubs, and in Brazil, **naphthoquinone epoxide** has recently been isolated from red propolis, and prenylated acids such as **4-hydroxy-3,5-diprenyl cinnamic acid** have been documented. An analysis of propolis from Henan, China found sinapinic acid, isoferulic acid, caffeic acid, and chrysin, with the first three compounds demonstrating antibacterial properties. Also, Brazilian red propolis, largely derived from *Dalbergia ecastaphyllum* plant resin, has high relative percentages of the **isoflavonoids 3-hydroxy-8,9-**dimethoxypterocarpan and medicarpin.

Other flavonoids commonlypresentinclude galangin and pinocembrin. Caffeic acid phenethyl ester (CAPE) is also a component of some varieties of propolis from New Zealand. Occasionally, worker bees will even gather various caulking compounds of human manufacture, when the usual sources are more difficult to obtain. The properties of the propolis depend on the exact sources used by each individual hive; therefore any potential medicinal properties that may be present in one hive's propolis may be absent from another's, or from another sample in the same hive. General medicinal uses of propolis include treatment of the cardiovascular and blood systems (anaemia), respiratory apparatus (for various infections), dental care, dermatology (tissue regeneration, ulcers, excema, wound healing - particularly burn wounds, mycosis, mucous membrane infections and lesions), cancer treatment, immune system support and improvement, digestive tracts (ulcers and infections), liver protection and support and many others. Some references to these applications can be found in the list of scientifically proven effects of propolis otherwise one might refer again to IBRA's collection of abstracts, Apimondia and the American Apitherapy Society.

ROYAL JELLY

Royal jelly is secreted by the hypopharyngeal gland (sometimes called the brood food gland) of young worker (nurse) bees, to feed young larvae and the adult queen bee. Royal jelly is always fed directly to the queen or the larvae as it is secreted; it is not stored. This is why it has not been a traditional beekeeping product. The only situation in which harvesting becomes feasible is during queen rearing, when the larvae destined to become queen bees are supplied with an over-abundance of royal jelly. The queen larvae cannot consume the food as fast as it is provided and royal jelly accumulates in the queen cells. The exact definition of commercially available royal jelly is therefore related to the method of production: it is the food intended for queen bee larvae that are four to five days old. The differentiation between queen and worker bees is related to feeding during the larval stages. Indeed, all female eggs can produce a queen bee, but this occurs only when, during the whole development of the larvae and particularly the first four days, they are cared for and fed "like a queen". Queen rearing, regulated by complex mechanisms within the hive, induces in a young larva a series of hormonal and biochemical actions and reactions that make it develop into a queen bee. A queen bee differs from a worker bee in various ways:

in its morphology: the queen develops reproductive organs while the worker bee develops organs related to its work such as pollen baskets, stronger mandibles, brood food glands and wax glands.

in its development period: on average the queen develops in *15.5* days while worker bees require 21 days.

in its life span: the queen lives for several years as compared to a few months for the worker bee,

and its behaviour: the queen lays up to several thousand eggs a day while workers lay eggs only occasionally. Unlike workers, the queen never participates in any common hive activities.

It is mainly the spectacular fertility and long life-span of the queen, exclusively fed on royal jelly, which have suggestively led people to believe that royal jelly produces similar effects in humans. In the early *1950's,* articles began to appear, particularly in the French beekeeping press, in praise of the virtues of royal jelly, referring to research conducted in several hospitals. Chauvin (1968) however, was unable to find the source of such information and therefore considered it unfounded. The myth of royal jelly started with an amazing biological phenomenon on the one hand and commercial speculation on the other, which, on the basis of initial results obtained by entomologists and physiologists, exploited the suggestibility and imagination of consumers willing to be seduced by the fascination of this rare and unknown product was exploited. In fact, royal jelly was so rare and so little known that it was impossible to verify its actual presence in many products claiming its content.

In the years immediately following its first marketing, royal jelly quickly became widely known and consumed and the increasing demand motivated experts to refine production techniques and led more and more beekeepers to specialize in this activity. At the same time, research on quality control of the commercial product and identification of its biological and clinical properties found growing support. Consumption of royal jelly has been growing ever since, even without its benefit to human health having ever been scientifically confirmed. The Western medical establishment has always been wary of the effects claimed for this product and in most cases refuses to consider it, largely because of the way royal jelly was initially promoted. In spite of a vast number of publications praising its virtues and the apparently abundant bibliography, there is still a serious lack of scientific data on the clinical effects of royal jelly.

Physical characteristics of royal jelly

Royal jelly is a homogeneous substance with the consistency of a fairly fluid paste. It is whitish in colour with yellow or beige tinges, has a pungent phenolic odour and a characteristic sour flavour. It has a density of approximately 1.1 g/cm^3 (Lercker et al., 1992) and is partially soluble in water. Aqueous solutions clarify during basification with soda. Viscosity varies according to water content and age - it slowly becomes more viscous when stored at room temperature or in a refrigerator at *5 °C.* The increased viscosity appears to be related to an increase in water insoluble nitrogenous compounds, together with a reduction in soluble nitrogen and free amino acids (Takenaka et al., 1986). These changes are apparently due to continued enzymatic activities and interaction between the lipid and protein fractions. If sucrose is added, royal jelly becomes more fluid (Sasaki et al.,1987). Such changes in viscosity have also been related to the phenomena which regulate caste differentiation in a bee colony. Certain debris in royal jelly, is a sign of purity as, for example, the ever present fragments of laarval skin. Wax fragments too, are encountered more or less regularly, but their presence is largely dependent on the collection method. Stored royal jelly often develops small granules due to precipitation of components.

The composition of royal jelly

Numerous chemical analyses of royal jelly have been published over the years. Only recently though, have highly refined technologies given detailed analyses of the unusual composition and complexity of this somewhat acidic substance (pH 3.6 to 4.2). The principal constituents of royal jelly are water, protein, sugars, lipids and mineral salts. Although they occur with notable variations the composition of royal jelly remains relatively constant when comparing different colonies, bee races and time. Water makes up about two thirds of fresh royal jelly, but by dry weight, proteins and sugars are by far the largest fractions. Of the nitrogenous substances, proteins average 73.9% and of the six major proteins (Otani et al., 1985) four are glycoproteins (Takenaka, 1987). Free amino acids average 2.3% and peptides 0.16% (Takenaka, 1984) of the nitrogenous substances. All amino acids essential for humans are present and a total of 29 amino acids and derivatives have been identified, the most important being aspartic acid and glutamic acid (Howe et al., *1985).* The free amino acids are proline and lysine. A number of enzymes are also present including glucose oxidase phosphatase and cholinesterase. An insulin-like substance has been identified by Kramer *et al.* (1977 and 1982).

Figure 7. Royal Jell

Table 9. Composition of royal jelly (form Lercker *et al.,*1984 and 1992)

	Minimum	Maximum
Water	57%	70%
Proteins (N x 6.25)	17% of dry weight	45% of dry weight
Sugars	18% of dry weight	52% of dry weight
Lipids	3.5% of dry weight	19% of dry weight
Minerals	2% of dry weight	3% of dry weight

The sugars consist mostly of fructose and glucose in relatively constant proportions similar to those in honey. Fructose is prevalent. In many cases fructose and glucose together account for 90% of the total sugars. The sucrose content varies considerably from one sample to another. Other sugars present in much lower quantities are maltose, trehalose, melibiose, ribose and erlose (Lercker et al., 1984, 1986 and 1992). The lipid content is a unique and from many points of view, a very interesting feature of royal jelly. The lipid fraction consists to 80-90% (by dry weight) of free fatty acids with unusual and uncommon structures. They are mostly short chain (8 to 10 carbon atoms) hydroxy fatty acids or dicarboxylic acids, in contrast to the fatty acids with 14 to 20 carbon atoms which are commonly found in animal and plant material. These fatty acids are responsible for most of the recorded biological properties of royal jelly (Schmidt and Buchmann, 1992). The principal acid is 10-hydroxy-2-decanoic acid, followed by its saturated equivalent, lO-hydroxydecanoic acid. In addition to the free fatty acids, the lipid fraction contains some neutral lipids, sterols (including cholesterol) and an unsaponifiable fraction of hydrocarbons similar to beeswax extracts.

The total ash content of royal jelly is about 1 % of fresh weight or 2 to 3 % of dry weight. The major mineral salts are, in descending order: K, Ca, Na, Zn, Fe, Cu and Mn, with a strong prevalence of potassium (Benfenati et al., 1986). The vitamin content has been the object of numerous studies, from the moment when the first research (Aeppler, 1922) showed that royal jelly is extremely rich in vitamins. Table 10 indicates the results obtained by Vecchi et al., (1988) with regard to water-soluble vitamins. Other authors report averages close to the minimum values of Table 10 (Schmidt and Buchmann, 1992). Only traces of vitamin C can be found. As far as the fat-soluble vitamins are concerned, it was initially thought that, given the enormous fertility of the queen bee, royal jelly would contain vitamin E. But tests have shown that it does not. Vitamins A, D and K are also absent (Melampy and Jones, 1939). During the first studies, much emphasis was placed on the search for sex hormones in royal jelly. The first positive tests were later proven wrong. Melampy and Stanley (1940) showed no gonadotropic effects on female rats and Johansson and Johansson (1958) clearly demonstrated the absence of any human sex hormones. Recently though, with much more sensitive radio-immunological methods, testosterone has been identified in extremely small quantities: 0.012 ~g/g fresh weight (Vittek and Slomiany, 1984). In comparison, a human male produces daily 250,000 to 1 million times the amount present in one gram of fresh royal jelly (Schmidt and Buchmann, 1992). No biological effect has been demonstrated for such small amounts.

Table 10. Vitamin content of royal jelly in m g per gram of fesch weight (Vecchi et al.,1988)

	Thiamine	Riboflavin	Pantothenic Acid	Pyridoxine	Niacin	Folic acid	Inositol	Biotin
Minimum	1.44	5	159	1.0	48	0.130	80	1.1
Maximum	6.70	25	265	48.0	88	0.530	350	19.8

Numerous minor compounds, belonging to diverse chemical categories, have been identified in royal jelly. Among these are two heterocyclic substances, biopterine and neopterine at 25 and 5 ijg/g of fresh weight respectively. These compounds are found in the food of worker bee larvae too, but at about one tenth of these concentration. Other substances identified include several nucleotides as free bases (adenosine, uridine, guanosine, iridin and cytidine) the phosphates AMP, ADP, and ATP acetylcholine (1 mglg dry weight and gluconic acid (0.6% of fresh weight, Nye et al., 1973). In all popular and scientific literature, there is a fraction of royal jelly described as "other, as yet unknown". This phrase not only emphasizes the incomplete state of analytical knowledge about the product, but also the lack of understanding of the biological activities (proven or presumed) of royal jelly. Up to now, despite many efforts, most of these activities have not been proven definitely, nor have they been attributed to any of the known components.

The physiological effects of royal jelly

On honevbees

The effect of royal jelly on honeybee larvae, for which it was originally intended as food, is briefly described since in addition to being a fascinating biological phenomenon, it is also the basis of the royal jelly "myth". In the 1950's, in the wake of new discoveries in the medical field of such wonder drugs as penicillin, hormones and vitamins became "popular" and were seen by many as the simple answers to many biological questions. The elusive "hormonal" effect of royal jelly on honeybee larvae led to the belief that its almost miraculous action on bee larvae could be similar on humans. By deduction these "hormonal" effects were not only responsible for the caste differentiation between worker and queen bee, but also for the enormous fertility of a queen genetically equal to a worker bee, distinguished apparently only by the food it ate. The same applies to the queen's longevity, unique for an adult insect. Though it is known that royal jelly is a necessary food for the queen's survival and productivity, it is not known which royal jelly fractions are essential, which ones can be replaced and what constitutes minimum or optimum requirements for a queen. Almost all the attention has been focused on the immature stages of development. Numerous studies were carried out to discover hormones or other substances powerful enough to induce all the necessary changes and give the queen such "superior" qualities. Indeed, the initial studies led to the belief that a "queen determinator" did exist and was an extremely unstable substance (as elusive as eternal life). It appeared to be so unstable that one day after secretion, it was already ineffective. However, the results of other studies did not confirm this hypothesis.

In an attempt to identify the queen determinator, all the components of royal jelly, particularly the more unusual ones or those with known biological activity or present in greater quantity have been tested. In the late 1980's the mystery had still not been solved and a number of contrasting hypotheses had produced equally convincing explanations. Rembold et al. (1974) ware thought to have been close to identifying a specific substance with queen determinator activity which they had isolated; other researchers proposed a differentiation mechanism based on the different proportions of nutrients in the food of worker and queen bee larvae. Weiss (1975) and Asencot and Lensky (1975) believed it was the sugar content of larval food (higher for the young queen bee larvae) that was supposed to cause the differentiation into queens. More recently, Sasaki *et al.* (1987) proposed yet another hypothesis incorporating the many contrasting results from other researchers and suggested the "correct" viscosity of royal jelly was a key factor together with higher consumption, but even this theory still has to be substantiated with proof. In other words, it is still not known how royal jelly works nor what is responsible for its amazing effects. However, if parallels are still being drawn between honeybees and royal jelly, and humans and royal jelly, then they should serve to emphasize the complexity and interdependence of different therapies and factors such as who is taking what, when and how much. Eating royal jelly, or rubbing it into the skin will not make anyone younger or live for a thousand years. On the other hand, using it to supplement and support other diets, activities or medicines may have synergistic effects which cannot be explained by a list of compounds and their individual effects. Tests of such a hypothesis in clinical and scientific trials are needed. There is plenty of circumstantial evidence, reviewed in the following section, that leads us to believe that royal jelly might be highly beneficial to mankind.

Unconfirmed circumstantial evidence

Royal jelly was initially advertised for its rejuvenating effects (De Belfever, 1958). The activities most frequently reported in advertisements and constantly confirmed in the declarations of those who have taken royal jelly are indicated in tables, citing the contents of one of Europe's most widespread and popular publication on the subject (Donadieu, 1978). Royal jelly, taken orally for 1-2 months by swallowing or letting it melt under the tongue in doses of 200-500 mg a day, is said to act as a tonic and stimulant, with a euphoric effect on healthy humans. In addition to these indications, users declared that royal jelly had solved most of their health problems. In many cases these were chronic or recurring disorders, for which other treatments did not lead to the desired results, so that the effects obtained by taking royal jelly have been considered "miraculous". It must be emphasised that these claims are unconfirmed by any scientific studies or documentation. There is no proof that the effects are exclusively or even mostly attributable to royal jelly. People who have taken royal jelly said that they soon experienced a feeling of general well-being, i.e. an effect on their physical output (resistance to fatigue), intellectual performance (greater learning capacity and better memory) and on their mental condition (greater self-confidence, feeling of well-being and euphoria). In other words, royal jelly appears to act as a general stimulant, improving immune response and general body functions.

Table 11. A list of properties, benefits and improvements attributed to royal jelly quoted from personal case histories and non-scientific literature.

Internal Use	External Use
Tonic	Skin conditions
Stimulant - physical performance, better memory, learning capacity and self-confidence	Epithelial stimulation and regrowth
General health improvement	Anti-wrinkle
Anorexia	Sebaceous secretion (fat secretions of skin glands) normalized
Increased appetite	
Skin conditions	
Sexual desire and performance	
Influenza	
Increased resistance to viral infections	
High blood pressure	
Low blood pressure	
Anaemia	
Arteriosclerosis	
Cholesterol levels	
Chronic and incurable disorders	

Scientific evidence

Royal jelly is neither toxic when injected into mice and rats at high dosages of up to 3 g per kg body weight per day (Hashimoto et al., 1977) nor mutagenic, as tested on DNA of Salmonella typimurium (Tamura et al., 1985). Takahashi et al., (1983) reported cases of allergic contact dermatitis in 2 out of 10 patients subjected to patch tests. In the context of allergic reactions it needs to be mentioned that intramuscular or intraperitoneal injections, the most common form of royal jelly administration in early years, have been completely abandoned (even under strict medical supervision) because of the risk of serious allergic reactions (Dillon and Louveaux, 1987) Today, royal jelly is most often administered orally and externally (in cosmetics). In vitro studies have confirmed that IO-hydroxydecanoic acid in royal jelly has antibiotic activity. The antibiotic effectiveness is thermostable, i.e. is not destroyed by moderate heating, but it decreases with improper or long-term storage. Antibiotic action has been proven against the following microorganisms: Escherichia coli, Salmonella, Proteus, Bacillus subtilis and Staphylococcus aureus (Lavie, 1968; Yatsunami and Echigo, 1985). It shows one quarter of the activity of penicillin against Micrococcus pyrogens and is also fungicidal. In vitro, antiviral effects have been described (Derivici and Petrescu, 1965) and better resistance to viral infections has been observed in mice. This same antibiotic action of fatty acids is neutralized by raising the pH above 5.6. Since injection into blood, muscle or the peritoneal cavity will raise the pH to 7.4, and the pH is above 5.6 in the intestines, the therapeutic value of the anti-bacterial activity of fatty acids is likely to be negligible for any internal applications, but will remain effective for topical use. In studies on the internal effects of royal jelly with live animals or humans the jelly is usually administered either by mouth or by injection. The latter allows better assessment of hormonal activities ascribed to royal jelly but carries a substantial risk of allergic reactions.

Oral administration

Positive effects on reproductivity, though not necessarily due to hormone-like action, have been reported at least for chickens, quails and rabbits. Rabbits reacted to a normal diet supplemented with 100-200 mg of royal jelly per kilogramme of body weight with increased fertility and embryonic development (Khattab et al., 1989). Japanese quail reached sexual maturity sooner and laid more eggs after supplementation of diets with high doses (0.2 g) of lyophilized (freeze-dried) royal jelly (Csuka et al., 1978). Bonomi (1983) increased egg production, fertility and hatching in laying hens by using 5 mg royal jelly per kg of feed, but Giordani (1961) found no histological changes in male or female reproductive organs or weight gain with higher doses of 10 to 40 mg per day. Growth rates of mice slightly increased with a dosage of 1 g of royal jelly per kg of feed, but decreased with higher dosages (Chauvin, 1968). Bonomi (1983) reported weight increases in chicken, partridges and pheasants with a supplement of S mg royal jelly per kg of feed and Salama et al. (1977) reported weight increases in rats when 10, 20 or 40 mg were injected directly into their stomachs. The administration of 0.02 g of royal jelly to calves less than 7 days old gave a weight gain of 11 - 13 % during the following 6 months in comparison with untreated controls (Radu-Todurache et al., 1978). They also mentioned that the treated calves showed lower mortality and higher resistance to infection.

Injections

Intravenous injections cause slight vasodilation (temporary enlarging of blood vessels) and have a hypotensive effect (lowering blood pressure); both due to acetylcholine in royal jelly

(Jacoli, 1956; Shinoda et al., 1978). Injections of royal jelly solutions induced higher blood sugar levels than oral applications (Chauvin, 1968). No hypoglycemic (insulin-like) reaction could be shown in rats (Fujii et al., 1990). Afifi et al. (1989) reported weight increases in guinea pigs after injection of 100-300 ing royal jelly per kilogramme of body weight. Small doses injected into cats raised haemoglobin and erythrocyte counts and repeated doses of up to 10 mg/kg of body weight stimulated motor activity and weight gains in mice. Repeated higher doses of 100 mg/kg in mice, however, caused weight loss and impaired cerebrocortical (brain cortex) cellular metabolism.

Animal tests

In other studies human diseases were simulated in animals in order to identify the mechanisms of royal jelly action. Thus it is known that royal jelly can reduce blood plasma levels of cholesterol and triglycerides (Cho, 1977) and cholesterol and arterial cholesterol deposits in rabbits when these disorders were induced experimentally (Carli et al. 1975). Nakajin et al., (1982) stated that although royal jelly has no effect on lipid levels in blood plasma in normal rabbits, it can reduce the cholesterol content in the blood of animals fed on a diet which induced high levels of blood cholesterol. Vittek and Halmos (1968) found that royal jelly promoted bone healing in rabbits. The healing of skin lesions was accelerated and anti-inflammatory action was shown for rats by Fujii et al. (1990).Other researchers tested royal jelly and some of its compounds on tumour cell cultures, showing the inhibitory action of lO-hydroxydecanoic acid (Townsend et al., 1960) and certain dicarboxylic acids. However, they also showed that the same acids could induce tumours in mice when royal jelly is mixed with the culture medium (several mg/ml at less than pH 5) prior to injection into the test animals (Morgan et al., 1960). Wagner et al., (1970) found no significant effects of prolonged survival in mice irradiated against experimentally induced tumours and treated with royal jelly (20 mg/kg of body weight) as compared to control mice which did not receive any royal jelly. More recently, Tamura et al., (1987) have shown tumour growth inhibition in mice with prophylactic and therapeutic oral administration of royal jelly. Inhibition of rapid-growth cancers (leukaemia) was insignificant but it was noticeable on slow-growing, solid tumours (Ehrlich and Sarcoma strains).

Human tests

Studies of the effects of royal jelly on humans are extremely numerous, particularly in Eastern Europe. A few early studies were presented in Russian by Braines (1959, 1960 and 1962). Most studies however, arc difficult to evaluate for the scientific value of the reported information. Although many are presented as scientific publications, they often lack details on test methods, use parameters difficult to quantify (well-being, euphoria and rejuvenation) do not entirely exclude effects from other concurrent treatments, or use subject numbers too small to exclude accidental effects or natural variation. Of all the works consulted and selected for this chapter, of which a few are summarized in table below, not one is totally without criticism. The information presented therefore must be considered only as an indication of possible effects requiring further clinical testing. The mechanisms of royal jelly's activity is not known and none of the numerous hypotheses have been confirmed. An early explanation (Johansson and Johansson, 1958) claiming high vitamin content as a contributory factor can be refuted on the grounds that the same effects should then be achievable with vitamin supplements or a glass of milk, which contains amounts of vitamins similar to the usual dose of royal jelly. Beneficial effects on intestinal flora through selected anti-microbial action can mostly be excluded due to pH. The action of some compounds on endocrine glands, or becoming part of enzyme systems or directly affecting intermediate metabolism has been suggested by Bonomi (1983).

Table 12. A list of some effects of royal jelly on humans.

Applications	Description	References
Premature bebies and those with nutritional deficiencies of various origins	8-100 mg orally, improvement of general condition; increase in weight, appetite, red blood cells and haemoglobin	Malossi & Grandi, 1956 Prosperi and Ragazzini, 1956 Prosperi et al., 1956 Quadri, 1956
Elderly (70-75 years), anorexic, depressed and low blood pressure patients	20 mg injected every second day, improvements on all accounts 20 mg taken orally every second day, improvements as above	Destrem, 1956 Destrem, 1956
Psychiatry	Improvements of asthenia, nervous breakdown, emotional problems and counteraction of side effects of psychoactive drugs	Telatin, 1956
Chronic metabolism	Mixture or royal jelly, honey and ginseng, improvements in weight gain and psychological conditions, but changes of blood characterisics	Borgia et al., 1984
Stimulating metabolism	Stimulating effects comparable to that by proteins, effect assumed to be due to activity of enzymatic complexes	Martinetti and Caracristi, 1956
Wound healing	5-30 mg/ml injected into burn blisters, improved regrowth of skin	Gimbel et al., 1962

WAX

The word wax describes a large variety of substances of plant and animal origin, as well as man-made products which are mostly petroleum derivatives. However, natural waxes are not single substances, but a mixture of various long-chain fatty acids and a variety of other constituents, depending on their origin. Each wax therefore has unique physical and chemical characteristics which are exploited in a multitude of applications. In particular, wax from the honeybee has an extremely wide spectrum of useful applications and occupies a very special position among waxes. Young bees in the hive, after feeding the young brood with royal jelly, take part in the construction of the hive. Engorged with honey and resting suspended for 24 hours together with many other bees in the same position, 8 wax glands on the underside of the abdomens of the young bees secret small wax platelets. These are scraped off by the bee, chewed and masticated into pliable pieces with the addition of saliva and a variety of enzymes. Once chewed, attached to the comb and re-chewed several times, they finally form part of this architectural masterpiece, a comb of hexagonal cells, a 20 g structure which can support 1000 g of honey.

Wax is used to cap the ripened honey and when mixed with some propolis, also protects the brood from infections and desiccation. Together with propolis, wax is also employed for sealing cracks and covering foreign objects in the hive. The wax collected by the beekeeper is that which is used in comb construction. Frame hive beekeeping produces wax almost exclusively from the cap and top part of the honey cells. For centuries, beeswax was appreciated as the best material for making candles. Before the advent of cheap petroleum-based waxes, tallow (rendered animal fat) was used for cheap candles and for the adulteration of beeswax. Ancient jewellers and artisans knew how to form delicate objects from wax and cast them later in precious metals. Colours of ancient wall paintings and icons contain beeswax which has remained unchanged for more than 2000 years (Birshtein et al., 1976). The wrappings of Egyptian mummies contained beeswax (Benson et al., 1978) and beeswax has long found use in medicinal practices and in creams and lotions. Of all the primary bee products it has been, and remains, the most versatile and most widely used material. Major compounds are those forming more than 1% of the fraction. The number in brackets indicates the number of compounds making up at least 1 % of the unfractionated, pure wax. The number of minor compounds, those with less than 1% of the fraction, is only an estimate.

Figure 8. Bee wax

Table 13. Composition of beeswax (after Tulloch, 1980).

Description	% of fraction	Number of components in fractoin	
		Major	Minor
Hydrocarbons	14	10 (5)	66
Monoesters	35	10 (7)	10
Diesters	14	6 (5)	24
Triesters	3	5	20
Hydroxy monoesters	4	6 (1)	20
Hydroxy polyesters	8	5	20
Acid esters	1	7	20
Acid polyesters	2	5	20
Free acids	12	8 (3)	10
Free alcohols	1	5	?
Unidentified	6	7	?
TOTAL	**100**	**74**	**> 210**

The ratio of ester values to acids, a character used by the various pharmacopoeias to describe pure beeswax is changed significantly by prolonged or excessive heating. At 100^0C for 24 hours the ratio of ester to acid is changed beyond the limits set for pure bees wax .Longer heating or higher temperatures lead to greater degradation and loss of hydrocarbons (Tulloch, 1980). These changes also influence the physical characteristics of the wax. Thus, excessive heating during rendering or further processing changes the wax structurally and alters the beneficial characteristics of many of its minor compounds, not only the aromatic and volatile compounds. Bleaching destroys at least the aromatic compounds of wax. Bleached wax no longer has the pleasant and typical aroma of wax and it can be assumed that it also lacks many of the other minor compounds. Various plant growth promoting substances, such as myricil alcohol (Weng et al., N-1979), triacontanol (Devakumar et al., 1986), gibberellin GA_3 (Shen and Zhao, 1986) and a rape oil steroid (Jiang, 1986) have been detected in and isolated from beeswax. Kurstjens et al., (1990) describe at least 11 proteins in the freshly secreted wax scales of A. mellifera capensis worker bees and 13 proteins in the wax combs of *A. m. scutellata and A. m. capensis.* The composition of wax from Asian honeybee species is much simpler and contains fewer compounds in different proportions (Phadke et al., 1969, 1971; Phadke and Nair, 1970, 1973 and Narayana, 1970). These ghedda waxes therefore cannot be used as substitutes for *Apis mellifera* wax in certain recipes. Since little is known about which compounds or mixtures cause the beneficial medicinal and dermatological effects of beeswax, no conclusions can be drawn from the composition data alone. Ghedda waxes are used locally in many of the same ways as *Apis mellifera* wax is used in other parts of the world. Meliponid waxes, which are less like honeybee wax than Ghedda wax, have been used by Amerindians for many of the same purposes, as honeybee waxes (Posey, 1978).

Beeswax is considered safe for human consumption and has been approved as an ingredient in human food in the USA (USA, 1978). It is inert, i.e. it does not interact with the human digestive system at all and passes through the body unaltered. However, substances dissolved or encapsulated in wax are slowly released. This property is exploited in many medicinal preparations. At the same time these properties can create a problem when wax is stored near toxic chemicals and pesticides or after treatment with various drugs inside the hive. Any fat soluble toxins can be absorbed and then released much later when the wax is consumed as food, used in cosmetics or given to bees in the form of foundation sheets.

The physiological effects of wax

Beeswax is inert, and has no direct effect on humans or larger animals. However, its indirect effects can be very strong. If mixed with medicinal drugs or poisonous baits, wax preserves the active materials longer and releases them slowly. It can be used to create thin non-corrosive, non-allergenic protective films on many surfaces from metals to fruits and human skin. Thus it protects against external damage such as corrosion and abrasion as well as against moisture loss. It is a good electric insulator and, when saponified with borax, allows the mixture of very stable and smooth emulsions for cosmetics. Even in small concentrations it improves other formulations in the same way. A very small anti-inflammatory and antioxidant activity can be observed in beeswax due possibly to some inclusions of propolis or other minor ingredients.

The uses of wax today

In the past, beeswax had a wide range of uses. Though in many cases beeswax can be replaced with cheaper, synthetic waxes, its very special characteristics, medicinal benefits, plasticity and aroma ensure its continuing use. Many of these characteristics cannot be achieved with artificial waxes. The trend for more natural products in cosmetics may also increase its use. Presently, there is a scarcity of beeswax in industrialized countries, at least seasonally. In industrialized countries, most nationally produced wax is used by beekeepers for foundation sheets. Approximately one third of imported wax is used for cosmetics, one third for pharmaceutical preparations one fifth for candles and the rest for other, minor uses (ITC, 1978). In developing countries with traditional beekeeping methods, wax is often wasted. If it is rendered, most is subsequently exported and only relatively small proportions are used by local manufacturers. This, however, depends very much on the local industry. There are many possibilities for good quality products in local emerging markets and in import substitution. Adj are (1984) listed over 150 uses of beeswax as described also in an old 1954 edition of " The Hive and the Honeybee" A few examples from the wide range of products in which beeswax can be included, together with a few recipes for small or home-based industrial production are described below. There are many types of synthetic waxes available today, often with superior characteristics for special applications Apart from price and availability however, beeswax has preferred characteristics in a wide range of applications and conditions. There are very few products which consist only of beeswax or in which only beeswax can be used, but the value or characteristics of most other products are enhanced or complemented by its inclusion.

APITHERAPY: BEE PRODUCTS IN MEDICINE

Introduction

Bee products have been used for medicinal purposes since ancient times, and they are still used in traditional and alternative medicine. Bee pollen is consumed to boost energy and stamina, propolis to maintain good health status, royal jelly to support the immune system and increase energy, whilst honey to treat burns, wounds, sore throats and as an antiseptic (1). Propolis has been used in medicine both internally and externally in many parts of the world since 300 BC (2). Egyptians, Greeks and Romans reported the use of propolis in different conditions and diseases. Bee venom has traditionally been used for the relief of pain and the treatment of chronic inflammatory diseases (1).

In addition to traditional and alternative medicinal use, the efficacy of bee products has repeatedly been reported by numerous in vitro tests, animal experiments and even clinical trials. Their antioxidant, anti-inflammatory, anticancer, immunomodulatory, and antimicrobial effects may lead researchers to develop new treatment options for a large group of diseases. In this text, it was aimed to summarize the properties and biological effects of bee products in the medical viewpoint, and the results of latest scientific researchs about the use of them in various clinical situations.

Composition of bee products

Honey is the best known bee product through the ages. Beyond being basically a natural solution supersaturated by sugars, honey consists of approximately 180 biologically active compounds including proteins, carotenoids, organic acids, amino acids, proteins, minerals, vitamins (e.g. ascorbic acid and α-tocopherol), enzymes (e.g. glucose oxidase and catalase) and a plenty of polyphenolic phytochemicals including phenolic acids and flavonoids (3). The most important sugars in honey are the fructose (38%) and glucose (31%) (4). But it should be kept in mind that there is a wide variety of the composition of honey depending on many factors including the pollen source, climate, environment and the production conditions.

Propolis, another well-known bee product, is a resinous substance which is collected from the exudates of plants by bees and is used to seal holes in the beehive. It composed of at least 300 biological compounds including resin (50%), wax(30%), essential oils (10%), pollen (5%), and other organic compounds (5%) (4). Among these organic compounds, there are phenolic compounds and esters, flavonoids, terpenes, beta-steroids, aromatic aldehydes and alcohols, sesquiterpenes, and stilbene terpenes (4). Similar to honey, its composition varies with different factors, such as source of the exudates, climate, and environmental conditions (4).

Royal jelly is the exclusive food of the queen honeybee larva. In its chemical composition, there are proteins (18%), carbohydrates (15%), lipids (3-6%), minerals (1.5%), vitamins, amino acids and a large number of biologically active substances including immunomodulating and antibacterial proteins, fatty acids (mostly 10-hydroxy-2-decanoic acid) and peptides (1,4).

Bee pollen is considered a highly nutritious food because of its rich content including proteins, carbohydrates, vitamins, minerals and fats. It has more amino acids and vitamins than many other amino acid containing products like beef, eggs, or cheese (5). Bee pollen consists of polysaccharides (50%), lipids, proteins, simple sugars, vitamin C, enzymes, essential amino acids, carotenoids, phytochemicals, alkaloids and flavonoids (5). As with other bee products, composition of bee pollen varies depending on the plant source and geographic region (5).

Bee venom contains at least 18 bioactive compounds including enzymes, peptides, and amines (Table 1) (6). Peptides, the major promising pharmaceutical compound found in bee venom, are melittin, apamin, adolapin, and the mast cell degranulating (MCD) peptide. It also contains enzymes (e.g., phospholipase A2), biologically active amines (e.g., histamine, dopamine, procamine, serotonin and epinephrine) and non-peptide components including lipids, carbohydrates and free amino acids (1,6,7). Melittin and phospholipase A2 are generally thought to responsible for inducing the irritation and allergic reactions of the bee stings (7).

Phenolic compounds in medicine

Phenolic compounds are found mainly in fruits, and contribute their color and taste (4). The functional properties of many foods and bee products appreciated for medicinal purposes, such as antioxidant capacity, antibacterial capacity, antiviral capacity, anti-inflammatory capacity, and cardio-protective effects are associated with these phenolic compounds present in many forms (4). The principal phenolic compounds found in plants are derivatives of cinnamic acid, cumarins, and flavonoids (4).

The most important property of polyphenols is that they possess a powerful antioxidant capacity, which is responsible for a wide spectrum of biological activity in the human body (8). Numerous studies have revealed that various mechanisms are responsible for the antioxidative activity of polyphenols including (i) inhibiting the activity of enzymes, which participate in the creation of reactive forms of oxygen (ROS), and thus inhibiting the appearance of them, (ii) chelating ions of metals involved in the process of free radical creation, (iii) scavenging ROS, thus interrupting the cascade of reactions leading to the peroxidation of lipids, and (iv) synergistic action with other antioxidants (8). The antioxidative activity of polyphenols depends on their structure (8).

Honey, propolis, and royal jelly contain a variety of phenolic compounds because bees collect them from the plants where they gather. Generally, most of the these compounds are in the form of flavonoids, and its composition and concentration depends on various factors, such as plant source, season, environmental factors, and geographic region (4). The main flavonoids present in honey, propolis and royal jelly are flavonols (quercetin, kaempherol, galangin, fisetin), flavanols (pinocembrin, naringin, hesperidin) and flavones (apigenin, acacetin, chrysin, luteolin) (4).

Phenolic compounds incorporated into the honey via nectar or pollen from plants visited by the honeybee contains two major classes of phytochemicals including flavonoids and phenolic acids (3). Phenolic acids frequently extracted from honey are p-coumaric, ferulic, caffeic, gallic, chlorogenic, syringic, vanillic and p-hydroxybenzoic acids (3). Flavonoids are classified according to their chemical properties into flavones, flavonols, flavanones, flavanonols, flavanols (or catechins), isoflavones, anthocyanins, and anthocyanidins. Within these groups, flavonols (e.g. quercetin, myricetin, kaempferol, galangin), flavones (apigenin, luteolin, diosmetin, chrysin, acacetin) and flavanols (catechin, epicatechin, epigallocatechin, epigallocatechin gallate) are the most abundant in honey (1,3). It also contains saccharides, amino acids, organic acids, vitamins, minerals, and carotenoids which contributes to its biological activity (1).

Similar to honey, propolis has a rich phenolic content consisting of polyphenols, flavonoid aglycones, phenolic acids (e.g. caffeic acid and caffeic acid phenethyl ester (CAPE), a caffeic acid derivative) and their esters, coumarins, phenolic aldehydes and ketones, and others compounds including eugenol, anethole, hydroquinone, pterostilbene, naphthalene, etc. (1,4,8). The exact composition and phenolic content of propolis, which represents its biological activity, mainly depends on its origin. For example, the antibacterial and antifungal activities of European propolis are mainly due to flavonones, flavones, phenolic acids and their esters, while such activities of Brazilian propolis are due to prenylated p-coumaric acids and diterpenes (2).

Bee venom compounds in medicine

Major peptides in bee venom appreciated for medicinal purposes are melittin, apamin, adolapin, and the mast cell degranulating (MCD) peptide. Melittin is a small cytotoxic polypeptide which constitutes about half of bee venom volume. This peptide integrates into and disrupts phospholipid bilayers of cellular membranes, and finally damages the integrity of cell wall that is essential for cellular vitality (6). The presence of such cytotoxic effect of melittin has made it a possible option for cancer treatment. Melittin also enhances the activity of phospholipase A2 (PLA2) enzyme (6). Also, melittin has anti-inflammatory and anti-arthritis effects, and it has been suggested that these effects are associated with the decrease in cyclooxygenase-2 (COX-2) and phospholipase A2 (PLA2) expression, the decrease in the cytokine levels (tumor necrosis factor alpha (TNF-α), interleukin (IL)-1 and -6), nitric oxide (NO) and oxygen reactive species (ROS), and the inhibition of the DNA-binding activity of nuclear factor kappa-B (NF-κB), a critical transcriptional factor regulating inflammatory gene expression (6).

Apamin, a neurotoxin, is another important peptide found in bee venom. It is a highly selective inhibitor of the calcium (Ca^{2+})-activated potassium (K^{+}) channels located in cellular membranes (6). These channels contribute the regulation of the ionic balance throughout the cell membrane which is responsible from resting and action potentials of viable cells, and the signal transfer through the nerves as well as contraction of the muscles. Apamin mediates the long-lasting after-hyperpolarization in neurons and muscle cells, and exerts a neurotoxic effect via this route (6). Also, apamin crosses the blood-brain barrier, and induces hyperexcitability (6). It has a mast cell stabilizing effect and significantly inhibits tracheal contraction and histamine release from lung tissues, suggesting that this compound reduces allergic airway inflammation (6). Besides, it was shown that apamin inhibits nitric oxide (NO)-induced relaxation of the spontaneous contractile activity of the myometrium in non-pregnant women (6). It has been suggested that apamin might play an important role in cancer treatment due to its cytotoxic effects and its nociceptive activity (6).

Adolapin have anti-inflammatory and analgesic properties (6). These effects of adolapin are thought to be associated with the inhibition of the prostaglandin (PG) synthesis through cyclooxygenase (COX) inhibition (6). A central mechanism may participate the action of adolapin because it was demonstrated that naloxone partially inhibits the analgesic effect of adolapin (6). Similar to other non-steroid analgesics, adolapin has an antipyretic effect through these action mechanisms. Adolapin also inhibits the activity of phospholipase A2 (PLA2) and lipoxygenase enzymes (6).

The mast-cell-degranulating (MCD) peptide has both allergic and anti-allergic properties. On the one hand, the MCD peptide has activities associated with allergies, which affects almost 20% of the population (6). On the other hand, it has an anti-allergic activity by inhibiting the release of histamine from mast cells (6). The MCD peptide binds to the mast cell receptors in a dose-response manner, and partially inhibits the binding of immunoglobulin E (IgE) to this receptor which is the mechanism responsible from allergic reactions (6). At very low concentrations, it is one of the most potent natural histamine secretagogues, and releases histamine which provokes the symptoms of an allergic reaction. But at higher concentrations, this peptide has been found to inhibit mast cell degranulation acting as an anti-allergic agent (6). It was suggested that disulfide exchange between IgE and the MCD peptide at high doses on the mast cell surface might inhibit the release of histamine (6).

Compositional diversity of bee products

One of the main problems of bee products limiting their use and standardization for medicinal purposes is that the composition of bee products is rather variable, depending on the floral source, species, seasonal and environmental conditions, foraging strategies and processing methods. For example, it was shown that the antibacterial activity of different honeys can vary by as much as 100-fold (9). Similarly, the composition of propolis depends upon the collection season as well as the plants of the area from which it is collected. Although propolis is collected from the same area in different seasons, it may exhibit high compositional diversity. While propolis collected from temperate zones (Asia, Europe, North America etc.) contains predominantly phenolic compounds (including several flavonoids, aromatic acids and their esters), the propolis collected from tropical zones (South America) are rich in polyprenylated benzophenones, various diterpenes and clerodane- and several labdane-type diterpenoids, which are virtually absent in propolis from temperate zones (10). Flavonoids are also reported from tropical propolis because of their wide distribution in the plant kingdom.

It is obvious that the composition of bee products influences their biological activity (8). Generally, bees, gathering their products in a specific region, do not change its chemical composition unless an environmental or seasonal change occurs, because they visit essentially the same vegetal sources (2). Although some degree of compositional diversity occurs in bee products depending on floral, geographic, seasonal, and procedural conditions, it should be emphasized that these products always have antibacterial, antiviral, antifungal, antioxidative, anti-inflammatory, and anti-cancer activities (8). Propolis does not represent a significant seasonal difference in the antibacterial activity.

Antioxidant properties

Free radicals are defined as any independently existed atom or molecule with unpaired electrons making them highly reactive. They can be originated from oxygen, nitrogen, or sulfur molecules. Free radicals derived from oxygen are called reactive oxygen species (ROS). The main ROS are superoxide ($\bullet O2^-$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and peroxynitrite ($ONOO^-$). ROS are natural byproducts of normal aerobic metabolism of cells during ATP production and an important part of immunity which are produced by leukocytes against microorganisms. ROS also function as signaling molecules regulating metabolism, development and pathogen defense responses (11).

The feature making ROS important is their capacity to cause oxidative damage to major cellular components including proteins, DNA, and lipids, which are certainly essential for cellular vitality. Under normal circumstances, cells protect themselves against ROS through different defense mechanisms, including enzymatic and free radical scavenging activities, calling antioxidant system that neutralizes free radicals or repairs any subsequent damage. As a consequence, a redox balance between ROS production and detoxification is achieved. However stress impairs this balance in favor of ROS production leading to substantial damage to cellular molecules. They are found to be associated with aging, mutagenesis, carcinogenesis, Parkinson's diseases, and Alzheimer's diseases. They also increase the risk of cardiovascular diseases probably by LDL lipoprotein oxidation (8).

Antioxidants are reducing chemicals that are able to scavenge free radicals, to inhibit or prevent oxidation processes, or to induce the expression of antioxidant enzymes, thus, ameliorating oxidative stress (12,13). Such chemicals are both produced within the body (e.g. superoxide dismutase, catalase, peroxidase) and taken from nourishment (e.g. tocopherol, ascorbic acid, polyphenols). Exogenous antioxidants supplied from dietary intake can reduce the deleterious effects of ROS (3). It is generally considered that such antioxidants have anti-inflammatory, anti-aging and health-promoting effects on the human body (13). Plants and herbs are rich sources of antioxidants due to their phenolic and polyphenolic content. As mentioned previously, honey and propolis has a rich phenolic and polyphenolic content because bees gather the main components of these products from the plants. The health promoting effects of honey (Table 2) and propolis depend on the presence and concentration of various antioxidant components including phenolic compounds, such as flavonoids and phenolic acids (3,4). There is a high degree of correlation between these substances and the antioxidant capacity of bee products.

Antioxidant properties of honey

Constituents of honey related to its antioxidant capacity are glucose oxidase, catalase, ascorbic acid, organic acids, Maillard reaction products, amino acids, proteins, and mainly phenolic acids and flavonoids (3,4). The capacity to scavenge active oxygen species and the enzymatic or non-enzymatic capacity to inhibit lipid peroxidation represent the antioxidant capacity of honey. Honey is capable of scavenging free radicals such as hydroxyl and superoxide radicals, acting as metal chelators, and modulating genes to induce the expression of enzymatic and non-enzymatic systems that regulate cellular redox balance (3). It is well known that flavonoids are very effective scavengers of the ROS as well as reactive nitrogen species (RNS) like nitric oxide and peroxynitrite. Also, the organic acids present in honey, such as gluconic, malic and citric acids, may contribute to antioxidant capacity through metal chelation, and increase the effect of flavonoids (4). Metal chelation causes the scavenging of iron and copper ions, co-factors of chain reactions occurred during ROS production, and provides the inhibition of free radical production.

The antioxidant capacity of honey originated from the ability to scavenge free radicals and to inhibit lipid peroxidation may also contribute to reduce inflammation in some diseases in which oxidative stress is involved (3).

Figure 9. A Topical Treatment for Wounds *

Figure 2a. Day 1: Before honey treatment (left cheek).

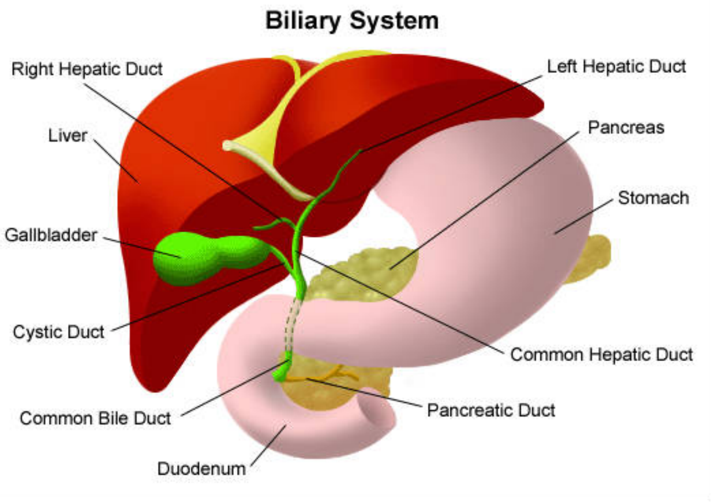
Figure 2b. 5 days after honey treatment began.

Figure 2c. After 3 weeks of honey treatment.

Figure 2d. After 6 weeks of honey treatment.

***** There are several mechanisms through which honey is thought to act on and heal wounds. When it is applied directly on a wound surface or via a dressing, it can act as a sealant, keeping the wound moist and free from contamination.

Figure 10. Honey and digestive system *



* **The honey** has a very strong impact on different types of **liver diseases**- even when we talk about cases when the **honey** is used pure, without any additives or some of the common medicines which are used for such types of **diseases**. **The regular** honey consummation referring to taking **the honey** every day literally successfully heals the patients who have identified certain acute liver **or** gallbladder illness.

Antioxidant properties of propolis

Various biological activities with the use of propolis, including anticancer, antioxidant, anti-inflammatory, antibiotic, antifungal and antihepatotoxic effects have been reported. Propolis mostly contains flavonoids and phenolic compounds, and the water extracts of propolis show a strong free radical scavenging activity (10). It was demonstrated that propolis has more potent free radical scavenging activity than the most commonly used antioxidants such as vitamin C, vitamin E and caffeic acid (10). Propolis contains caffeic acid phenethyl ester (CAPE), a derivative of caffeic acid. CAPE is an antitumor constituent, inhibits 5-lipoxygenase, and blocks the production of the ROS in neutrophils even in small concentrations (10). Propolis also contains α-tocopherol, a type of Vitamin E, one of well-known antioxidant drugs, and contributes antioxidant capacity of flavonoids and phenolic compounds (10).

Anti-inflammatory effects

Traditionally, propolis is commonly used for the treatment of some inflammatory skin diseases. In animal experiments, the ethanol extract of propolis was shown to have a powerful anti-inflammatory activity in rats equal to that of indomethacin, an anti-inflammatory drug (10). It was found that propolis suppresses prostaglandin and leukotriene generation by macrophages during acute inflammation, and also significantly suppresses the lipoxygenase pathway of arachidonic acid metabolism. CAPE was considered the major constituent responsible for the anti-inflammatory activity and the most potent modulator of the arachidonic acid cascade among the tested propolis constituents (10).

The anti-inflammatory activity of propolis and honey is thought to result from their flavonoid and phenolic acid content. It is a consequence of both the antioxidant activity of these constituents and the decreased synthesis of arachidonic acid metabolites including prostaglandin E2, thromboxane A2 and leukotriene B4, and NO. Inhibition of some important enzymes including phospholipase A2, lipoxygenase, cyclooxygenase (COX-2) and nitric oxide synthase (iNOS) reduces the synthesis of these active metabolites, which take important part in inflammation, and contributes the anti-inflammatory activity (8,10). Moreover, it was demonstrated that ROS functions as a signaling molecule in intracellular pathways, and activates various transcription factors, such as mitogen-activated protein kinases (MAPK), Akt and nuclear factor kappa B (NF-κB) (14). When activated, these pathways induce DNA to produce cytokines, which enhances the inflammatory process and triggers apoptosis of the cell, and to express various adhesion molecules on the cell surface, which activates and recruits leukocytes from the circulation, and stimulates them to release toxic products (12). Therefore, antioxidants also inhibit important inflammatory pathways, and exhibit subsequent anti-inflammatory activity.

In addition to propolis and honey, bee venom may have anti-inflammatory activity. It was reported that bee venom strongly inhibits production of ROS (superoxide and hydrogen peroxide) from the leukocytes (6). Melittin was shown to have a high affinity to calmodulin, and binding to calmodulin inhibits the ROS production from the leukocytes. This finding suggests the possible antioxidant and anti-inflammatory action of melittin in the treatment of inflammatory diseases.

Cardiovascular diseases

Today, cardiovascular diseases are the most frequent cause of death in developed countries. Atherosclerosis, narrowing or total occlusion of the arteries by fatty plaques located within the arterial wall, is the most important cause of cardiovascular diseases. Numerous cellular and molecular mechanisms contribute the disease process but they are not fully understood yet. However, recent evidences have revealed that atherosclerosis may be considered as a chronic inflammatory disease, and that there is a strong association between systemic inflammation and the future risk for symptomatic cardiovascular disease (15). Emerging data have suggests that oxidative stress and inflammatory process are possibly concurrent events in atherosclerosis, because intracellular oxidative signals induce the expression of vascular inflammatory genes to produce inflammatory mediators and cell adhesion molecules.

Although the endogenous antioxidant mechanism of the body, such as the enzymes catalase, superoxide dismutase (SOD), and glutathione peroxidase, protect the cells from ROS, and readily repair the resultant damages, the oxidative stress condition in which the rate of ROS formation exceeds the capacity of the antioxidant system initiates the oxidation-mediated signals and inflammatory reactions in the vascular cells (15). It is well-known now that oxidative stress and inflammatory processes take an important part in the development of atherosclerotic cardiovascular diseases. For that reason, agents possessing antioxidant and anti-inflammatory actions have promising options for the prevention and treatment of different heart and vascular diseases. As mentioned previously, propolis and honey have an appreciated antioxidant and anti-inflammatory activity due to a variety of phenolic compounds in their mixture, and can be used in cardiovascular diseases.

Propolis and cardiovascular diseases

In recent studies, it was showed that propolis has preventive effects against atherosclerosis. Propolis administration improves the lipid profile, and decreases the levels of pro-inflammatory cytokines and chemokines (8). Propolis also has a modulating effect on the synthesis of nitric oxide which is associated with a protective effect on the vascular cells during the inflammation (8). Flavonoids inhibit xanthine oxidase, an endogenous enzyme responsible from the ROS production during hypoxia/ischemia, on vessel endothelium and cardiac muscle. This activity decreases the production rate of free radicals during ischemia (8). Also, polyphenols have beneficial influence on coronary circulation and have a hypotensive effect. These effects may be related to the enhanced activity of endothelial nitric oxide synthase (eNOS) and the inhibition of angiotensin convertase enzyme (ACE), which both enzymes exert a potent vasodilator effect (8).

In laboratory animals, it was demonstrated that propolis reduces the cholesterol levels and the triglyceride synthesis in the liver of rats, and has cardioprotective effects in the rats with experimental cardiomyopathy (8).

In addition to arterial diseases, polyphenol compounds, mainly flavonoids, stabilize and reinforce the veins. Therefore, they are used in the prevention of bleeding and the treatment of ecchymoses and varicose veins. They also decrease vessel permeability and reduce limb swelling (8).

Honey and cardiovascular diseases

Honey was shown to have protective effects against cardiovascular diseases by inhibiting inflammation, improving endothelial function, improving the plasma lipid profile and increasing low-density lipoprotein (LDL) resistance to oxidation (3). Studies have been demonstrated the important role of lipoprotein oxidation in the pathogenesis of atherosclerosis. In an in vitro model performed with honey, it was reported that there is a significant correlation between the antioxidant capacity of honey and the inhibition of lipoprotein oxidisability in human serum, and this finding was concluded as an evidence for the protective effect of honey against the oxidative damage (3). The antioxidant compounds present in honey may play an important cardioprotective role through reducing acute and chronic free radical induced pathologies in the body, including inflammation, endothelial dysfunction and lipid oxidation (3).

Hypertension is a major public health concern because it has high prevalence, and is an important risk factor for the development of cardiovascular diseases, end-stage renal disease, stroke, and death. It was demonstrated that there may be a relationship between oxidative stress and hypertension (3). In hypertensive animal models, chronic treatment with dietary quercetin was shown to lower blood pressure, and to restore endothelial dysfunction (3). It can be hypothesized from this result that honey may exert a cardioprotective effect against hypertension induced cardiac disorders and vasomotor dysfunction through its antioxidant capacity as well as mineral and vitamin content (magnesium, sodium, chlorine, vitamin C) enhancing the release of nitric oxide (NO), which is also a vascular relaxing factor and reduces systemic blood pressure (3).

Kaempferol, one of the common flavonoids found in honey, has a protective effect against endothelial damage associated with improving NO production and decreasing asymmetric dimethylarginine (ADMA) levels (3). It seems to have the ability to enhance both endothelium-dependent and endothelium-independent relaxations, without its antioxidant properties (3). Glycosylated form of kaempferol also has protective effects on cardiovascular system. Studies has showed that kaempferol-3-O-sophoroside (KPOS) inhibits lipopolysaccharide (LPS)-induced barrier disruption, expression of cell adhesion molecules, neutrophil adhesion and trans-endothelial migration of neutrophils, and suppresses the production of TNF-α and the activation of NF-κB by lipopolysaccharides (3).

Honey may have positive effects on the glycemic response by reducing blood glucose, serum fructosamine or glycosylated hemoglobin concentration in healthy subjects (3). Compared with other sweeteners including dextrose and sucrose, honey was shown to attenuate post-prandial glycemic response in non-diabetic volunteers (3). Honey consumption decreases glycemic post-prandial response, serum insulin levels and C-peptide concentrations compared to artificial honey, glucose or the combination of glucose-fructose solution (3).

Honey also has beneficial effects on weight loss, reduction of total cholesterol, LDL, triglyceride, plasma glucose, homocysteine and C-reactive protein levels, and the increase of HDL level, all associated with the pathogenesis of atherosclerosis (3). In animal studies, quercetin treatment was demonstrated to attenuate the symptoms of metabolic syndrome, including abdominal obesity, and cardiovascular remodeling, which the most likely mechanism is the antioxidant and anti-inflammatory effects (3). It may suggest that honey may also reduce elevated cardiovascular risk induced by the disorders of lipid metabolism and metabolic syndrome.

Erythrocytes, red blood cells, are the most abundant cells in the human body, and they are continuously under threat of oxidative damage due to their structural and functional characteristics (3). They carry oxygen, have a large surface of lipoprotein cell membrane susceptible to oxidative damage, reach every distant part of the body increasing the likelihood of confronting free radicals and inflammatory mediators, and do not have cellular nucleus and organelles, which makes them unable to produce antioxidant defense enzymes and proteins when required. Oxidative damage causes lipid peroxidation of the erythrocyte membrane, which alters its fluidity and flexibility, an important feature providing the erythrocyte to enter the capillaries even smaller than its diameter, as well as the functions of membrane-bound enzymes and receptors essential for cellular activity and vitality. This leads cell injury and death calling hemolysis (3). Also, perfusion defects in the distant tissues may occur due to the loss of membrane fluidity and flexibility of the erythrocytes since they become more rigid, and cannot bend and deform enough to enter the smaller capillaries. Polyphenol extracts from honey inhibit oxidative hemolysis, reduce the extracellular ferricyanide, protect against intracellular depletion of glutathione (GSH) and superoxide dismutase (SOD) activity, and decrease the susceptibility of lipid membrane to peroxidation (3).

Cancer

An interesting finding was reported by McDonald et al. that the incidence of death from cancer in beekeepers was slightly lower than expected, and the frequency of lung cancer in male beekeepers was significantly lower, while the other cancers were similar to expectation (16). This finding suggests that bee products may prevent the death from cancer, especially from lung cancer. Such results have encouraged the researchers to study the importance and characteristics of the anticancer activity of bee products.

Bee products have been found to have anticancer activity in vitro on various cultured tumor cell lines, including renal, lung, prostate, bladder, melanoma, osteosarcoma, mammary and lymphoid cancers (1). It was proposed that anticancer activity of bee products is mediated through apoptosis, necrosis, and lysis of the tumor cells (1). Anticancer potential of phenolic compounds in bee products increasingly attracts more attention in the cancer therapy.

Anticancer effect of honey

Anticancer activity of honey has been observed in various tumor cell lines including breast cancer, cervical cancer, leukemia, renal cell carcinoma, bladder cancer, colon cancer, prostate cancer, oral cancer, osteosarcoma and brain cancer (3).The results of in vitro studies have showed that honey exhibits significant antimutagenic and antiproliferative effects in cell cultures which includes these cancer cells (3). It enhances the immune response against the tumor cells (1). Honey was also shown to induce apoptosis (3). Apoptosis is a natural mechanism which regulate the cell death in controlled manner, which is induced by externally, via TNF receptor stimulation, or internally, via mediated by mitochondria and pro-apoptotic proteins including cytochrome c (1). Both pathways are extensively studied due to powerful anticancer potential. The activation of caspase-3, -7 and -9 was observed in all honey-treated cancer cells indicating the involvement of mitochondrial apoptotic pathway (3). Honey also has antimetastatic effect in murine tumor models (3). It also potentiates the anticancer effect of standard chemotherapy (such as 5-flourouracil or cyclophosphamide) (1).

Polyphenols and rich sugars content of honey may be responsible for antimutagenic and antiproliferative activity (3). Flavanoids have anticancer properties through the antioxidant activity which regulates ROS-mediating signaling pathways, including stimulation of tumor necrosis factor-alpha (TNF-α), inhibition of cell proliferation, induction of apoptosis, and cell cycle arrest (1). Quercetin, one of the most common flavonoids found in honey, has been shown to have a significant antiproliferative activity in different tumor lines (3). The antitumor effects of quercetin are reported in tumor cell models including leukemia, breast cancer and brain cancer (3). Quercetin supplementation may enhance the efficacy of drug therapy widely used in the anticancer treatment (3). Besides quercetin, other flavonoids found in honey such as kaempferol and caffeic acid have significant antiproliferative and chemopreventive effects (3). Caffeic acid was demonstrated to significantly inhibit the cell proliferation of colon cancer (3). Other phenolic compounds in honey including epigallocatechin-gallate, lycopene, genistein and resveratrol have been used for treatment of prostate cancer [33,34] (1).

Anticancer effect of propolis

Phenolic compounds are known to have anticancer activity on animal models. Propolis contains many phenolic substances including caffeic acid, caffeic phenyl ester, artepillin C, quercetin, naringenin, resveratrol, galangin, and genistein, which are known to stimulate cell proliferation or apoptosis (8). The interest in propolis for cancer treatment is due to its ability to induce apoptosis (1). Propolis may induce apoptosis through activating the caspase-dependent mitochondrial pathway (1). Chrysin was shown to induce apoptosis in many cell lines, especially leukemia, by activation of caspases, suppression of anti-apoptotic proteins (1).

In animal models, flavonoids contained in propolis was shown to inhibit the development of lung, oral, skin, esophagus, stomach, colorectal, liver, prostate and breast cancers (8,10). It was demonstrated that propolis has a cytotoxic effect on human hepatocellular carcinoma, human lung carcinoma, skin tumors, and Ehrlich carcinoma (10). Diterpenoids, 3-(2,2-dimethyl-8-prenylbenzopyran-6-yl)propenoic acid, caffeic acid phenethyl ester (CAPE), and artepillin C in propolis were shown to have cytotoxic effects by the induction of DNA fragmentation and apoptosis (10). Also, caffeic acid, CAPE and quercitin inhibit cancer cell growth (1).

The antitumor activity of propolis and some of its constituents was found to be associated with their immunomodulatory action through the augmentation of macrophages activation (2).

Anticancer effect of bee venom

Bee venom has anti-cancer activity through the capacity to kill cancer cells (6). It is thought that this cytotoxic effect, an important mechanism of anti-cancer activity of bee venom, is the result of the activation of phospholipase A2 (PLA2) enzyme by melittin (1,6). Melittin induces cell necrosis, uncontrolled cell death (1). Anticancer activity of melittin has been shown in various tumor cell lines including renal, lung, liver, prostate, bladder, mammary cancers, and leukemia cells (6). In addition to the cytotoxic effect and necrosis, the induction of apoptosis through the activation of caspase and matrix metalloproteinases (MMP) is an important mechanism for anti-cancer effects of melittin (1,6). Melittin also inhibits calmodulin as well as the growth and clonogenicity of leukemic cells (1,6). It was shown that there is a good correlation between the calmodulin inhibition activity of drugs and their cell growth inhibition activity, and the cytotoxic effect of melittin is proportional to the antagonistic effect of calmodulin (6). Besides, melittin increases the toxicity of bleomycin, an anticancer drug (6). In addition to melittin itself, the melittin fragment and the melittin/avidin conjugate have anticancer activity (6).

Gene therapy is an alternative approach in the cancer treatment to selectively kill the cancer cells. When a vector carrying the killer gene is transfected into tumor cells, the corresponding prodrug encoded on the killer gene is expressed by the cancer cell and produced to selectively kill the cancer cell itself (6). Melittin transfection as a killer gen and synthesis has attracted considerable attention in gene therapy efforts (6). The antitumor activity of melittin in vivo through gene therapy has been reported. (6)

The intravenous administration of bee venom to mice was shown to significantly reduce the number of the lung metastases (6).

Bee pollen in cancer treatment

Bee pollen was found to be effective in reducing adverse effects of cancer treatment. The adverse effects of radiation, such as anorexia, nausea, alopecia, inflammation, leucopenia, and sleeplessness, are less in the patients consuming bee pollen (5).

Wounds and burns

Honey has been used as wound dressing since ancient times, and it has continued to be used into present-day folk-medicine (Table 3) (9). In history, treatment of sunburn and ulcers with honey was written by Dioscorides (c.50 AD), a Greek physician, pharmacologist and botanist in Roman era and the author of *De Materia Medica*, a 5-volume encyclopedia about herbal medicine and related medicinal substances (9).

Honey used in wound dressing provides the rapid clearance of bacteria from infected wounds, the removal of odor, and the debridement of slough and necrotic tissue, making surgical debridement unnecessary (9). In most cases, healing is rapidly achieved. Also chronic wounds respond well to honey dressing. It promotes tissue regeneration through the growth of fibroblasts, epithelial cells and new vessels, and reduces the need for skin grafting (9). Randomized controlled clinical trials have showed that honey provides significantly more rapid healing of superficial burns than silver sulfadiazine, polyurethane film, and amniotic membrane with a lower incidence of hypertrophic scar and post-burn contracture (9). Healing with honey dressing has numerously been reported in resistant wounds even unresponsive to conventional treatment (9). In animal experiments, it was observed that honey provides faster healing and lesser inflammation in burns, uninfected full-thickness wounds and wounds infected with Staphylococcus aureus (9).

Beneficial effects of honey on wounds result from components other than the sugar as well as sugar itself (9). Honey does not cause dehydration in the wound because it induces the fluid from surrounding tissue and underlying circulation to move toward wound through its osmotic effect (9). This creates a film layer of diluted honey under the dressing, and prevents adherence of the dressing to the wound base, which preserves the newly formed healing tissue during changing the dressings (9). The antibacterial activity of honey prevents bacterial growth in the wound (9). Also, honey components provide nourishment for the traumatized tissue, and increase the rate of granulation tissue formation (9). The hydrogen peroxide produced by honey causes rapid autolytic debridement of wounds via the activation of proteases in the wound tissue (9). The anti-inflammatory action of honey reduces edema of the wound tissue, which thus improves the circulation through capillaries and oxygenation (9). The antioxidant and anti-inflammatory actions of honey also reduce the damage caused by the free radical production during inflammation (9). All these effects enhance the healing and reduce the pain.

Infections

Antimicrobial properties of honey

Honey exerts an antimicrobial activity through the peroxide-dependent and peroxide-independent mechanisms. The peroxide-dependent mechanism of antibacterial activity of honey is associated with its specific hydrogen peroxide content while the peroxide-independent mechanism is due to its high osmolarity and acidity as well as to methylglyoxal, bee defensing-1 and flavonoid contents (3,4).

Sugars, the major components of honey, possess antibacterial activity due to their osmotic effect (4). The action of the hydrogen peroxide in honey is produced by glucose oxidase in the presence of light and heat, and exerts the antibacterial action (4). The inhibition of bacterial proliferation by honey is not only caused by its osmolarity or sugar content, but the compounds other than sugar have important effects on the antibacterial action. Especially methylglyoxal, a compound formed from sugars during heat treatment or prolonged storage, is responsible for its peroxide-independent antibacterial activity (3). There is a strong correlation between the methylglyoxal levels and the antibacterial action of honey on S. aureus (3). Another antibacterial component in honey is bee defensin-1 peptide, which is identified in honeybee hemolymph, head and thoracic glands of honeybee and royal jelly. It has a powerful antibacterial activity against Gram-positive bacteria including B. subtilis, S. aureus, and Paenibacillus larvae (3). Also, honey contains lysozyme, a powerful antimicrobial agent (4). Flavonoids found in honey exert the antibacterial activity, and additionally neutralize the bacterial toxins (3). Thus, it prevents the spread of toxic effects of infection. Flavonoids, such as pinocembrin, galangin, and caffeic acid phenethyl ester

(CAPE), inhibits bacterial RNA polymerase (4). Quercetin increases membrane permeability, leading the bacteria to lose the capacity of ATP synthesis, membrane transport and motility (4).

Studies have shown that S. aureus is the most sensitive microorganism to the antimicrobial activity of honey, while E. coli is moderately sensitive, and P. aeruginosa is the most resistant (3). In general, Gram-positive bacteria are more sensitive to the antimicrobial action of honey than Gram-negative bacteria (3). Honey also have inhibitory activity against Bacillus anthracis (anthrax), Corynebacterium diphtherine (diphtheria), Klebsiella pneumoniae (pneumonia), Mycobacterim tuberculosis (tuberculosis), Salmonella typhi (typhoid fever), and Vibrio cholerae (cholera) (3).

Antimicrobial properties of propolis

Bees collect propolis to seal their hive, to prevent diseases and parasites from entering the hive, to inhibit fungal and bacterial growth, and to prevent putrefaction within the hive sealing the carcass in propolis, essentially mummifying it and making it harmless. Thus, propolis is considered to have antimicrobial activity (10). It has been demonstrated in various studies that propolis has antifungal activity against dermatophytes and Candida species, antibacterial activity against gram-positive bacteria, and antiviral activity against avian influenza virus (10).

Propolis inhibits the growth of some gram-positive bacteria and Candida albicans, but not the growth of gram-negative bacteria (10). Propolis has a powerful antibacterial activity on Staphylococcus aureus strains. But weak antibacterial activity against E. coli was observed. Generally, the antibacterial activity of propolis and honey is greater against Gram positive bacteria than Gram negative ones (8). The ethanol extract of propolis was found to have the antibacterial activity against H. pylori (10). The antibacterial activity of propolis was determined against Mycobactrium tuberculosis and Mycobacterium avium (8). There was a synergistic activity with several antituberculotic drugs (streptomycin, rifamycin, isoniazid) and other antibiotics (for example, chloramphenicol, gentamicin, vancomycin, tetracycline, clindamycin, netilmicin) (8). Propolis may also show synergistic effects with other antimicrobial drugs (2).

Antiviral properties of propolis

Propolis and its derivates were shown to have the capacity to inhibit virus propagation via inhibition of the DNA and RNA of different viruses, including Herpes simplex type 1, Herpes simplex type 2, adenovirus type 2, vesicular stomatitis virus, and poliovirus type 2 (4). Besides, it was found that propolis may suppress HIV-1 replication (10). Flavonoids in propolis, such as chrysin, acacetin, and apigenin, inhibit the activation of HIV-1 in latent models of infection (4). Caffeic acid phenethyl ester (CAPE), quercetin and kaempferol interrupt the replication of HIV-1 by inhibiting HIV-1 integrase (8). Chrysin and campherol inhibit the replication of several herpes viruses, adenovirus, and rotavirus (4). Galangin has antiviral effect against herpes simplex virus (HSV) and Coxsackie B virus (4). Quercetin shows antiviral activity against HSV, syncytial virus, poliovirus, and Sindbis virus (4).

Immunomodulation

Immunomodulation[1] is described as adjustment of the immune response (function of the defense system of the body) to a desired level, as in immunopotentiation, immunosuppression, or induction of immunologic tolerance. It has been demonstrated that propolis exhibit an immunomodulatory activity through affecting various components of the immune system, and enhancing the immune response. Caffeoylquinic acid derivatives (such as 5-caffeoylquinic acid, chlorogenic acid, 4-caffeoylquinic acid, 3,5-dicaffeoyl-quinic acid and 3,4-dicaffeoylquinic acid) extracted from propolis was found to enhance the motility and spreading of murine macrophages, a type of white blood cell that clears cellular debris, foreign substances, microbes, and cancer cells in a process called phagocytosis (2,10). This effect is thought to be limited to only macrophages, but not to lymphocytes (2). Propolis may activate macrophages and increase their antimicrobial activity. Besides, propolis enhances the activity of natural killer cells against tumor cells. Propolis also has the ability to modulate antibody synthesis and to increase antibody production due to the potent effect on different cells of innate immune response (2). It was showed that propolis inhibits the both classical and alternative pathways of the complement system, an important component of the innate immune system that induces the ability of antibodies and phagocytic cells to clear pathogens from an organism (2,10). Due to its immunomodulatory activity, propolis was suggested to use in vaccines as an adjuvant (2).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease associated with chronic inflammatory demyelization of the central nervous system, destruction of the insulating covers of nerve cells by own immune system of the patient, while the exact cause and mechanism of the diseases is not clear (7). Some positive results with the use of bee products have been reported in the treatment of the disease. In a study, apitherapy including concurrent bee venom, bee pollen and honey used in a treatment plan over one year improved the symptoms of patients with multiple sclerosis (MS) (5). But there was not a control group to compare results and to conclude the superiority of apitherapy over standard therapy. Bee venom has been reported to have beneficial effects on inflammatory diseases including multiple sclerosis (MS) and rheumatoid arthritis and their experimental models through its anti-inflammatory and immunosuppressive effects, caused by the inhibition of cyclooxygenase-2 expression, pro-inflammatory cytokines (TNF-alpha and IL-1 beta) production and prostaglandin E-2(PGE-2) synthesis (7). But no significant reduction in relapse rates and no improvement of disability, fatigue, and quality of life was found with bee venom (7). Furthermore, immunostimulant properties of bee venom may aggravate the attacks, and limit the efficacy of bee venom in the treatment of MS (7).

Rheumatic diseases

The anti-arthritis effect of bee venom has been demonstrated in animal models (6). Bee venom was shown to inhibit the arthritic inflammation and bone changes, and to suppress the erosion of articular cartilage and inflammatory cell infiltrations into the interphalangeal joint in rats (6). It was concluded that these inhibitory and suppressive effects are comparable to those induced by prednisolone, a synthetic derivative of cortisol that is used to treat a variety of inflammatory and auto-immune diseases (6). Bee venom has strong

[1] Dorland's Medical Dictionary for Health Consumers. (2007). Retrieved April 8 2015 from http://medical-dictionary.thefreedictionary.com/immunomodulation

inhibitory effects on COX-2 activity, but not on COX-1 activity, and inhibits the production of TNF-α and IL-1β (6). The anti-arthritis effect of bee venom was reported to be associated with the decrease in COX-2 and PLA2 expression, and the decrease in TNF-α, IL-1, IL-6, NO and ROS levels, suggesting that the anti-arthritis effect of bee venom may be related to its anti-inflammatory action (6). Bee venom and melittin inhibit the DNA-binding activity of NF-κB leading to a decrease in the expression of the inflammatory gene (6). In addition to the anti-inflammatory effect, bee venom exerts the anti-arthritis effect through another mechanisms including the inhibition of the proliferation of rheumatoid synovial cells by inducing apoptosis via caspase-3 activation (6).

Gastric ulcers

Both honey and propolis have anti-ulcerous capacity, and this ability is attributed to the phenolic compounds, particularly the flavonoids including especially campherol, quercetin, hesperitin and naringin (4). It was suggested that flavonoids increase the mucosal content of prostaglandins, which protects the gastric mucosa and thus prevents the occurrence of ulceration (4). Another mechanism proposed for the anti-ulcer effect of flavonoids is that ulcers are associated with the reactive oxygen species, and flavonoids inhibit them, protecting the gastric mucosa (4).

Additionally, propolis has antibacterial activity against Helicobacter pylori, a Gram-negative bacterium found in the stomach, which is linked to chronic gastritis, gastric ulcers, duodenal ulcers and stomach cancer. This activity may also be associated with anti-ulcerous property of propolis. p-Coumaric acid, artepillin C and 3-phenyl-4-dihydrocinnamylocinnamic acid are effective against H. pylori (8).

Respiratory system

Bee pollen is often used as a pollen and spore antidote during allergy season to control allergic symptoms including respiratory complaints such as bronchitis, sinus congestion, and common rhinitis (5). In a study performed in adolescent swimmers with bee pollen, it was found that the number of training days missed due to upper respiratory tract infections is significantly less in the pollen treatment group than in the placebo group (5).

Honey is more effective in relieving cough than “no treatment” in symptomatic children, thus improving sleep quality for both children and parents (17). It was shown that honey may also be better than diphenhydramine for symptomatic relief of cough, but not better than dextromethorphan (17).

Pain

Bee venom may have a particular importance in the treatment of chronic pain, although it paradoxically causes acute pain. Pain-producing substances of bee venom are melittin, histamine and PLA_2 (6). Injection of bee venom produces an initial nociceptive effect, tonic pain and hyperalgesia, following a prolonged anti-nociceptive effect on inflammatory pain (6). The anti-nociceptive effects of bee venom, including the thermal, visceral and inflammatory pain responses, have experimentally been demonstrated (6). It selectively alleviates the mechanical, visceral and inflammatory pain responses through the modulation of the central or spinal α2-adrenergic, serotonergic, opiod receptors activity (6). Bee venom may also relieve the pain and edema associated with chronic inflammatory diseases through its anti-inflammatory activity (6).

Hepatoprotective effect

Propolis has been showed to possess a hepatoprotective effect in the animal models of acute hepatotoxicity induced by both chemical (CCl_4, acetoaminophen, alcohol and D-GalN) and immunological mechanisms (D-GalN/lipopolisaccaride) (10). Dicaffeoylquinic acid derivatives, such as methyl 3,4-di-O-caffeoylquinate, 3,4-di-O-caffeoylquinic acid, methyl 4,5-di-O-caffeoylquinate and 3,5-di-O-caffeoylquinic acid, have a significant hepatocyte protective activity against chemically induced cell injury (10). Because free radicals are involved in chemically induced liver injury models, the antioxidative properties of propolis and dicaffeoylquinic acid derivatives may play an important role in hepatoprotective activity (10).

In the immunologically induced liver injury model, pro-inflammatory cytokines, such as TNF-α, interleukin-1 (IL-1) and IL-6, are released from macrophages stimulated by lipopolisaccaride (LPS), and induce hepatocyte apoptosis and neutrophil transmigration causing cell death and tissue necrosis (10). Hepatic lesions induced by this model resemble those of human hepatitis which is mediated by similar inflammatory mechanisms (10). Because ROS are known to mediate the signaling pathways of inflammatory reactions, antioxidants exert the anti-inflammatory activity and hepatoprotective effects in this type of liver injury. The antioxidative properties of propolis and its phenolic constituents seem to be responsible for its hepatoprotective effect. Flavonoids (3,5,7-trihydroxy-49-methoxyflavanol, betuletol, kaempferide and ermanin), prenylated phenolic compounds (4-dihydrocinnamoyloxy-3-prenylcinnamic acid, 4-hydroxy-3-prenylcinnamic acid and (E)-3-[2,3-dihydro-2-(1-methylethenyl)-7-prenyl-5-benzofura- nyl]-2-propenoic acid) and the labdane-type diterpenes (isocupressic acid, agathic acid, 15-acetoxyiso- cupressic acid and cupressic acid) have a potent inhibitory effects (10). Most of these compounds have stronger hepatoprotective effects than silibinin, a clinically used drug (10). Propolis also contribute to the improvement of the activity of hepatic enzymes, lipid profile parameters and bilirubin content in the case of inflammation and liver damage (8). Hepatoprotective effects of methanol extracts of propolis are stronger than the corresponding water extracts (10).

Other effects

Other beneficial effects of bee products are listed below:

- Oral consumption of royal jelly decreases the total serum cholesterol level (1).
- The royal jelly improves the recovery from 5- fluorouracil-induced damage (4).
- Propolis has beneficial effects on glucose metabolism through protecting the insulin-producing β-cells against streptozotocin toxicity, stimulating insulin synthesis, increasing insulin secretion, and inhibiting the glucose production in the liver (8,10).
- Propolis has an antihyperalgesic effect (10).
- Caffeic acid phenethyl ester (CAPE) in propolis protects the spinal cord from ischaemia-reperfusion injury by eliminating oxygen radicals and inhibiting polymorphonuclear leukocyte infiltration (10).
- Caffeic acid phenethyl ester (CAPE) in propolis also displays estrogenic activity by activating estrogen receptors (8).
- Quercetin and propolis prevents the development of cataracts in diabetics (8,10).
- Flavonoids also display anti-aggregating activity on blood platelets (8).

Side effects

Propolis and honey primarily consists of different plant products. It is possible that bees may gather hazardous or toxic substances including asphalt, metals such as iron (Fe), zinc (Zn), copper (Cu) and magnesium (Mn), and even heavy metals such as lead (Pb) antimony (Sb), arsenic (As), and cadmium (Cd) (4,10). Radioactive particles concentrated in the soil may horrifically contaminate the plants, bees and bee products (2). Presence of grayanotoxin, a group of toxins found in plants and cause a poisonous reaction, in honey may cause intoxication events manifested by cardiac dysrtythmias, hypotension, respiratory depression, and altered mental status (4). The surrounding environment is the main factor influencing the presence of these materials. It can be proposed that bee products may also be used as an environmental contamination and pollution indicator (2).

Although honey has an antimicrobial activity, a limited variety of yeasts and spore-forming microorganisms, such as Bacillus cereus, Clostridium perfringes, or Clostridium botulinum, which can cause serious illnesses in humans, may be colonized in honey, indicating the sanitary or commercial quality (4). The use of honey containing viable spores of Clostridium botulinum in wound dressing may cause wound botulism (9). But honey can be sterilized by gamma-irradiation without loss of activity, and should be sterilized before wound dressing (9).

Allergic reactions has been reported with propolis due to its content (10). Royal jelly can cause anaphylactic reactions in atopic individuals (1). Indeed, bee venom has a real risk for serious allergic reactions (7).

Conclusions

Bee products have essentially been used for medicinal purposes as well as a valuable food through the ages. The powerful methods and instruments of modern medicine give us new opportunities to reveal the potential benefits hiding in these products and to find new treatment alternatives for the diseases of current-days with the best results. Studies have showed that bee products contain a plenty of phytochemical compounds gathered from the plants by bees, and posses evident antioxidant, anti-inflammatory and immunomodulatory actions coming from these compounds. These effects may produce promising results for the treatment of a large group of diseases which involves oxidative injury and inflammation in their pathogenesis. Besides, bee venom, a unique bee product, may provide new treatment options especially in cancers and inflammatory diseases through anti-inflammatory, apoptotic and cytotoxic effects. The efficacy of bee products, which has repeatedly been demonstrated by numerous in vitro tests and animal experiments, should be proved in the clinical level by challenging randomized controlled clinical trials.

Table 13. Components of bee venom and its major medical effects (6).

Components		Contents (% dry BV)	Major effects
Peptides			
	Melittin	40-50	Enhance of PLA2 activity Cytotoxic effects against cancer cells Anti-inflammatory and anti-arthritic effects
	Apamin	2-3	Inhibition of Ca2+-activated K+ channel Cytotoxic effect against cancer cells Nociceptive effect
	MCD peptide	2-3	Anti-inflammatory and analgenic effect Histamine release (low dose) Histamine release inhibition (high dose) Anti-allergic effect
	Adolapin	1	Inhibition of PLA2 and COX activity Anti-inflammatory activity -Analgesic effect
	Protease inhibitor	<0.8	
	Minimine	2-3	
	Procamine A, B	1.4	
	Secarpin	0.5	
	Tertiapin	0.1	
	Melittin F	0.01	
	Cardiopep	<0.7	
Enzymes			
	PLA2	10-12	Cytotoxic effects against cancer cells Inflammatory effects -Anti-tumor effects
	Hyaluronidase	1.5-2	Selectively attacks tissue hyaluronic acid polymers Increase the capillary permeability Immune response and tissue-spread properties Antigenic

	Glucosidase	0.6	
	Acid phosphomono-esterase	1	
Amines			
	Histamines	1.5	
	Dopamine	0.13-1	
	Norepinephrine	0.1-0.7	
Others			
	Carbohydrates	1.5	
	r-Aminobutyric acid	0.13-1	
	B-Aminoisobutyric acid	0.1-0.7	

Table.14 Effects of honey consumption on health (3).

Cardiovascular diseases (CVD)	
	Reduction of cardiovascular risk factors
	Inhibition of inflammation
	Improvement of endothelial function
	Improvement of plasma lipid profile
	Increase of low-density lipoprotein (LDL) resistance to oxidation
	Inhibition of Red Blood Cells (RBCs) hemolysis
	Improvement of eritrocytes uptake capacity
	Protection of RBCs against intracellular depletion of GSH and SOD activity
	Decrease of the susceptibility of RBCs lipid membrane against oxidative damage
	Maintenance of the body weight in overweight or obese subjects
Hypertension	
	Reduction of systolic blood pressure and MDA levels
	Amelioramen of susceptibility of kidneys to oxidative stress
Cancer	
	Antimutagenic capacity
	Induction of apoptosis

	Antiproliferative effect
	Citotoxic effect on several cancer cell lines
	Antimetastatic effect
Diabetes	
	Reduction of glycaemia
	Reduction of serum fructosamine
	Reduction of glycosylated hemoglobin concentration
	Attenuation of post-prandial glycemic response
	Increase serum insulin concentration and reduce insulin resistance
Microbial infection	
	Inhibition of microorganisms of clinical relevance

Table 15. Types of wounds on which honey has been used successfully (9).

Wounds	
Infected wounds arising from trauma and surgery	
	Amputation wounds
	Vulvectomy wounds
	Burst abdominal wounds following Cesarean delivery
	Donor sites from split-thickness skin grafting
Burns	
Skin lesions from menigococcal septicemia	
Fournier's gangrene	
Pressure sores	
Skin ulcers	
	Leg ulcers
	Varicose ulcers
	Diabetic ulcers
	Tropical ulcers
	Foot ulcers in patients with leprosy

	Sickle cell ulcers
	Malignant ulcers

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