Bee Products: The Rediscovered Antibiotics

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Abstract: Honey and other bee products have been subjected to laboratory and clinical investigations over the past few decades, the most significant discovery being their antibacterial activity. The emergence of antibiotic-resistant strains of bacteria has made the current use of antibiotic therapy problematic, resulting in earlier remedies being reassessed. Honey, propolis, royal jelly and bee venom, all exhibit strong antibacterial activity. Even antibiotic-resistant strains such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) have been found to be as sensitive to honey as the antibiotic sensitive strains of the same species. The main problems in using bee products for medical purposes involve dosage and safety. The increased availability of licensed medical products containing bee products means that clinical use will probably grow and further evidence will become available. Use of such products in professional treatment centers should be limited to those which are safe and that exhibit proven antibacterial activities.

Keywords: Antibacterial, antibiotic resistance, bee product, bee venom, honey, royal jelly, propolis.

INTRODUCTION

The rapid emergence of antibiotic-resistant pathogens poses increasingly serious health concerns worldwide. Approximately 70% of bacteria that cause infections in hospitals are resistant to at least one of the antibiotics most commonly used to treat infections. This antibiotic resistance is driving up health care costs, increasing the severity of disease, and the fatality of certain infections. The annual cost of treating antibiotic-resistant infections in the USA is estimated to be as high as $30 billion. Sepsis is another serious medical condition resulting from severe inflammatory response to systemic bacterial infections [1]. Antimicrobial peptides (also known as natural antibiotics) comprise a large group of molecules that are capable of killing a broad spectrum of pathogens with similar activities against both antibiotic-susceptible and resistant bacterial strains and with extremely low risks of developing resistance [2]. Many also have the capacity to bind bacterial endotoxin and neutralize bacterium-induced inflammatory response. Due to their dual capability to eliminate bacteria and neutralize endotoxins, these antimicrobial peptides potentially represent a new class of antimicrobial and anti-sepsis agents [3]. As natural products become ever more popular in the medical field, the emergence of antibiotic-resistant strains of bacteria has made the current use of antibiotic therapy problematic. This in turn has led to the reassessment of older remedies, such as honey, royal jelly, propolis and bee venom. Honey, propolis and royal jelly, all originating from the bee hive, are also desirable ingredients for healthy foods. Several aspects of honey indicate that it possesses functions such as antibacterial [4], antioxidant [5] and anti-inflammatory [6] capacities. Propolis is a resinous substance produced by honeybees. It has been used in folk medicine since ancient times due to its many biological properties, including antioxidant, antimicrobial, anti-inflammatory and immunomodulatory effects [7]. The many biological properties attributed to royal jelly means that it enjoys considerable commercial appeal and is today used in many sectors, ranging from the pharmaceutical and food industries to the cosmetic and manufacturing sectors [8]. Royal jelly has been shown to possess numerous functional properties, such as antibacterial and anti-inflammatory properties [9, 10]. Biological activities of honey, propolis and royal jelly are mainly attributed to phenolic compounds, such as flavonoids. Recent studies have also shown that bee venom exhibits antibacterial activity [11, 12].

Royal jelly has been reported to exhibit higher antibacterial activity than other bee products. The most sensitive test organisms reported are S. aureus, followed by B. subtilis and E. coli [13]. Ratanavalachai and Wongchai [14] evaluated the antibacterial activity and potency of intact royal jelly from northern Thailand, together with lipid extract and defatted extract, and found that intact royal jelly exhibited the highest antibacterial activity. The lipid extract, which contained mostly acidic polar compounds, was more effective than the defatted extract when assayed against non-spore forming bacteria, but less effective in spore-forming bacteria such as B. cereus. Antimicrobial activity of royal jelly was attributed to different agents, such as apideacins, which have been isolated from the lymph fluid of the honey bee. These are highly active against gram negative bacteria, actinomycetes and certain species of fungi. Another agent is the principal royal jelly fatty acid, trans-10-hydroxy decanoic acid (10-HDA). Recently, “royalisin”, a potent antibacterial protein in royal jelly, has been shown to exhibit selective growth inhibition against gram positive bacteria, such as Lactobacillus.
**Bifidobacterium** and **Leuconostoc**, at effective concentrations below 1 µM [15].

The presence of substances such as benzyl alcohol, 1,4-dihydroxybenzene, terpenes and 2-hydroxybenzoic acid, its low protein content and low redox potential also contribute to honey’s antimicrobial property [16].

Honeys produced by stingless bees from the genera *Melipona* and *Trigona* from the subfamily *Meliponinae*, which inhabit tropical and subtropical regions, also demonstrate healing properties. Honeys produced by stingless bees from the genus *Trigona* are used in Ethiopia to treat conditions such as gastric disorders, tonsil infections, coughs, sore throat, gastric and intestinal ulcers, chills, diseases of the mouth and in mucosal structures and wound dressings [17]. Very high levels of the antimicrobial compound methylglyoxal (MGO) have recently been discovered in manuka honey. In general, MGO is formed from sugars during heat treatment or prolonged storage of carbohydrate-containing foods and beverages. However, the high levels of MGO in manuka honey are the result of conversion of dihydroxyacetone (DHA) present at exceptionally high concentrations in the nectar of *Leptospermum scoparium* flowers [18].

The major components of bee pollen are carbohydrates, crude fibers, proteins and lipids, other minor components being minerals and trace elements, vitamins and carotenoids, phenolic compounds, flavonoids, sterols and terpenes. Pollen is consumed in large quantities around the world as a dietary supplement due its nutritive value. Bee pollen is sometimes referred to as the “only complete food,” as it contains all the essential amino acids required by the human body. However, the composition of bee pollen is highly dependent on the plant source and geographic origin, together with other factors such as climatic conditions, soil type and beekeeper activities [19].

Bee venom and derived polypeptide (melittin) have been shown to exhibit antibacterial activity against a penicillin-resistant strain of *S. aureus* [20]. Attalla et al. [15] investigated the potent antibacterial activities of three bee products, bee venom, propolis and royal jelly, against three gram positive bacteria, *S. aureus*, *Bacillus subtilis* and *Listeria monocytogenes* and two gram negative bacteria, *Escherichia coli* and *Salmonella enteritidis*. They determined that bee venom is the most active product against the tested strains, followed by propolis and then royal jelly. Yu et al. [21] found that bee venom exhibited prominent antifungal activities against *Trichophyton mentagrophytes* and *Trichophyton rubrum*, much stronger than those of fluconazole, one of the commercial antifungal drugs used in the treatment and prevention of superficial and systemic fungal infections.

**BEE PRODUCTS AS ETHNO-MEDICINES**

Many products based on traditional knowledge are important sources of income, food and health care for large parts of populations throughout the world. By the time ancient civilizations began to evolve, a large number of treatments had been discovered by prehistoric and primitive peoples alongside a body of “magical” or “mythological” therapies, and won widespread use [22]. Honey has been used for centuries for its nutritional as well as medicinal properties. Human use of honey dates back some 8000 years, as evidenced by Stone Age paintings. Various traditional systems of medicine have highlighted the role of honey as a medicinal product. Sumerian clay tablets (6200 BC), Egyptian papyri (1900-1250 BC), Vedas (5000 years), the Holy Koran, the Talmud, the Old and New Testaments of the Bible, sacred texts from India, China, Persia and Egypt [23, 24], and the writer Hippocrates (460-357 BC) [25] all describe the uses of honey. The latter described its use for baldness, contraception, wound healing, laxative action, cough and sore throat, eye diseases, topical antisepsis, and the prevention and treatment of scars [26].

Ever since very ancient times, honey has been used extensively in toilet preparations, and poultices were often mixed with honey in early skin remedies. Historical records from predynastic times in Upper Egypt show that nomadic tribes from the Tasinian culture (around 4500 BC) mixed malachite, copper, spar, oil, fat and honey to produce eye cosmetics [27]. Other ancient accounts of honey being used in cosmetics appear in the works of Aristotle, Dioscorides and Pliny, as well as prophetic texts belonging to the main religious traditions, such as the Bible, Koran, Torah and Talmud [28].

In antiquity, honey was frequently used like gum as a binder, to hold other ingredients in a paste, or as a vehicle for various creams and lotions [29]. In his poem *The Art of Beauty/De Medicamine Faciei*, the Roman poet Ovid (43 BC-17/18 AD) provided various recipes for face-packs that contained honey and other herbal ingredients [30]. A rare instance of a Medieval cosmetic treatise penned by a woman, Trotula de Ruggerio, at the Schola Medica Salernitana (southern Italy) reports various uses of honey, including as a skin moisturizer, hair dye, lip softener and face mask ingredient [31]. An anonymous 13th century Anglo-Norman treatise on the adornment of the body describes the manufacture of a product intended to encourage hair growth by mixing honey with parsley juice, pig blood and white wine [32].

In Venice, women used to dye their hair a gold color using a product made of alum, sulfur and honey [33]. Two manuscripts from the 17th century from the archives of Nantes (France) report various galenic forms containing honey and beeswax for external use in therapeutics and beauty care [34]. A review of herbal cosmetics in ancient India lists different formulae from sources earlier than the 18th century, including a face pack based on Masura, a type of lentil widely found in India (*Lentilus Medik.*), ground with honey. Applied to the face over seven nights, this paste is reported to bestow the luminosity of white lotus petals [35]. Other important ancient uses of honeybee products concern the preservation of tissues. Beeswax was used in embalming techniques by the Egyptians, and honey is also presumed to have been employed for the same purpose [36].

Japanese women kept their hands smooth through daily applications of honey, while Chinese women mixed crushed fruit seeds with honey to make a cream for pimples and other skin problems. The Creole women of Louisiana rub their bodies with a lotion consisting of honey and water mixed with various herbal substances. This is used as a cosmetic, for skin ailments and as a protective potion against evil spirits. Anti-aging face masks prepared by Arab women consist
of honey mixed with egg yolk, avocado, lemon and yogurt [37].

The medicinal use of honey for skin ailments is cited in a number of ethnopharmacological and ethnomedical surveys. In these, honey is commonly used as a vehicle for the external application of herbal extracts, as well as for its own therapeutic properties. In traditional Chinese medicine, honey is thought to prevent scarring, eliminate discoloration and freckles and improve the general appearance of the skin. In Arab medicine, honey is used, together with other remedies, to treat fungal dermatological infections [37], while in Burkina Faso in Africa, it is used as a skin cleansing agent by manual laborers, presumably due to its bactericidal and sterilizing properties [38]. One review of healing techniques using animal products from the eastern Mediterranean reports uses of honey to treat skin complaints as far back as the Middle Ages [39]. An ethnobotanical study carried out in the state of Assam, India, showed that honey is used for the topical application of powdered plants with disinfectant properties. Alternatively, it can be mixed with rice flour and egg yolk to produce a paste that is applied to the face to smooth the skin and to combat acne [40]. Similarly, in female communities of northern Pakistan, honey is used as a cream base for mixtures containing herb extracts with various skin care properties, including body skin smoothening, eyelid and face protection and the treatment of freckles and white spots [41]. In skin remedies from central Italy, honey is used in the preparation of toner and cleansing compresses, against furuncles, as a cream base for silicon-rich horsetail extracts applied to the finger and toenails, as a skin emollient together with calcium bicarbonate, as a soothing poultice for swelling [42], or mixed with ground oleander (Nerium oleander) leaves as a treatment for scabies [43]. In Bosnia Herzegovina, special balms are prepared by mixing fresh herbal parts with warmed conifer resins, cow or pig lard, olive oil and honey. These ointments are used for cosmetic purposes or else to treat wounds and rheumatism [44].

THE USE OF BEE PRODUCTS IN MODERN TIMES

Studies of raw royal jelly have shown that its antimicrobial properties can inhibit the growth of several types of microbes, including some bacterial-resistant bacteria such as MRSA. Moreover, a synergistic effect of mixing royal jelly with other products, such as starch or honey, significantly improves antibacterial activity against dangerous pathogens such as P. aeruginosa and S. aureus [45, 46]. The mechanism of action of royal jelly peptides (royalisin) against bacterial growth has also been described. These inhibitor activities of royal jelly might potentially be applied to develop novel antibiotics to overcome the problems of antibiotic bacterial resistance, and its components might be used as effective food preservatives. Advanced purification methods need to be developed to discover new antibacterial peptides from royal jelly. Further studies on the antimicrobial components of should be conducted to standardise composition, quality and bioactivity.

The therapeutic effects of honey have been demonstrated in the treatment of burns, assisting rapid healing of wounds with less scarring [47]. A significant range of microorganisms may colonise the burn wound, proliferate on and within the eschar, progress in depth and trigger systemic infections which represent a major cause of death among burn victims [48, 49]. Any means of preventing this will lead to higher survival rates in burn patients.

Prevention and treatment of burn wound infection involves proper wound dressing [50], surgical debridement and systemic and topical antimicrobial therapy [51, 52]. Third-degree burn wound eschar is avascular and frequently located at several millimeters’ distance from the patient’s microvasculature. Systemically administered antimicrobial agents may therefore not achieve therapeutic levels by diffusion to the wound, where high microbial numbers are generally observed [51]. In addition, systemic antibiotics can lead to the development of drug-resistant respiratory and urinary tract infections [53]. Although silver sulfadiazine cream (SSD) is efficacious, it nevertheless involves a number of systemic complications, including neutropenia, erythema multiforme, crystalluria and methemoglobinemia [54]. The emergence of antibiotic-resistant bacteria, particularly methicillin-resistant S. aureus (MRSA), has led to problems in the management of chronic wound infections. MRSA is now the major cause of nosocomial infections [55, 56] and is increasing in prevalence in burns units. Infection-related mortality and morbidity are greater when originating from antimicrobial-resistant bacteria [57]. Pseudomonas aeruginosa is one of the main organisms implicated in drug resistant nosocomial infections, particularly among burn victims [58, 59]. More alarmingly still, increased resistance to vancomycin in S. aureus has recently been reported [60]. Many studies [60-64] have shown that honey exhibits antibacterial activity in vitro, and clinical case studies have shown that application of honey to severely infected cutaneous wounds is capable of removing infection from the wound and improving healing. Honey has an osmolarity sufficient to inhibit microbial growth [63]. When it is used as a wound contact layer, however, dilution by wound exudate may reduce the osmolarity to a level that is no longer capable of controlling infection [65]. The fact that the antimicrobial properties of honey increase when it is diluted was clearly observed and reported in 1919 [66]. This apparent paradox was resolved by the realization that honey contains an enzyme that produces hydrogen peroxide when diluted [67]. This agent was referred to as ‘inhibine’ prior to its identification as hydrogen peroxide [68]. Hydrogen peroxide is a well-known antimicrobial agent, widely used for its antibacterial and cleansing properties when it entered clinical practice [67]. It has since become less popular, however, because of inflammation and damage to tissue [69-71]. However, the level of hydrogen peroxide in honey activated by dilution is some 1,000 times lower than that in the 3% solution commonly used for antiseptic purposes [72]. Although the level of hydrogen peroxide in honey is very low, it is still effective as an antimicrobial agent. Hydrogen peroxide is reported to be more effective when provided by continuous production with glucose oxidase than when added alone [73]. Additional non-peroxide antibacterial factors have also been identified [74]. Due to differences in levels of peroxide and non-peroxide factors, which vary depending on floral source and processing, honeys differ in terms of antimicrobial activity. This antimicrobial activity is measured as the minimum inhibitory concentration (MIC), i.e. the minimum concentration neces-
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sary for complete inhibition of growth. While there are insufficient data to clearly identify the antibacterial activity of all honeys, evidence has been reported of high levels in honey-dew honey from the coniferous forests in mountainous regions of central Europe [75] and in manuka honey (Leptospermum scoparium) from New Zealand [72]. Willix et al. [76] investigated the effectiveness of 26 types of honey against bacterial strains isolated from wounds. They reported that manuka honey exhibited the highest levels of non-penoxic activity. Methylyglyoxal has recently been isolated and shown to be the dominant antibacterial fraction contained in manuka honey [77-79]. Antibiotic-resistant strains have also been investigated and reported to be equally sensitive to honey as the antibiotic-sensitive strains of the same species [60-64]. Wounds infected with MRSA have been freed from infection and healed using honey. These have included leg ulcers [65], cavity wounds resulting from hematomas [80] and surgical wounds [81]. Vancomycin-resistant enterococci (VRE) have also been shown to be sensitive to honey [82-84]. The most frequently isolated bacteria from burns and wounds, S. aureus and P. aeruginosa, are also reported to be sensitive to honey [85,86].

Manuka honey appears to inhibit cell division in MRSA [87]. With P. aeruginosa, however, it destabilizes the cell wall, resulting in lysis [88]. Buckwheat honey has also been reported to cause bacterial DNA degradation in pathogens [89]. As well as inhibiting planktonic bacteria, honey can also prevent biofilms [90,91] developing, for example, on surgical implants and thus leading to prosthesis failure and patient distress. Other bee products have also been shown to have antimicrobial activity. Propolis and the apalbumins in royal jelly have been reported to inhibit bacteria [92]. Propolis also has a synergistic effect with anti-microbial drugs in the treatment of experimentally induced S. aureus keratitis and reduces the resistance of the bacterial cell walls to antibiotics. The effect of propolis on oral Streptococcus mutans also suggests that this might be developed as a cariostatic agent against caries and other infectious diseases of the mouth [93].

CONCLUSION

Natural products may exhibit a wide variation in therapeutic components depending on their origin. The floral source of honey thus plays an important role in its biological properties. It is therefore not improbable that the provenance of honey may determine its antibacterial properties. It is also possible that the mixing of bee products affects their antibacterial activity, since those with lower antibacterial activities may mask the higher antibacterial activity of others. Bee products intended for medicinal purposes have to meet specific criteria. There must be no trace of residual herbicides, pesticides, heavy metals or radioactivity. Sterilization is also essential to prevent secondary infections. The problem of antibiotic residues also needs to be considered. However, antibiotic residues will continue to pose a risk in bee products if producers continue to use antibacterial drugs to control apian diseases. Although the relevant institutions have allowed a maximum residue limit (MRL) for each molecule, consumers prefer honey containing no residues since they regard this as a pure, natural product. Only bee products that are certified as containing no antibiotic residues free should be employed against infections. Quality is also of the greatest importance, no matter which bee product is used for medicinal purposes. Further studies revealing the antibacterial properties of hive products are needed if their use in the clinical management of infections is to be optimized.

Further advances in skin care applications using bee products will emerge from studies investigating ethnopharmacological, chemical and biological activities and the entry into use of chemically modified forms of honey. This will allow novel therapeutic approaches to be validated in clinical trials and permit the formulation of novel ingredients for the exploitation of bee products in an increasingly broad product spectrum. Such innovations will add market value to api products and potentially also assist agricultural economies in developing and underdeveloped countries.

CONFLICT OF INTEREST

Author confirms that the content of this article has no conflict of interest.

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