

REVIEW ARTICLE



Bee products and their potential use in modern medicine

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Introduction

The medical use of bee products, especially honey, can be traced back thousands of years to ancient Egypt, Greece and China. Healing properties and nutritional benefits are mentioned in many religious texts including the Veda, Bible and Quran. Over time bee products have lost their importance and, today, bee products only play marginal roles in modern Westernised medicine. However, people in developing countries and followers of holistic approaches still use bee products on a large scale. In developed countries the use of bee products is often referred to as apitherapy, which is mainly applied by lay practitioners. Several books describe ways in which bee products can be used for several every day problems; however, there is not sufficient scientific evidence for most applications. Often, the indiscriminate recommendations of apitherapists have worsened the reputation of bee products because many people did not distinguish between dubious apitherapists and serious approaches. The crucial questions in relation to that stated above are:

- why bee products disappeared from modern medicine,
- what bee products may still be reasonably used,
- how, and which, bee products could be reintroduced to modern medicinal practice.

Before answering these questions it seems important to look briefly into the history of pharmacology. In the beginning of medicine, medical treatments mainly represented medications which consisted of multiple substances, like herbal extracts. Some of these medications may have had favourable properties, others were inert and some may even have had adverse effects. This type of medicine was common from antiquity up to the Middle Ages when early pharmacology was founded by Avicenna, Peter of Spain and John of St. Amand. Pharmacology, in the modern sense, was not established

until the mid-nineteenth century. The first pharmacology department was set up by Rudolf Buchheim in Dorpat, Estonia in 1847, in recognition of the need to understand the working mechanisms of drugs and poisons. Until then the actions of drugs such as morphine or digitalis were explained vaguely with reference to extraordinary chemical powers and affinities to certain organs or tissues. Within time, pharmacology developed as a biomedical science which applied the principles of scientific experimentation to therapeutic contexts.

In order to find the working principles behind pharmacologically active mixtures, it was reasonable to search for active substances and isolate them from inactive ones and those which might be harmful. Then, the preparation with the active drug could be standardised and investigated regarding its chemical properties, interactions, toxicology, medical applications, anti-pathogenic capabilities and pharmacokinetic measures like half-life and volume of distribution. This was necessary as many substances require exact dosages in order to achieve effects or because of limited therapeutic indices.

Over time, plant extracts and other natural preparations have widely disappeared from daily medical practice in conventional medicine. Instead, the working principles and active substances were discovered which were then produced in large quantities using chemical or biochemical syntheses. This approach is well in line with pharmacological research and can explain the organism's reactions via direct interactions between the drug and its target, which can be enzymes, receptors or other cellular functional structures. As a result there are only a few examples of therapeutic substances which consist of multiple components which have not been added intentionally for reasons of stability or galenics. Modern pharmacology propagates the "one drug - one effect" concept. Accordingly, specific drugs cause dose-dependent therapeutic effects. This concept has led medicine to many outstanding successes in the treatment of

many diseases. However, treatments with a single drug could be less efficient than the use of the same substance in the natural working environment. A good example is lycopene which works less efficiently alone compared to the efficacy of tomato products with a comparable lycopene concentration. Although many investigations were carried out in order to identify the queen-making substance, all efforts were in vain (Reibold, 1987). Bee products are mixtures with different pharmacological substances acting in unison.

Today, many patients ask for treatments with natural products which are thus increasingly offered by medical practitioners. But phytotherapeutic drugs are also subject to registration and it is necessary that these preparations fulfil the same quality requirements as conventional medical products and contain standardised amounts of active substances.

Bee products in modern medicine

If bee products are to be used in modern medicine they will have to fulfil the same requirements regarding safety and efficacy as normal allopathic drugs. The problems which will have to be solved can be summarised as follows.

- There are no standards for bee products with regard to their biologically active substances.
- There are very few pharmacological studies which include dose response relationships for bee products and their components.
- Knowledge on the biological and pharmacological action of bee products has to be improved.
- Many biologically active substances in the products are yet to be identified.
- The biological activities of honey, pollen and propolis depend on their botanical origin.
- The production methods for the bee products also have to fulfil certain criteria in order to guarantee optimal pharmaceutical quality.
- Improper processing methods are sometimes used (e. g. honey-heating, filtration).

In conclusion, bee products are very heterogeneous and in general do not fulfil the requirements of pharmaceutical and medical products. This means that there are many different biologically active substances which might exert synergetic, but also opposing, effects. Therefore most bee products must be considered as pleiomorphic substances, i.e. having multiple biochemical effects. This property is due to the mixture of different biologically active molecules present in most bee products.

Considering the requirements of pharmaceutical products regarding their application in medicine, the use of bee products seems justified under the following conditions.

- The healing properties of the bee products are manifold, irrespective of changes in composition of the product.
- Bee products have healing properties absent in established modern drugs.
- Bee products have comparable healing properties to established drugs but fewer side effects.
- Products comparable to bee products cannot be produced.

Biological potential of bee products for applications in medicine

Here we will briefly summarise the biological and pharmacological properties of the bee products which explain their potential for medical application.

The nutrients: Honey, pollen and royal jelly

In early times there was no separation between food and medicines and early societies followed the advice of Hippocrates: *"Let food be thy medicine and medicine be thy food"*. Today foods and medicines are regarded as separate. By this logic honey, pollen and royal jelly are regarded as foods and medicinal claims for these products are not allowed. Only honey is consumed in large amounts and may be thus considered a real nutrient. In contrast pollen and royal jelly should be regarded rather as functional food. The biological and pharmacological properties of these products are summarised in Table 1. The uses of honey, pollen and royal jelly are fairly safe but in some cases there have been problems with allergy to royal jelly and bee pollen (Leung *et al.*, 1997). Future tasks are to explore the composition and also the biological properties of honey and pollen in relation to their botanical origin and then to produce unifloral products which are more likely to guarantee constant pharmacological action. Also, an important task is to review the functional properties of bee products in order to enable specific health claims to be made (Mateescu, 2008). Such health claims are possible according to EU and USA food laws, but specific health claims are only possible if they are scientifically proven and accepted by the food authorities.

Propolis and bee venom

Both products have potent biological and pharmacological properties and can be considered as drugs from the bee hive. Bee venom has a very wide variety of biological and pharmacological properties (Table 1) and has shown interesting properties regarding the treatment of rheumatism and other diseases (see next section). Propolis has a wide spectrum of biological and pharmacological healing properties which have been intensively researched in cell and animal experiments (Table 1) but so far there is no propolis-containing pharmaceutical product on the market in the developed countries.

As mentioned before, the chemical composition and the associated biological properties of propolis largely depend on its botanical origin (Baknova, *et al.*, 2007). Thus, standards for each propolis type, including biologically relevant properties, should be established in order to guarantee optimal biological action.

Main applications of bee products in modern medicine

To our knowledge there is only one book in which the application of all bee products in modern medicinal practice is discussed in detail. This is the monograph on apitherapy by the late Dr. E. Ludyanski (1994). He was the head of a department in a large Russian hospital and described the use of bee products in modern medical practice, with extensive reference to the literature published in Eastern Europe. Apart from that, the knowledge on current clinical applications of bee products is spread over numerous separate publications. In the following section we have explained reasonable medical applications for the various bee products.

Honey

Probably the best studied area for honey is wound healing. At present there are also commercial medi-honey products (Gray *et al.*, 2005). It seems that both honey and medi-honey have similar antibacterial properties (Lusby *et al.*, 2005). CE-certified honey (CE =

Conformité Européenne – European conformity) dressings with standardised antibacterial activity are irradiated because of a potential risk regarding clostridia-associated infections (Simon *et al.*, 2008). Manuka honey is favoured by many authors but there have not been randomised trials to show its superiority over other types of honey. It seems that the presence of methylglyoxal as an antibacterial component in manuka honey makes it distinct from other honeys. Some systematic reviews have independently analysed the outcome of more than 2000 patients with various types of wounds in more than 20 trials, and 533 wounds on experimental animals in 16 trials. They conclude that there is evidence favouring the use of honey in wound healing (Molan, 2006; Brady *et al.*, 2008; Jull *et al.*, 2008).

Perhaps one of the most interesting arguments for the use of honey is the fact that honey eliminates meticillin-resistant *Staphylococcus aureus* (MRSA) better than conventional wound treatments (Gethin and Cowman, 2008). Honey also has great potential for the treatments of burns (Postmes, 2001; Subrahmanyam *et al.*, 2001). However, too little is known about the antibacterial activity of honeys. As shown quite recently, many honeys have a low antibacterial potential. Thus it is necessary to select those with the highest potential and also those without presence of potentially pathogenic organisms. Although no infections have been traced to honey the possibility of infecting vulnerable patients exists. Since sterile, quality-assured, honey containing wound care products are on the market; the use of non-sterile honey

Table 1. Biological and pharmacological properties of bee products as described from in cell and animal experiments

Product	Biological and pharmacological properties	Potential side effects	References
Honey	antibacterial, antifungal, antiviral, antioxidative, probiotic, anti-inflammatory, anticarcinogenic	allergy	Bogdanov <i>et al.</i> , (2008)
Pollen	antibacterial, antifungal, antioxidative, immunomodulating, radioprotective, antianaemic, antiatherosclerosis, antidiarrhoeac and helps to prevent osteoporosis	allergy	Dixit & Patel, (1964) Münstedt & Franke, (2005)
Royal jelly	antibacterial, antifungal, antiviral, antioxidative, biostimulating, immunomodulating, radioprotective, anticarcinogenic, antifatigue, antistress, antihypoxia, antitumour, anti-inflammatory, both antihypertensive and anti-hypotensive, vasodilatative, antiatherosclerosis, cardio-protective, tranquilising, neuroprotective, anti-osteoporosis	allergy	Bopgdanov & Gallman (2008) Leung <i>et al.</i> , (1997)
Propolis	antibacterial, antifungal, antiviral, antioxidative, antiparasitic, immunomodulating, anti-inflammatory, analgesic, hepatoprotective, anticarcinogenic, local anaesthetic, pain soothing, spasmolytic, hepatodetoxiquant and hepatoprotecting, anticoagulant, improving blood circulation	contact allergy	Burdock (1998) Fearnley (2001) Marcucci (1995) Münstedt <i>et al.</i> , (2007)
Bee venom	antibacterial, antiinflammatory, immunoactivating, immunosuppressive, analgesic, radioprotective, anticarcinogenic, accelerates heart beat, increases blood circulation, lowers blood pressure, improves haemoglobin synthesis, anticoagulant, lowers cholesterol levels, membrane effects on blood cells, influences immuno-active blood cells and hormone levels, antiarrhythmic, heart stimulating therapeutic effects, improvement in hypertension and arteriosclerosis	inflammation, allergy, cytotoxic, haemolysis	Krilov (1995) Schkenerov and Ivanov (1983)

samples cannot be promoted (Cooper and Jenkins, 2009).

Another use of honey for the treatment of radiation-induced mucositis seems to be reasonable, as stated in a systematic review (Brady *et al.*, 2008). Here, conventional medicine offers no comparable treatment alternatives. Other potential uses of honey in medicine were recently reviewed. They include treatments by honey ingestion for peptic ulcers, gastritis, diarrhoea and hepatitis A and also for reducing risks for cardiovascular diseases (Bogdanov *et al.*, 2008).

An example of a more pharmacological advancement regarding honey is Lifemel®. It is made by honey bees fed on a diet which includes selected herbs such as *Eleutherococcus senticosus*, *Echinacea* and *Uncaria tomentosa*. Lifemel® may not be considered as honey but the production mechanisms are standardised so a honey-like product with similar characteristics can be obtained throughout the year. A study has shown that Lifemel® can improve haematological toxicity in patients undergoing chemotherapy and the effect is attributed to the combination of the ingredients in natural honey and the above mentioned herbs. Although the claims of the product need further investigation, the basic principles behind it are interesting (Zidan *et al.*, 2006).

Pollen

Cernilton, a preparation based on rye pollen, has shown positive effects on chronic prostatitis in several clinical studies (Becker and Ebeling, 1988; Buck *et al.*, 1989; Dutkiewicz, 1996; Elist, 2008; Hayashi *et al.*, 1986; Münstedt and Franke 2005). Beekeepers claim similar effects for pollen from flowering plants but until recently there were no clinical studies on this type of pollen (Hellner *et al.*, 2006), with only one animal study with bee pollen having shown promising results in dogs with prostatitis (Lin *et al.*, 1990). Very recently, a positive double blind study with ingestion of bee pollen extracts by humans was published and showed that the positive effects are also true for bee pollen (Murakami *et al.*, 2008). The mechanisms of action for this beneficial effect are under investigation and may be due to flavonoids or to phytosterols present in pollen (Wilt *et al.*, 1999). More research is necessary to definitely identify the active substances for this effect and also to identify the pollen types which are most potent for use against prostatitis. Pollen ingestion in the form of Cernilton by humans also resulted in a reduction of atherosclerosis lipid factors (Wojcicki *et al.*, 1983).

Ludyanski mentioned successful treatments using bee pollen of human gastritis, impotency, anaemia and posttraumatic stress disorder but these indications still need further investigation (Ludyanskii, 1994).

Royal jelly

The natural role of royal jelly in the bee colony is to stimulate and increase the growth of larvae in order to produce the bee queen.

The role of royal jelly in nutrition and health is reviewed elsewhere (Bogdanov and Gallmann, 2008). Many promising effects have been reported in animal and cell experiments (Table 1).

Concerning clinical use with humans there are currently only a few applications. Royal jelly may be an interesting substance in the treatment of hypercholesterolemia (Guo *et al.*, 2007), diabetes (Münstedt *et al.*, 2009), or male infertility (Abdelhafiz and Muhamad 2008), as well as paediatrics, geriatrics and anti-cancer treatments (Bogdanov and Gallmann, 2008).

Ludyanski mentions successful treatments of hypertension, hypotension, sexual dysfunction, cerebral insufficiency and menopausal symptoms, but confirming studies are needed (Ludyanskii, 1994).

Propolis

Propolis has many different promising biological and pharmacological properties, mostly tested in very numerous cell and animal experiments (Table 1). In humans it has been used for treatment of surgical diseases (Hartwich *et al.*, 2000), wounds (Fedorov *et al.*, 1975) and minor burns (Gregory *et al.*, 2002).

Propolis is very widely used in dentistry (Oliviera and Murgu, 2006). Propolis inhibits in the mouth different pathogenic microbes such as bacteria, fungi and viruses (Hayacibara *et al.*, 2000; Santos *et al.*, 2003; Sauvager, 1992; Silici *et al.*, 2007) and can be successfully applied against the different stomatological pathologic conditions: stomatitis, paradontosis, gingivitis and caries (Amaral *et al.*, 2006; Hayacibara *et al.*, 2005; Koo *et al.*, 2002; Ludyanski, 1994; Martinez *et al.*, 1988; Oliviera *et al.*, 2006; Samet *et al.*, 2007).

One major threat for women is the human papilloma virus (HPV) infection which can lead to cervical cancer, which is the most frequent cancer in women, especially in underdeveloped countries. But even in Western countries there are many HPV-associated dysplasias which require surgery by means of cervical conisation or even hysterectomy. Two studies have shown that propolis-containing local therapy can eradicate HPV infections within six months. In a randomised trial, HPV infections were present after three months of treatment in 28% of patients treated with propolis compared to 90% in the control group (Ilijazovic *et al.*, 2006). Similarly, another study described an improvement in cytological PAP smears (*Papanicolaou test*) of 76% with the use of propolis (Imhof *et al.*, 2005). Here, treatment with bee products offers an interesting approach which could avoid invasive surgery.

According to Ludyanski, propolis can also be used in paediatric diseases, radiculitis, polyradiculoneuritis, gastric ulcers and baldness (Ludyanskii, 1994). In a monograph dedicated to the use of propolis in medicine, successful treatments of the following diseases were mentioned: tuberculosis, psoriasis, skin mycosis, and inflammations of the stomach and duodenum (but general use in these cases can not be recommended) (Tichonov *et al.*, 1998).

Bee venom

From a pharmacological point of view bee venom is the most potent bee product. Many interesting pharmacological effects of bee venom have been reported (Table 1).

The most interesting application of bee venom in humans is its application to the treatment of rheumatoid arthritis. Recently, the use of bee venom in the treatment of arthritis was extensively reviewed (Son *et al.*, 2007). Clinical studies mention success rates between 70% and 90% (Feraboli, 1997; Son *et al.*, 2007; Steigerwaldt *et al.*, 1966). The mechanism of action of bee venom was clarified as follows: bee venom blocks the building of proinflammatory substances and inhibits the proliferation of rheumatoid synovial cells. Today, bee venom is applied directly via sting or injection. This practice was initiated in 1964 in Russia (Ludyanski, 1994) and has been further developed since then, mostly in the Far East (Lee *et al.*, 2008). Recently, bee sting therapy has been combined with acupuncture and is referred to as apipuncture. The effectiveness of apipuncture to treat arthritis seems to be better than traditional bee venom therapy but independent studies are necessary (Lee *et al.*, 2008; Münstedt and Hackethal, 2006; Son *et al.*, 2007).

Another promising application of bee venom may be against multiple sclerosis (Mirshafiey, 2007). However, further clinical trials are necessary in order to decide whether its use is justified.

Bee venom may also have some potential in the treatment and prevention of cancer. Beekeepers have been reported to have a slightly lower cancer incidence and a significantly lower incidence of lung cancer compared to the general population (McDonald *et al.*, 1979).

Ludyanski (1994) reviews successful treatments in hospitals in Russia and Eastern Europe of diseases of the central and peripheral nervous system, such as back pain, limb pain, neuralgia, neuritis, radiculitis, polyneuritis and ear inflammation. These effects are explained by the well documented action of bee venom against pain but, again, this needs further investigation (Son *et al.*, 2007).

Beeswax

Since ancient times, the basic recipe for creams and ointments has consisted of a mixture of beeswax and oil in various proportions according to the desired consistency. Beeswax has unique properties that make it an ideal substance for skin creams and ointments. It builds stable emulsions; improves water binding of creams; reinforces the action of detergents, giving the skin a protective layer and improving its elasticity; improves the protective action against ultraviolet light of sun creams; does not provoke allergy and has antibiotic and warming properties. These properties have made beeswax an irreplaceable ingredient of cosmetic creams and ointments. The proportion of beeswax varies from a few percent to as much as 50%. Application of beeswax in cosmetics should meet

modern standards (Bogdanov 2004). Interestingly some substances in beeswax have recently been found to be hepatoprotective (Anilakumar *et al.*, 2007).

Bee products as raw materials for the development of medications

Pharmacological and biochemical analyses could identify the relevant substances in bee products, and procedures for their large scale production could be developed. These procedures would also separate active ingredients from inactive ones, and from those with undesired side effects. A good example in this area is the fractionation of bee venom, which contains very toxic components, most of all hyaluronidase and phospholipase A. Procedures for isolating pharmacologically active components like melittin, apamin, mcd-peptide and adolapin have been proposed (Shkenderov and Ivanov, 1983).

Technology for the isolation of the different propolis components has been developed, based on fractional extraction and cryology. On this basis specific propolis drugs for specific applications have been developed (Tichonov *et al.*, 1998).

Some bee products have ingredients with very interesting features. For example, royal jelly was found to influence serum glucose levels, and there are insulin-like substances which could perhaps be developed further to create new treatment options for diabetes (Dixit and Patel, 1964; Münstedt *et al.*, 2009).

Side effects

Bee products, excepting bee venom, have relatively few side effects. This makes them good candidates for clinical application. Most side effects concern allergies. Allergies against ingesting of honey, pollen, royal jelly, pollen and propolis have been reported but in rates similar to other natural foods and medicines. Propolis has allergenic substances which act as contact allergens (Münstedt *et al.*, 2007). Bee venom is also allergenic. Thus, the application of bee venom should be restricted to experienced physicians in order to avoid complications.

Concluding Remarks

According to Ludyanski (1994), bee products can be applied successfully in specific diseases in most areas of medicine. This is in accordance with some databases which reveal more than 1000 publications on many different aspects of apitherapy in animal and human diseases. However, many of these publications do not meet the current standards required by drug registration bodies in developed countries. This is because the application and registration of bee products for modern clinical use must be based on well-

designed studies, preferably prospective randomised trials.

In summary, bee products are very interesting and can either be developed further into medicinal products when they offer new and better treatment alternatives, or form the basis for the identification of new drugs which can be used according to the principles of pharmacology and pharmacy. In either case, much effort will be necessary in order to establish their position in modern medicine.

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