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Bioactive Compounds from Boney Bee Products: An Overview of Therapeutic Properties

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Abstract

There has been an increasing demand for natural products, particularly the bee products in the Covid-19 pandemic situation. Honeybees produce honey, royal jelly, propolis, bee venom, bee pollen, and beeswax, which potentially benefit to humans. Bee bread and pollen are widely used for apitherapeutic purposes due to the nutritional and medicinal properties. These include about 200 different substances, especially enzymes, free amino acids and vitamins. Clinical standardization of these products is usually hindered due to chemical variability and inconsistency of bee products depending on honeybee and botanical sources. The major bioactive compounds in honeybee products include phenolics, methylglyoxal, royal jelly proteins (MRJPs), and oligosaccharides. Royal jelly consist of antimicrobial jelleins and royalisin peptides, MRJPs, and hydroxy-decenoic acid derivatives, notably 10-hydroxy-2-decenoic acid (10-HDA), which has potent antimicrobial, anti-inflammatory, immunomodulatory, neuromodulatory, metabolic syndrome preventing, and anti-aging activities. Caffeic acid phenethyl ester and artepillin C found in propolis shows good antiviral, immunomodulatory, anti-inflammatory and anticancer effects. The major components of bee venom consists of toxic peptides like melittin (pain-inducing), apamin (SK channel blocking), and phospholipase A2 (allergenic). Bee pollen rich in vitamins, antioxidant and anti-inflammatory plant phenolics. Bee pollen also contains antiatherosclerotic, antidiabetic, and hypoglycemic flavonoids, unsaturated fatty acids, and sterols. Beeswax is pharmaceutical as well as widely used in cosmetics and makeup. Given the importance of drug discovery from natural sources and present Covid-19 pandemic situation, this review is aimed at providing an exhaustive screening of the bioactive compounds detected in honeybee products and of their curative or adverse biological effects.

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Keywords

Bee pollen, Bee venom, Beewax, Honey, Propolis, Royal jelly, Covid-19.

Introduction

Honeybees are social hymenopteran insects belonging to the genus Apis, reared in artificial hives for honey, bee bread, bee venom, bee pollen, propolis and royal jelly (Cornara *et al.*, 2017; Basa *et al.*, 2016; Didaras *et al.*, 2020; Mohammad *et al.*, 2021). Two domesticated species are currently known, i.e., the western *A. mellifera*, native to Europe, Asia and Africa, and introduced into America, and the eastern *A. cerana*, distributed in southern and south-eastern Asia (Moritz *et al.*, 2005; Yadav *et al.*, 2017; Gupta, 2014; Roopa *et al.*, 2020).

Human beings are associated with honey bees from ancient time (Nimmo, 2015; Kuropatnicki *et al.*, 2018;

Cianciosi *et al.,* 2018; Samarghandian *et al.,* 2017; Basa *et al.,* 2016). Honey is a natural sweetener used widely across the world from ancient times (Kuropatnicki *et al.,* 2018; Allsop and Miller, 1996; Cianciosi *et al.,* 2018). It is widely used for various applications including clinical and contains 200 distinct chemical compounds (Rao *et al.,* 2016; Nolan *et al.,* 2019). Honey is viscous in nature and contains fructose and glucose (80-85%), water (15-17%), ash (0.2%), proteins and amino acids (0.1-0.4%) with trace amounts of enzymes, vitamins and phenolic compounds (Ismail, 2017; Rao *et al.,* 2016; Abdallah *et al.,* 2014). The major biological properties of honey includes antioxidant, anti-inflammatory, anti-bacterial, antiviral, anti-ulcer, antihyperlipidemic, antidiabetic and anticancer properties (Erejuwa *et al.,* 2010; Kishore *et al.,* 2011; Viuda-Martos *et al.,* 2008; Rao *et al.,* 2016; Yaghoobi and Kazerouni, 2013; Kumar *et al.,* 2010).

The use of bee products dates to the ancient times where Greeks believed that honey and pollen are the food of kings, maintain vigour and vitality in life (Gupta and Stangaciu, 2014; Rao *et al.,* 2016). The bee pollen is mentioned in the holy scriptures, including the Bible (Kieliszek *et al.,* 2018; Bakour *et al.,* 2017). Many ancient enmities like Hippocrates, Pliny the Elder, and Pythagoras believed that pollen has therapeutic effect (Kuropatnicki *et al.,* 2018; Campos *et al.,* 2020; Çelik and Aşgun, 2020). Bee products in ancient times were considered highly valued products and played a major role in the religious rites (Kieliszek *et al.,* 2018; Bakour *et al.,* 2017). Larger scale use of pollen for human consumption started only after the Second World War, with the evolvement of improved and easily accessible pollen traps (Campos *et al.,* 2010; Kieliszek *et al.,* 2018; Brown, 1989).

Bees and bee keeping in India is not new, and find an important position in religious epics such as Vedas, the Ramayana, the Quran and many other ancient Sanskrit books. The knowledge on bees and honey collection methods has been expanding through generations. During the Vedic period, information's were available on different species of honey bees, types of honey, different habitats, nectar and pollen sources. Honey has been considered as a nutritious food and valuable medicine in Rigveda. In Atharva Veda, honey is placed with honour as a valuable nature's gift to mankind. Information's about honey bees, nesting, stinging behaviours found in ancient post-Vedic literatures like the Brahmanas, Upanishads, Puranas and Ramayana. Susruta, the renowned ancient Indian surgeon highlighted the application of honey in surgery and wound healing, recognising eight varieties of honey depending on the honey bee species.

Although honey and honey bees are known to human beings for long time, collecting honey from wild bee colonies by smoking away the bees and squeezing away combs. In India, the first attempt to keep bees in movable frames and hives were started in 1882 in Bengal followed by Punjab with little success. The history of bee keeping in India dates back to 1910 when Father Rev. Newton in South India devised a hive suitable for *Apis cerena* names as Newton hives. During 1911-1917, he trained many people in South India and helped them to achieve bee keeping as a livelihood option. Travancore state took up bee keeping in 1917 while Mysore in 1925.

During 1928, the royal commission on agriculture recommended bee keeping as a cottage industry and many states like Madras (1931), Punjab (1933), Coorg (1934) and Uttar Pradesh (1938) adopted bee keeping (Abrol, 2013). In 1938, bee keepers of India organized and formed All India Bee keepers association. Indian council of agricultural research established central bee keeping research station in Punjab in 1945 and six years later at Coimbatore (Tamil Nadu), Baptala (Andhra Pradesh) and Sundernagar (Himachal Pradesh). After Independence, Government of India constituted All India Khadi and Village Industries Board for the bee keeping development and later reconstituted as Khadi and Village Industries commission (KVIC).

Today, the use of products of natural origin is gaining much attention among different levels of consumers (Venkatesh, 1995; Skuras and Vakrou, 2002).

The concept of sustainable development of bee products, which could become an alternative to the products already present in the market, is a very important (Huber,2000; Ilbery and Maye, 2005). Modern consumers tends and behaviour shows the need for developing new products and technology based production (Lundvall *et al.,* 1988; Yeung and Morris, 2001; Young *et al.,* 2010). An increase in the environmental awareness and health consciousness of the consumers constitutes the demand for the diversification of many food industries to start the production of organic products (Hughner *et al.,* 2007; Rana and Paul, 2017).

Bee products characterized by wide range of biological properties will definitely satisfy the health promoting search aspects of consumers (Campos *et al.,* 2010; Kieliszek *et al.,* 2018; Brown, 1989).

Bee products

Substances of natural origin with biological activity is always focus a great interest to humans (Kieliszek *et al.*, 2018; Gnat *et al.*, 2020). Due to the powerful healing effects, the bee products fall in this (Campos *et al.*, 2010; Kieliszek *et al.*, 2018; Brown, 1989). The desire and exploration of bee products contributes to the development of apitherapy, over the last three decades, has been the subject of documented scientific research (Lorenz and Stark, 2015; Kieliszek *et al.*, 2018; Velardi *et al.*, 2021). Expanding the knowledge of bee products and their use can be only done with the improved of apiary methods and engagement of people (Vercelli *et al.*, 2021; Jeil *et al.*, 2020; Vazhacharickal and Jose 2016; Vazhacharickal and Jose 2018).

Bee products are multicomponent natural substances including: honey, pollen, bee bread, propolis, royal jelly and bee necessary for the proper course of basic life reactions (Bobis *et al.*, 2010; Kieliszek *et al.*, 2018; Gnat *et al.*, 2020). These include the following: honey, pollen, and extracts derived from it, especially bee bread, propolis, royal jelly, and bee venom. Bee products demonstrate a wide range of healing effects, increase the level of ATP, neutralizing toxins, increase immunity of an organism, and improve the energy balance of tissues. They have active role in protein metabolism, involved in the synthesis of nucleic acids and are essential to the proper functioning of the circulatory system of living organisms (Cornara *et al.*, 2017; Kieliszek *et al.*, 2018; Gnat *et al.*, 2020).

Honey is the main and popular and honeybee product which derives from digestive processing of nectar foraged from flowers, and is stored in honeycomb cells. Honey is widely accepted for its nutritive properties, used in traditional medicine and folk remedy (Molan, 1999; Cornara *et al.*, 2017). Other products derive from honeybee gland secretions and different botanical materials include royal jelly, beeswax, propolis, bee pollen, and bee venom. These products have been used by humans since ancient times for nutritional and curative purposes. Various scientific studies prove therapeutic properties of various bee products and uses as nutraceutical, pharmaceutical and cosmetic ingredients (Viuda-Martos *et al.*, 2008; Burlando and Cornara, 2013; Cornara *et al.*, 2017). The pharmacological and medicinal standardization of these products seems very difficult due to chemical variability, depending on honeybee varieties and botanical sources. Different molecules or classes of compounds have been isolated from bee products and are pharmacologically characterized, suggesting the importance of honeybee products for natural drug discovery (Cornara *et al.*, 2017). Based on above background, this review is aimed to provide a brief illustration of the bioactive compounds detected in honeybee products and of their curative or adverse biological effects.

Honey

Honey is produced by honey bees that collect flower nectar and later process it through repeated digestion and regurgitation (Cornara *et al.*, 2017; Liyanage and Mawatha, 2017; Zafar *et al.*, 2020). The acidic pH in honey bee stomach, together with invertase, diastase and amylase enzymatic activities, give rise to a supersaturated aqueous solution composed by 80% sugars, mainly fructose and glucose, with minor amounts of sucrose, maltose, and other complex sugars (Cornara *et al.*, 2017; Machado De-Melo *et al.*, 2018; Wang and Li,2011). The honey is the major energy source and stored as reserve food for honey bees (Requier *et al.*, 2015; Cornara *et al.*, 2017; Brodschneider and Crailsheim, 2010). Amino acids and peptides are the major nitrogen sources in honey (Lewkowski *et al.*, 2019; Lee *et al.*, 2015; Cornara *et al.*, 2017). Proline is the most abundant amino acid in honey, followed by glutamic acid, alanine, phenylalanine, tyrosine, leucine and isoleucine (Hermosín *et al.*, 2003; Cornara *et al.*, 2017; Sakač *et al.*, 2019). Honey also contains low amounts of protein and the most abundant peptides are defensin-1 and royal jelly protein (MRJP) isoforms (Erban *et al.*, 2019; Cornara *et al.*, 2017; Jamnik *et al.*, 2012). Major enzymes include glucose oxidase, diastase (amylase), α-glucosidase, catalase, and acid phosphatase (Kubota *et al.*, 2004; Di Girolamo *et al.*, 2012; Chua *et al.*, 2015). The protein profile of honey is different due to honey bee diversity, climatic conditions and difference in plant peptides (Bong *et al.*, 2021; Cornara *et al.*, 2017).

Honey has an average pH of 3.9, due to the presence of about 0.57% organic acids, predominantly gluconic acid and citric acid (Serra Bonvehí *et al.*, 2004; Gündoğdu *et al.*, 2019; Cornara *et al.*, 2017). Small amounts of vitamins (vitamin B complex and ascorbic acid) are also present in honey due to the presence of pollen grains (Kitzes *et al.*, 1943; de Arruda *et al.*, 2013; da Silva *et al.*, 2016). Minerals range between 0.04 and 0.2%, with potassium as major element accounting for about one third of total mineral content (da Silva *et al.*, 2016; Nayik and Nanda, 2016; Kek *et al.*, 2017; Cornara *et al.*, 2017).

Honey chemical composition also depend on the botanical species visited by bees and the climate of the area from which nectar is harvested (Cornara *et al.*, 2017; Bong *et al.*, 2021). The most diversified fraction in honey is the Aroma compounds with over 500 volatile compounds in different types of honey (Jasicka-Misiak *et al.*, 2012; Clarke and Ndip, 2011). Phenolics are the most abundant phytochemicals, usually ranging from 50 to 500 mg/kg (Ramanauskiene *et al.*, 2012; da Silva *et al.*, 2016; Cornara *et al.*, 2017).

Antioxidant activity

Phenolics are responsible for the antioxidant capacity of honey and variable with respect to floral origin (Gheldof *et al.*, 2002; Petretto *et al.*, 2015).

Antimicrobial activity

Honey inhibit the growth of various microorganisms, make them a potential candidate in clinical medicine, and marketing of medical grade Manuka honey (Klein *et al.*, 2020; Sarheed and Debe, 2020; Cornara *et al.*, 2017). For this Manuka honey, a scale of antibacterial activity has been defined, known as Unique Manuka Factor (UMF), representing equivalents of a phenol solution yielding a certain inhibition in a radial diffusion assay on *Staphylococcus aureus (*Allen *et al.*, 1991; Kwakman and Zaat, 2012).

The antibacterial factors of honey has been studied by sequential neutralization, which reveals the mechanisms of action are complex and variable (Cornara *et al.*, 2017; Danihlík *et al.*, 2015; Al-Waili *et al.*, 2011). Basic factors that provide antibacterial actions are low water activity and low pH. Glucoseoxidase secreted by bees, which by low dilution converts glucose into H_2O_2 and gluconic acid. Measurements of minimum inhibitory concentration and DNA degradation on *Escherichia coli* and *Bacillus subtilis* suggests the presence of other components in addition to honey H_2O_2concentrations for bacterial growth inhibition (Brudzynski *et al.*, 2011). Two major non-peroxide antibacterial factors are methylglyoxal (MGO) in Manuka honey and defensin-1 in Revamil source (RS) honey with a lower MGO when compared to the former honey. The RS honey is the source product for RevamilR medical grade honey (Kwakman and Zaat, 2012).

Manuka honey is derived from the nectar of the manuka myrtle *Leptospermum scoparium*, growing in southeast Australia and New Zealand. The high amounts of MGO accounts from dihydroxyacetone, present at elevated levels in manuka nectar, through non-enzymatic process during honey storage. Due to the high content of MGO (up to1,500 mg/kg), makes manuka honey an efficient antibacterial agent, including methicillin-resistant *S. aureus (*Mavric *et al.*, 2008; Kwakman *et al.*, 2011).

Defensin-1 is an important immunoactive peptide secreted by the honeybee hypopharyngeal gland which are ultimately mixed with honey. This peptide is responsible for the antibacterial activity against Gram-positive bacteria in RS honey. Studies showed that activity of defensin-1 is enhanced by synergistic interaction with other honey components especially H_2O_2 and MGO on *E. coli* and *P. aeruginosa (*Kwakman and Zaat, 2012).

Defensin-1 and H_2O_2 as major antibacterial factors and responsible for antibacterial mechanisms in RS honey while in manuka honey the antibacterial activity has been derived mainly by MGO (Kwakman *et al.*, 2011). Lack of defensin-1 in manuka would be due to an inactivation of the peptide caused by MGO-induced modifications (Majtan *et al.*, 2012).

Glycoproteins with high-mannose N-glycans are other antibacterial factors isolated from honey and displayed agglutinating and bactericidal activity on different clinical isolates of multi drug resistant strains. Q-TOF-MS analysis has shown extensive homology of these peptides with the MRJP-1 precursor, which harbors three antimicrobial jelleins typical of royal jelly. (Brudzynski and Sjaarda, 2015; Brudzynski *et al.*, 2015).

Fractionation of an n-hexane extract of Citrus gold crest honey has led to the identification of a complex fraction with inhibitory activity against a clarithromycin/ metronidazole resistant *Helicobacter pylori* strain (Manyi-Loh *et al.*, 2012). Honey is also known for antimycotic effects especially against non-pathogenic (*Aureobasidium pullulans* and *Cladosporium cladosporioides*) and pathogenic (*Candida parapsilosis*, *C. tropicalis*, and *Rhodotorula sp*.) (Kuncic *et al.*, 2012; Moussa *et al.*, 2012). Flavonoids like quercetin, kaempferol, chrysin, galangin, and apigenin may beinvolved in honey activity against *C. Albicans (*Candiracci *et al.*, 2011).

Antiparasitic activity

Peptides (2 to 200 kDa) from *Ziziphus sp*. honey have shown antiprotozoal activity against the intestinal

parasite *Giardia lamblia* (Mohammed *et al.,* 2015). In addition, three different honeys from Plectranthus, Ziziphus, and acacia, have been found to possess nematicidal activity against *Caenorhabditis elegans (*Sajid and Azim, 2012).

Anti-inflammatory activity

Honey, containing the flavonoids daidzein, apigenin, genistin, luteolin, kaempferol, quercetin, and chrysin, has inhibited the release of pro-inflammatory TNF-α and IL-1β from LPS stimulated N13 microglia cells (Candiracci *et al.,* 2011). Due to the neuroinflammation properties, honey flavonoid fraction can be used in neurodegenerative diseases like Alzheimer or Parkinson.

Honey proteins shows immunomodulatory effects especially the MRJP-3 has been found to suppress IL-2, IL-4, and IFN-γ production by antigen-stimulated T cells (Okamoto *et al.,* 2003). Glycopeptides and glycoproteins (2 to 450 kDa) isolated from Ziziphus honey, ranging from, have inhibited ROS release by zymosan-activated human neutrophils and murine macrophages, NO production and phagocytosis by LPS-activated murine macrophages, and production of TNF-α by human monocytic cells (Mesaik *et al.,* 2015). The honey protein apalbumin-1, aka MRJP-1, block the mannose receptors of human phagocytic cells and inhibits phagocytosis (Molan and Rhodes, 2015).

Anti-diabetic activity

Honey has potent anti-diabetic activity and reduce blood glucose levels various animal models and in patients with impaired glucose tolerance or diabetes. Fructose is a potential antidiabetic agent, while the presence in honey of a balanced mix of fructose and glucose could play a synergic role in promoting liver glucose metabolism (Erejuwa *et al.,* 2012).

Dietary oligosaccharides, especially fructo-oligosaccharides, galactooligosaccharides, and lactulose, prevent obesity, insulin resistance, and diabetes mellitus, by acting as prebiotics on the intestinal flora. Due to the presence of oligosaccharides, honey shows antidiabetic, antihyperlipidemic and hepatoprotective functions (Erejuwa *et al.,* 2014).

Wound healing

Honey has long been traditionally used for its healing capacity on wounds and burns (Molan, 2006; Vandamme *et al.,* 2013). Revamil R and Surgihoney T M are medical grade honey especially for wound-dressing consisting of engineered honey with enhanced antimicrobial power (Al-Waili *et al.,* 2011).

Antimicrobial activity is considered the most important factor for honey wound healing and specifically act on skin cells (Majtan *et al.,* 2010; Ranzato *et al.,* 2012). The immunomodulatory and immunostimulatory properties of honey promote fast wound healing.

A 5.8 kDa constituent from manuka honey stimulates TNF-α production by macrophages via toll-like receptors (Tonks *et al.,* 2007), while MRJP-1 induces TNF-α and metalloproteinase 9 (MMP-9) expression in keratinocytes (Majtan *et al.,* 2010). Kanuka honey from Kunzea ericoides, a close relative of the manuka myrtle L. scoparium, contains type II arabinogalactans of plant origin that have been shown to promote TNF-α production (Gannabathula *et al.,* 2012). Phenolics from fir honeydew honey inhibit TNF-α-induced MMP-9 production by human keratinocytes, with a possible role for kaempferol and apigenin (Majtan *et al.,* 2013).

Anticancer activity

Inhibitory effects of honey on various kinds of cancer have been studied both in vitro and in animal models (Erejuwa *et al.,* 2014). Polyphenols are known to possess chemopreventive properties, and honey with higher phenolic charge is more potent in inhibiting cancer cell proliferation (Jaganathan and Mandal, 2009). Various polyphenols shows anticancer properties and polyphenols occurring in honey includes caffeic acid and its phenyl esters, caffeoylquinic acid derivatives, rosmarinic acid and derivatives, ellagic acid, as well as the flavonoids chrysin, luteolin, acacetin, fisetin, myricetin, wogonin, apigenin, hesperidin, galangin, quercetin, kaempferol, pinobanksin, and pinocembrin (Jaganathan and Mandal, 2009; Abubakar *et al.,* 2012). A unique trihydroxyketone (E-4- (1,2,4-trihydroxy-2,6,6-trimethylcyclohexyl)-but-3-en-2-one) from thyme honey, endowed with antibacterial activity, has been shown to induce apoptosis on PC-3 prostate cancer cells (Kassi *et al.,* 2014).

Adverse effects

Various occurrences of toxic compounds in honey have been reported, such as polycyclic diterpene grayanotoxins in honey from rhododendron plants like *R. luteum* and *R. ponticum*. It is named as “mad honey”

since it may produce severe neural intoxication up to fatal emergencies. Grayanotoxins are known to affect voltage-dependent Na+ channel gating. Possibly due to this kind of action, and despite its toxicity, mad honey is used as folk medicine for hypertension, sexual dysfunction, and other ailments (Koca and Koca, 2007; Silici and Atayoglu, 2015).

Plants like Boraginaceae, Asteraceae, and Fabaceae produce pyrrolizidine alkaloids that are later converted into harmful pyrrolic metabolites by liver after honey ingestion. The presence of these alkaloids in typical honey botanical sources, make these compounds a potential hazard for honey consumers (Edgar *et al.*, 2002).

Intoxication from honey consumption, characterized by delirium, seizures, and memory loss, have been related to honey contamination by the neurotoxicsesquiterpene lactones tutin and hyenanchin. These oxygenated sesquiterpene picrotoxanes, targeting GABAergic and glycinergic receptors, are ingested by honeybees collecting honeydew produced by passionvine hoppers (*Scolypopa australis*) feeding on sap of the poisonous shrub tutu (*Coriaria spp*.) (Fields *et al.,* 2014; Larsen *et al.,* 2015). Plant secondary metabolites, which are found in honey and could induce deleterious effects to humans, include hyoscyamine and hyoscine from Solanaceae, saponins from Sapindaceae, strychnine and gelsemine from Gelsemiaceae, oleandrin and oleandrigenin from Apocynaceae (Islam *et al.,* 2014).

Besides naturally occurring phytochemicals, honey can also be contaminated by environmental pollutants, like heavy metals, pesticides, and antibiotics. Moreover, prolonged honey storage or heating maygive rise to Maillard reaction products, such as the furans 5-hydroxymethyl furfural from hexoses and furfural from pentoses (Islam *et al.,* 2014).

Royal jelly

Royal jelly is a secreted by honeybee hypopharynx and mandibular salivary glands. It is a white-yellowish, gelatinous, acidic colloidal in nature shows variability according to sources. Royal jelly consist of about 67% water (w/w), 16% sugar, 12.5% protein and amino acids, and 5% fat. Other minor royal jelly constituents include enzymes, vitamins, phenolics, and minerals (Melliou and Chinou, 2005). Dry matter fraction of the royal jelly predominated with proteins, consisting of more than 80% of soluble glycoproteins named major royal jelly proteins (MRJPs), consists of nine members. These proteins shows ancestral resemblances with Yellow protein family genes (Drapeau *et al.,* 2006).

MRJP-1 is the most abundant one occurring in monomeric and oligomeric forms, ranging between 350 and 420 kDa, can be separated into 55 and 5 kDa units, identified as MRJP-1monomers and the 5 kDa protein apisimin. MRJP-2, MRJP-3, MRJP-4 and MRJP-5 glycoproteins ranging between 49 and 80 kDa (Tamura *et al.,* 2009).

The lipid fraction mostly comprises of medium chain fatty acids which are terminally and/or internally hydroxylated, either saturated or monounsaturated at the 2-position. Major constituents are the 10-carbon atoms fatty acids trans-10-hydroxy-2-decenoic acid (10-HDA), 10-hydroxydecanoic acid with minor amounts of sterols (Li *et al.,* 2013).

Royal jelly is fed until the 3rd day of life to larvae developing into female workers and male drones. It is also fed until the end of the larval period to selected individuals developing into queens and depending on the certain like emergency queen rearing. Moreover, it is an exclusive food for adult queens throughout their life (Fujita *et al.,* 2013). The induction of larval development into queen has been ascribed to major royal jelly proteins (MRJPs) and a 57-kDa protein known as royalactin (Kamakura, 2011; Buttstedt *et al.,* 2013).

Royal jelly has been used traditional medicine, especially in Asiatic apitherapy and in the ancient Egypt. It is currently marketed as a functional food and widely used in the pharmaceutical and cosmetic fields. Royal jelly possess good antimicrobial activities against bacteria, fungi, and viruses, with hypotensive, antitumor, anti-hypercholesterolemic, and anti-inflammatory activities in animal models (Ramadan and AlGhamdi, 2012).

Royal jelly also shows good antidiabetic properties, positive effects on benign prostatic hyperplasia, and wound healing of diabetic foot ulcers (Siavash *et al.,* 2015; Khoshpey *et al.,* 2016).

Antioxidant activity

Small peptides consisting of 2–4 amino acid residues have been reported to possess strong antioxidant activity. Tyrosine residues at the C-terminal makes them more active, allowing hydroxyl radical and H_2O_2 scavenging activities (Guo *et al.,* 2009).

Antimicrobial activity

The jelleins are four 8–9 amino acid peptides, of which jellein-I, -II, and -IV are cleavage products of MRJP-1. Jellein-I and -II is effective against the grampositive (*S. aureus*, *S. saprophyticus*, and *B. subtilis*), the gram negative (*E. coli*, *E. cloacae*, *K. pneumoniae*, and *P. aeruginosa*), and the yeast (*C. albicans*) showing broad spectrum activities. The other jelleins, especially jellein-III is less active, and jellein-IV has no antimicrobial effect (Fontana *et al.,* 2004).

Royalisin is a 51 amino acid peptide, homologous to the haemolymph defensin-1, with antibacterial activity against various gram-positive strains (Staphylococcus, Streptococcus, *B. subtilis*, *Micrococcus luteus*, *Sarcina lutea*, Clostridium, Corynebacterium, *Lactobacillus helveticus*, *Paenibacillus larvae*, and Leuconostoc, with no inhibition against the gram negative *E. coli* and *Serratia marcescens*.

Antifungal activity against *Botrytis cinerea* has also been reported for royalisin (Fujiwara *et al.,* 1990; Bachanova *et al.,* 2002). Apalbumin 2a, a variant of MRJP-2 has been found to inhibit the growth of *P. larvae*, *B. subtilis*, and *E. coli* (Bilikova *et al.,* 2009).

Royal jelly carboxylic acids exert antimicrobial properties against gram-positive, gram-negative bacteria, and fungi. 10-HDA has strong antibacterial, especially against *B. subtilis*, *S. aureus*, and *E. coli (*Alreshoodi and Sultanbawa, 2015). It interfere with the adherence to cell surfaces of the oral pathogen *S. mutans*, by interfering with the expression of the glucosyl transferases gtfB and gtfC (Yousefi *et al.,* 2012). Sebacic acid shows strong antifungal activity against *C. albicans*, *C. tropicalis*, and *C. glabrata (*Melliou and Chinou, 2005).

Anti-inflammatory activity

Animal model studies showed that royal jelly potential for digestive trait diseases and 10- HDA protect gastric ulcer (Fang *et al.,* 1994). 10-HDA anti-inflammatory mechanism is due to the inhibition of LPS induced NF-κB activation observed in the murine macrophage cell line RAW264 (Sugiyama *et al.,* 2012).

10-HDA and 4-hydroperoxy-2-decenoic acid ethyl ester have therapeutic potential against atherosclerosis due to inhibition of histone deacetylase activity, thereby enhancing the expression of extracellular SOD release by leukaemia THP-1 cells (Makino *et al.,* 2016).Modifications of histone acetylation have also emerged from a study showing 10-HDA inhibition of fibroblast-like synoviocytes from rheumatoid arthritis patients, suggesting potential therapeutic effects against chronic inflammation degenerative disease (Wang *et al.,* 2015).

Immunomodulatory activity

Royal jelly shows immunomodulatory properties, monomeric and oligomeric MRJP-1, have been reported to stimulate the proliferation of in vitro cultured hepatocytes and monocytes (Kamakura *et al.,* 2001; Kimura *et al.,* 2003).

MRJP-1 and MRJP-2 have been found to exert immunostimulatory and proinflammatory activities by stimulating cytokine release, especially TNF-α, from macrophages (Simuth *et al.,* 2004; Majtan *et al.,* 2006). MRJP-3 suppress interleukin production by T cells both in vitro and in vivo, showing antiallergic properties (Okamoto *et al.,* 2003).

Immunomodulatory activities of 10-HDA, includes reduced T cell proliferation, inhibition of interleukin-12 production by spleen dendritic cells, and block of LPS- and IFN-β-induced NO production in macrophages (Gasic *et al.,* 2007; Sugiyama *et al.,* 2013).

Hydroxyl fatty acid, 3,10-dihydroxydecanoic acid, stimulate the maturation of human monocyte derived dendritic cells and their Th1 polarizing capability make them effective in antitumour and antiviral immunity (Dzopalic *et al.,* 2011). The immunomodulatory properties of royal jelly lipids suggest their possible use in interventions on autoimmune diseases.

Metabolic syndrome preventing activity

The royal jelly proteins especially MRJP-1, MRJP-2, and MRJP-3 have been shown to possess bile acid-binding properties with MRJP-1 most active (Kashima *et al.,* 2014). Royal jelly has antihypertensive mechanisms, MRJP-1 has been transfected into vascular smooth muscle cells, leading to a reduction of contraction, migration and proliferation (Fan *et al.,* 2016).

10-HDA enhances insulin-independent muscle glucose uptake via AMP-activated protein kinase activation and GLUT4 translocation to the plasma membrane and improve hyperlipidemic condition in animal models (Takikawa *et al.,* 2013; Xu *et al.,* 2002).

Anti-ageing activity

Royal jelly extend the lifespan of honeybees especially in the case of queendue to royalactin. Similar effects observed in other insect species, like *Drosophila melanogaster*, as well as in non-insect species, like the nematode *C. Elegans (*Detienne *et al.*, 2014).10- HDA has been found to increase longevity and confer thermal and oxidative stress tolerance to *C. elegans*, by dietary restriction and TOR kinase signalling (Honda *et al.*, 2015). Royal jelly has estrogen-like effects, which in different studies have been ascribed to the ability of different lipids to act as weak activators of estrogen receptors. These constituents include 10-HDA, trans-2-decenoic, 10-hydroxydecanoic, 3,10- dihydroxydecanoic, and sebacic acids, and steroid 24-methylenecholesterol suggests pharmacological basis for an anti-menopause use of royal jelly (Suzuki *et al.*, 2008; Moutsatsou *et al.*, 2010).

10-HDA promote collagen synthesis and production of the collagen promoting factor, transforming growth factor β1, in human skin fibroblasts make royal jelly to protect skin against UVB induced photoaging (Koya-Miyata *et al.*, 2004; Park *et al.*, 2011). In addition to promoting collagen synthesis, 10-HDA has been found to inhibit the release of the MMP-1 and MMP-3 from rheumatoid arthritis synovial fibroblasts (Yang *et al.*, 2010; Wang *et al.*, 2012). 10-HDA also prevented UVA-induced JNK/p38 activation and MMP-1 and MMP-3 upregulation in fibroblasts capable of skin dermal protection and antirheumatoid activity (Zheng *et al.*, 2013).

Synthetic 10- HDA counterpart, known as HydroxydecineR, activate keratinocyte differentiation in vitro, restore skin barrier function, and to improve UV-induced xerosis in humans (Duplan *et al.*, 2011).

Neuromodulatory activity

10-HDA and 10-hydroxydecanoic acid have been shown to act as potent agonists of the human TRPA1 and TRPV1 receptors (Terada *et al.*, 2011). Docosahexaenoic acid is essential for brain development and function and has shown positive effects in a rat Parkinson's model (Hattori *et al.*, 2007).

Neurogenerative potentials of royal jelly fatty acids especially 2-decenoic acid ethyl ester, a derivative of the royal jelly 2-decenoic acid, has promoted functional recovery in a rat model of spinal cord injury (Hirakawa *et al.*, 2010).

Adverse effects

Environmental contaminants can also reduce the quality of royal jelly especially pesticides belonging to organochlorines, organophosphorus, carbamates and the highly toxic, zero-tolerance chloramphenicol (Bogdanov, 2006). Consumption of royal jelly occasionally lead to contact dermatitis, asthma and anaphylaxis due the presence of MRJP-1 and MRJP-2 as major allergens (Rosmilah *et al.*, 2008).

Propolis

Propolis is a resinous substance that foraging bees produce by collecting resin from buds and other plant tissues and then mixing it with wax and pollen to have a malleable, compact substance that they use as hive repairing material and sanitizer (Sun *et al.*, 2015). The chemical composition of propolis is usually dependent on honey bee species, geographical and floral origins. Raw propolis generally contains more than 300 different compounds, mostly consisting of triterpenes (50% w/w), waxes (25–30%), volatile mono- and sesquiterpenes (8–12%) and phenolics (5–10%) (Huang *et al.*, 2014). Volatile mono- and sesquiterpenes gives propolis its typical resinous odor. European and Asian propolis contain simple phenolic acids (Bankova *et al.*, 2002), while lignin'saremain compounds in tropical propolis (Petrova *et al.*, 2010). Caffeic acid phenethyl ester (CAPE) is found in European, Asian and American propolis (Omene *et al.*, 2013). Brazilian green propolis is characterized by the presence of the 3,5-diprenyl-4-hydroxycinnamic acid artepillin C, together with other prenylated cinnamic acids and caffeic acid derivatives (Marcucci *et al.*, 2001). In addition to this, propolis common constituents include organic acids, ketones, aldehydes, hydrocarbons, and minerals (Wagh, 2013).

Antioxidant activity

Propolis is the bee product containing the Due to the presence of high amount of phenolics in propolis, it is widely studied for antioxidant and radical scavenging activities (Viuda-Martos *et al.*, 2008). The components of proplis possess strong antioxidant and antiradicalic activities, especially pinocembrin, chrysin, and pinobanksin (Sun *et al.*, 2015). In DPPH and ORAC tests, pinobanksin-3-acetate has been indicated as the strongest antioxidant constituent (Boisard *et al.*, 2014).

Antimicrobial activity

The propolis shows potent antimicrobial activity against Gram positive and negative strains which has been demonstrated in clinical, in vivo, and in vitro studies (Noronha *et al.,* 2014). The sensitive strains include MRSA, VRE, Streptococcus species, and *H. pylori (*Kosalec *et al.,* 2005; Coelho *et al.,* 2007).

Flavonoids especially galangin, pinocembrin, rutin, quercetin, and naringenin increase bacterial membrane permeability and responsible for the antibacterial properties of propolis (Stepanovic *et al.,* 2003). Galangin and pinocembrin inhibit bacterial RNA polymerase (Speciale *et al.,* 2006). The antimicrobial activity of Brazilian red propolis depend on its peculiar content in isoflavones (Freires *et al.,* 2016).

Antibacterial effectiveness has been demonstrated for different propolis volatile fractions, including β-eudesmol and δ-cadinene in Bulgarian propolis, α-pinene and transβ-terpineol in Greek propolis, β-eudesmol and benzyl benzoate in Hungarian propolis, nerolidol, spatulenol and ledol in Canary Island propolis, and farnesol, dihydroeudesmol and guaiolin Polish propolis (Bankova *et al.,* 2014). The antibacterial activity of Brazilian propolis has been demonstrated for its volatile fractions containing nerolidol, spatulenol, p-cimen-8-ol, ethylphenol, β-caryophyllene, acetophenone, α-pinene, β-pinene and limonene (Bankova *et al.,* 2014).

Propolis possess antifungal activity against pathogenic yeasts like *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata (*Al-Waili *et al.,* 2012; Mutlu Sariguzel *et al.,* 2016). Volatile compounds from Brazilian propolis, viz. α-pinene, β-pinene and δ-cadinene, and from Turkish propolis, viz. phenyl-, ethyl-, and benzylalcohol, and decanal also showed antifungal activity (Ioshida *et al.,* 2010). Iranian propolis ethanolic extracts shows strong anti-*C. albicans* activity due to inhibition of germ tube development by phenolic, aromatic, and aliphatic acids (Haghdoost *et al.,* 2016). Ethanolic extract containing CAPE and other caffeic acid derivatives has been effective against *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*, with an MFC of 125-500 mg/L, while red Brazilian propolis richin triterpenes and isoflavones, such as medicarpin, vestitol and formononetin, has shown the same MFC range (Freires *et al.,* 2016).

Antiviral activity

Propolis has good antiviral activity, which in some cases can exceed that of standard drugs due to the presence of CAPE and related compounds. An ointment containing Canadian propolis has produced better results than acyclovir or placebo in the clinical treatment of genital herpes simplex (Vynograd *et al.,* 2000). CAPE has been found to inhibit the activity of HIV-1 by acting on viral integrase (Costi *et al.,* 2004), and to suppress hepatitis C virus replication in vitro (Zhang *et al.,* 2003). Turkish Hatay propolis containing caffeic acid derivatives has been effective on herpes simplex virus 1 and 2 (Yildirim *et al.,* 2016). 3,4-Dicaffeoylquinic acid, a major constituent of Brazilian green propolis, has repressed influenza A virus in mice by upregulating the TNF related, apoptosis-inducing ligand (TRAIL) (Takemura *et al.,* 2012).

Immunomodulatory activity

The extent of antimicrobial and antiviral activities of propolis could be better explained due to its modulation of immune responses (Orsi *et al.,* 2000). Brazilian green propolis standardized in 18.9% w/w polyphenols, 9.85% flavonoids and 2.3 artepillin C, administered to old mice, has enhanced phagocytosis, production of antibodies against sheep erythrocytes, and ear swelling (Gao *et al.,* 2014).Brazilian green propolis and artepillin C have both inhibited in vitro alloreactive CD4+ T cell responses, together with the expression of IL-2, IL-17, and IFN-γ (Wang *et al.,* 2010).

Anti-inflammatory activity

Studies showed that anti-inflammatory properties of propolis, possibly linked to the presence of phenolic acids. CAPE is a strong anti-inflammatory constituent, able to specifically target NF-κB signalling (Armutcu *et al.,* 2015), modulate ERK MAPK signalling in T cells and mastocytes (Cho *et al.,*2014), and to regulate PI3K/Akt pathway in different human cell lines (Li *et al.,* 2017). Major downstream effects of these anti-inflammatory mechanisms may include the down regulation of key inflammatory enzymes, like xanthine oxidase, cyclooxygenase, matrix metalloproteinases, and inducible nitric oxide synthase (Armutcu *et al.,* 2015; Li *et al.,* 2017).

Anti-inflammatory properties of propolis are widely commercialized in mouthwash products. Antigingivitis activity has been ascribed to phenolics, especially CAPE (Li *et al.,* 2017). Mouth rinse products containing Brazilian green propolis rich in artepillin C have

alleviated gingivitis to the same extent of aNaF/cetylpyridinium chloride rinse or a chlorhexidine solution (Bretz *et al.,* 2014).

Propolis is widely used in cosmetics and skin lotions by topical application. Australian and Romanian propolis have induced photoprotective effects on animal models, possibly due to the anti-UV properties of polyphenols (Cole *et al.,* 2010; Bolfa *et al.,* 2013).

Wound healing and skin protection

Animal models and clinical trials have shown the healing effect of propolis on diabetic foot ulcers and other problematic tissue injuries (Henshaw *et al.,* 2014; Abu-Seida, 2015). Propolis wound healing activities are enhanced by the immunomodulatory, antioxidant and antiseptic effects due to phytocomplex diversity (Martinotti and Ranzato, 2015). Propolis modulates fibronectin expression and collagen I and III deposition in burns (Olczyk *et al.,* 2013). Indian propolis containing flavonoids, phenolic acids and terpenes, topically applied to rats with excision wounds, has upregulated hydroxyproline, hexosamine, uronic acid, nucleic acids and protein levels in wounded tissue, similar to the effect of nitrofurazone (Iyyam Pillai *et al.,* 2010). Brazilian green propolis rich in artepillin C has found superior wound healing activity with respect to Brazilian red propolis (Batista *et al.,* 2012).

Anticancer activity

Propolis shows good anticancer effects in various animal models. Propolis from Aydin, Turkey, rich in CAPE and flavonoids, has shown a concentration-dependent apoptotic effect on CCRFSB lymphoblastic leukemic cells involving the modulation of different miRNA expressions (Yilmaz *et al.,* 2016). New Zealand propolis and its constituents chrysin, galangin, CAPE, benzyl ferulate, benzyl isoferulate, pinostrobin, 5-phenylpenta-2,4-dienoic acid, and tectochrysin, have exhibited antiproliferative effects on DLD-1 colon cancer, HCT-116 colon carcinoma, KYSE-30 oesophageal squamous cancer, and NCI-N87 gastric carcinoma cells (Catchpole *et al.,* 2015). Polish propolis rich in phenolic acids and flavonoids possess dose dependent antiproliferative and proapoptotic activities on HCT 116 colon cancer and Me45 malignant melanoma cells (Kubina *et al.,* 2015). Various mechanisms of action have been disclosed for CAPE, especially suppression of tyrosine kinase activity and induction of cell cycle arrest in G1 or G2/M phase (Patel, 2016), block of migration and invasiveness through Wnt inhibition and ROR2 upregulation (Tseng *et al.,* 2016), voltage-gated sodium channel block leading to reduction of breast cancer cell motility and invasiveness (Fraser *et al.,* 2016), and selective inhibition of cancerous cell viability (Kuo *et al.,* 2015).

The flavone chrysin in propolis has exerted an antiproliferative effect on human Hep-3B, TCC, A549, HeLa, and colorectal cancer cells (Patel, 2016), while possible mechanisms of action include TRAIL-induced caspase activation and STAT3 inhibition (Lirdprapamongkol *et al.,* 2013), as well as p38 and Baxactivation (Pichichero *et al.,* 2011). Artepillin C induces an antiproliferative effect on prostate cancer cells by reducing TRAIL resistance and inhibiting NF-κB, while a proapoptotic effect of galangin has been related to the induction of MAPK phosphorylation (Zhang *et al.,* 2013).

Pinobanksin, pinobanksin-3-O-propanoate, pinobanksin-3-O-butyrate and pinobanksin-3-O-pentanoate exert an antiproliferative effect on M12.C3.F6 B-cell lymphoma cancer cell line by inducing loss of mitochondrial membrane potential and activating caspases 3, 8 and 9 (Alday *et al.,* 2015). Phenolic lipids cardanol and cardol extracted from Thai propolis showed antiproliferative effects on several human cancer cells (Teerasripreecha *et al.,* 2012), while cardanol has also induced apoptosis in BT-474 breast cancer cells, upregulated p21, stimulated ERK, p38 and JNK phosphorylation, and down regulated cyclin D (Buahorm *et al.,* 2015). Finally, the polycyclic, polyisoprenylated benzophenone nemorosone from Cuban propolis has shown anticancer effects on estrogenreceptor-positive MCF-7 cells by blocking cell cycle in G0/G1, and reducing MAPK and Akt phosphorylation (Popolo *et al.,* 2011).

Adverse effects

Clinical and in vivo studies have reported that propolis is well tolerated and non-toxic on many animal models. The No Observed Adverse Effect Level (NOAEL) on mice and rats is over 1,470 mg/Kg/day at 60 days, and over 2,470 mg/Kg/day at 90 days (Burdock, 1998).

In humans, toxic effects occur at dosages as high as 15 g/die (Castaldo and Capasso, 2002). Propolis can cause common allergic reactions especially 1.2–6.6% of patients with dermatitis are sensitive to propolis (Walgrave *et al.,* 2005; Burdock, 1998).

Bee venom

Bee venom, also known as apitoxin, is a complex fluid secreted by the bee venom gland located in the abdominal cavity and injected into victims by a stinger, causing local inflammation and swelling, anticoagulant effect, and immune response. Stingless bees does not have sting and venom. Bee venom constituents include amphipathic polycationic peptides, of which major ones are melittin and apamin, enzymes such as phospholipase A2, and low-molecular weight compounds including active bioamines such as histamine and catecholamines (Lee *et al.*, 2016).

The bee venom has been traditionally used in acupuncture and apitherapy asanalgesic, against chronic pain and inflammation, and for otherpurposes such as immunotherapy and Parkinson's treatment. Bee venom shows anticancer effects, antimutagenic, antinociceptive, and radioprotective properties (Moreno and Giralt, 2015; Sobral *et al.*, 2016). However, different bee venom constituents are allergenic especially in hypersensitive people and can cause fatal outcome (Gelder *et al.*, 1996).

Melittin

Melittin is a peptide of 26 amino acid residues, with hydrophobic N-terminus and a hydrophilic C-terminus. The toxicity mechanism consists in the disruption of phospholipid bilayers, leading to cell lysis and the release of tissue injurious compounds such as lysosomal enzymes, serotonin, and histamine, triggering inflammation and pain (Raghuraman and Chattopadhyay, 2007). Hyaluronidase and phospholipase A2 act simultaneously with melittin and cause venom allergenic properties. The major cause of pain induction by the bee venom, through activation of TRPV receptors and release of algogens from injured cells (Chen *et al.*, 2016). Despite of its toxicity, melittin is known as a traditional anti-inflammatory remedy for various diseases, especially dermatitis, neuritis, liver inflammation, atherosclerosis, and arthritis (Lee and Bae, 2016). The anti-atherosclerotic effects of melittin consists in the inhibition of vascular smooth muscle proliferation through the hindrance of platelet-derived growth factor beta-receptor signalling (Son *et al.*, 2007).

Methicillin can interact with biological membranes confers strong antimicrobial properties to against human pathogens, such as methicillin resistant *S. aureus* (Choi *et al.*, 2015), as well as plant pathogens (Stockwell and Duffy, 2012). Melittin shows anticancer activities (Gajskiand Garaj-Vrhovac, 2013), induces apoptosis in human ovarian cancer cells, SKOV3 and PA-1, by increasing the expression levels of the DR3, DR4, and DR6 death receptors (Jo *et al.*, 2012). Despite many indications of possible therapeutic applications of melittin, in vivo injection is known to entails side effects like hemolysis and liver injury, which have stimulated studies for the development of non-toxic hybrid derivatives. Engineered melittin peptides developed for different biotechnological applications especially to enhance antimicrobial properties or promote siRNA release from endosomes into target cells (Moreno and Giralt, 2015).

Apamin

Apamin is a 18 amino acids peptide, tightly cross-linked by the presence of two disulphide bonds (Habermann, 1984). It has a specific toxicity mechanism, consisting in a block of small conductance Ca2+-dependent K+ channels (SK channels)expressed in the central nervous system and in other districts, like the cardiovascular system and smooth muscle (Adelman *et al.*, 2012).

Due to selective targeting SK channels, apamin has been used as a tool for the physiological characterizations of this kind of K+ conductance and facilitates learning and memory (Castle *et al.*, 1989). Apamin can cross the blood-brain barrier, and its administration to animalsimproves cognitive deficits, suggesting that SK channels would be appropriate apamin targets in the treatment of these neural disorders and as a blood-brain barrier, drug-delivery shuttles (Deschaux and Bizot, 2005; Brennan *et al.*, 2008; Oller-Salvia *et al.*, 2013).

SK channels are known to be involved in the pathogenesis of Parkinson's disease and neuro-therapeutic uses of apamin derives from its ability of protecting dopaminergic neurons from degeneration in experimental models of Parkinson's (Alvarez Fischer *et al.*, 2013). Apamin shows antiatherosclerotic effects in mice (Kim *et al.*, 2012), while as a K+ channel blocker, apamin can be useful for long-term whole blood storage.

Phoshpholipase A2

Phospholipase A2 (PLA2) hydrolyzes complex lipids to produce a fatty acid and various reaction products, including lysophosphatidic acid, lysophosphatidylcholine, and sphingosine phosphate.

Fig.1 Description of the different honeybees identified in Bengaluru a) Rockbees; *Apis dorsata* b) *Apis florea* comb showing the brood; c) *Apis florea* brood showing honey storage area; d) *Apis dorsata* worker bee e) *Apis florea* worker bee f) *Apis cerena* colony showing brood and stored honey and pollen g) *Apis mellifera* collecting pollen and nectar.

Fig.2 Stingless bees (*Tetragonula iridipennis*) stored pollen.

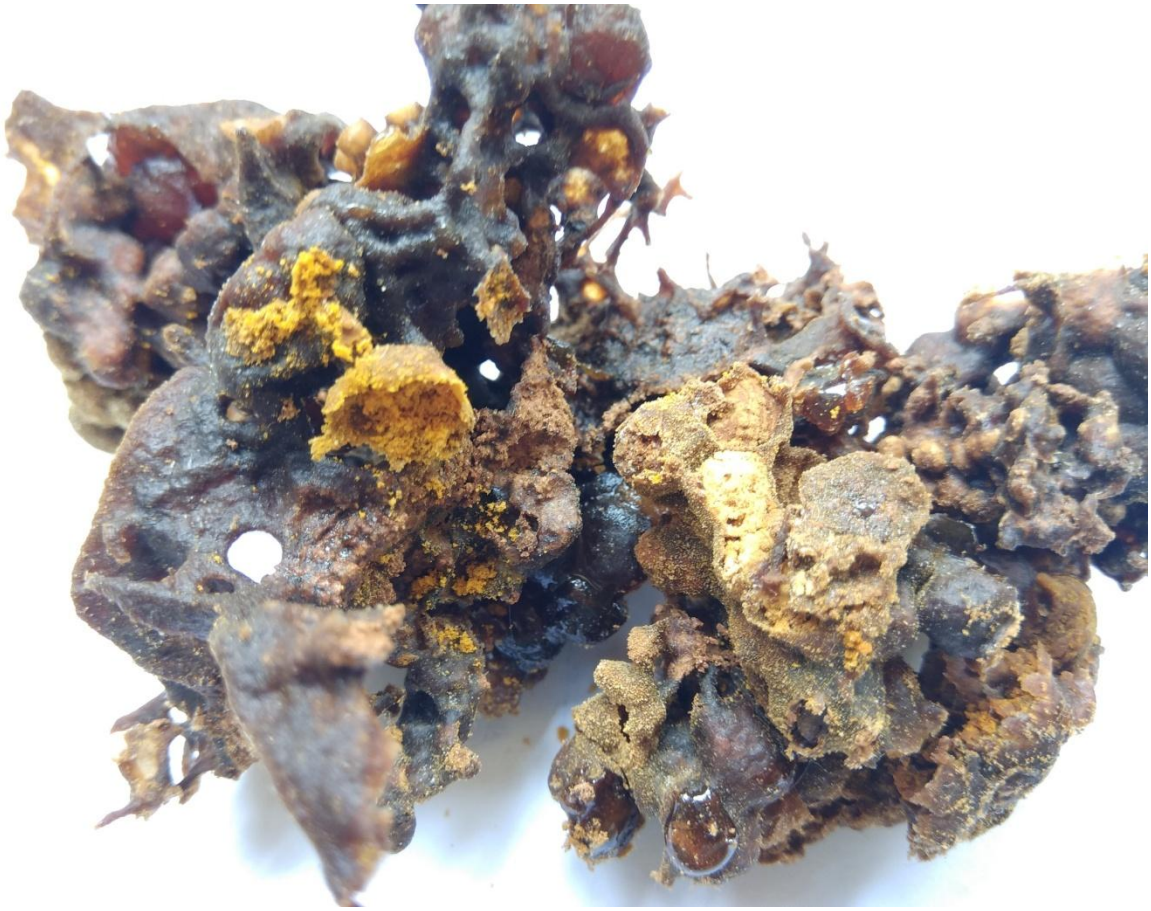


Fig.3 The process of making bee bread by the honey bees.

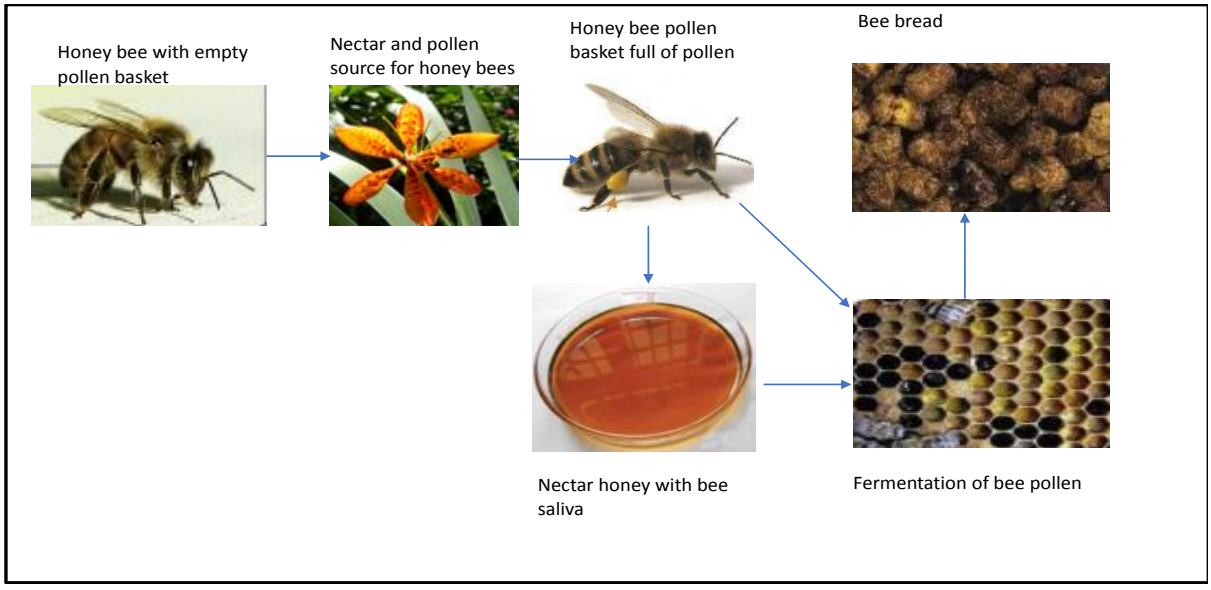


Fig.4 The chemical structure of flavonoids most commonly found in pollen and bee bread; a) Kaempferol, b) Quercetins, c) Chlorogenic acid, d) Tetrahydrocannabinol.

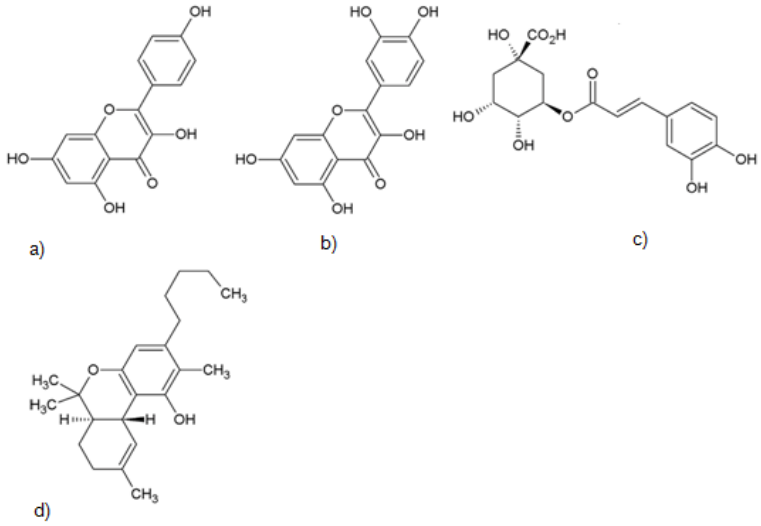


Fig.5 The bee bread. Adapted from Kieliszek *et al.*, 2017.

Fig.6 Schematic representation of the therapeutic effects of honey. Adapted from Rao *et al.*, 2016.

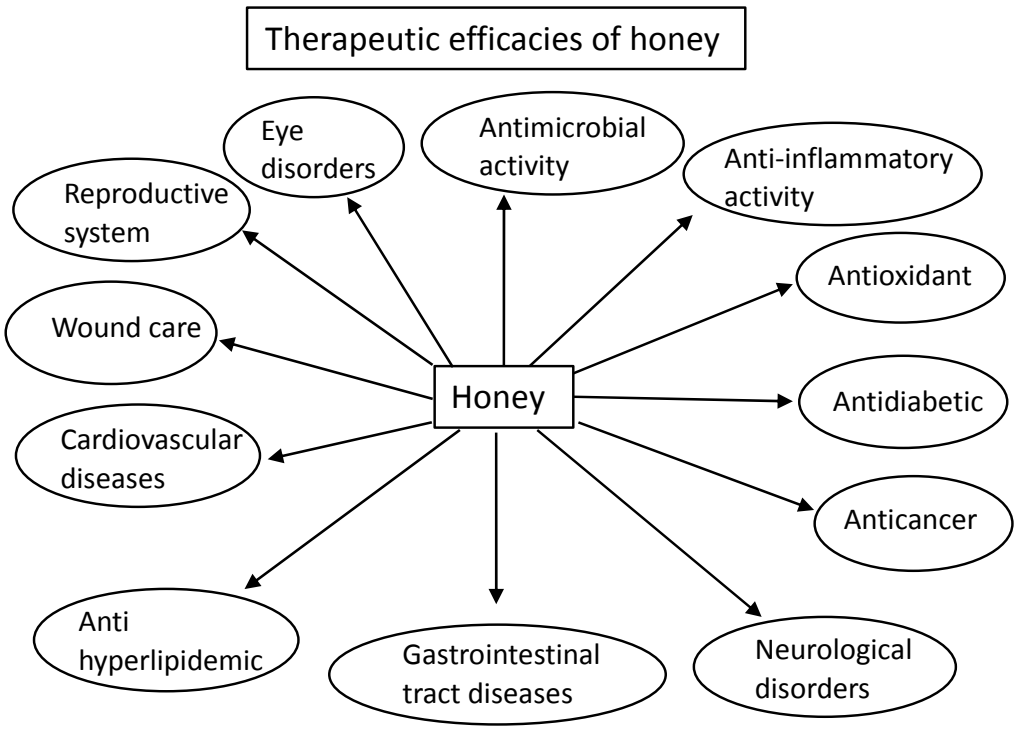
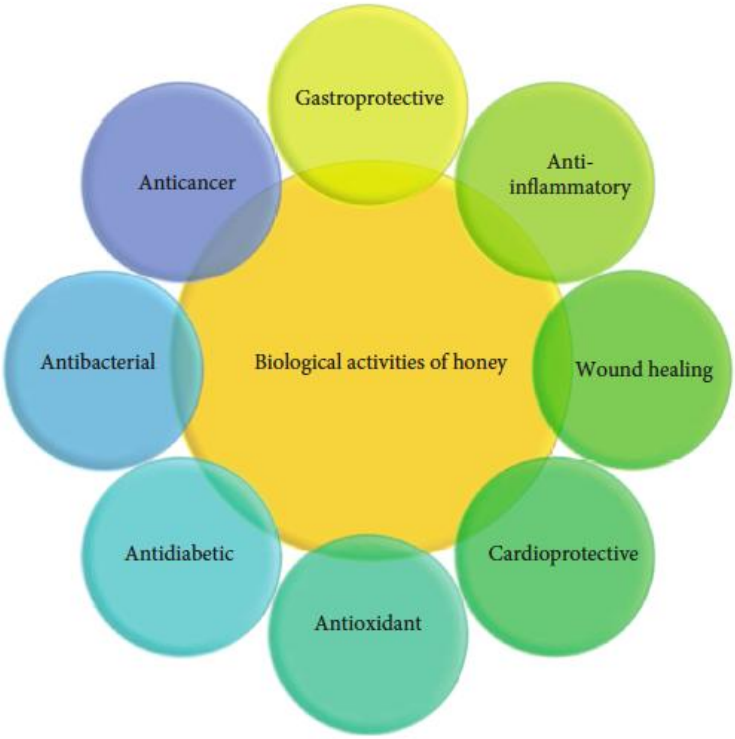


Fig.7 Various types of biological activities of honey products. Adapted from Pasupuleti *et al.*, 2017.



These compounds exert cytotoxic and immunostimulatory effects on various cell types, eventually triggering immune responses and inflammation. Phospholipase A2 is the major allergen of bee venom, containing three peptide and one glycopeptide T cell epitopes recognized by allergic and non-allergic subjects (Dhillon *et al.,* 1992; Okano *et al.,* 1999). PLA2 has exerted neuroprotective effects in a mouse model of Parkinson's disease by activating regulatory T lymphocytes (Chung *et al.,* 2015). Systemic PLA2 administration in animal models has alleviated cold and mechanical allodynia through the activation of α2-adrenegic receptors (Li *et al.,* 2015). PLA2 works cooperatively with phosphatidylinositol- (3,4)-bisphosphate in inducing in vitro lysis of different tumor cell lines (Putz *et al.,* 2006).

Minor peptides and enzymes

The second major allergen of honeybee venom is hyaluronidase (Padavattan *et al.,* 2007), while other allergenic peptides include icarapin isolated from *A. cerana* (Wong *et al.,* 2012), and two serine proteases named Api SI and Api SII belonging to the prophenoloxidase activating factor II family (Georgieva *et al.,* 2011). Aserine protease enzyme, named Bi-VSP, has a dual behavior, since in arthropods it triggers the phenoloxidase cascade inducing a lethal immune response, while in mammals it acts as a toxic thrombin-like and plasmin-like fibrinolytic protease (Choo *et al.,* 2010).

Secapin is a serine protease inhibitor-like peptide exerting anti-fibrinolytic and anti-elastolytic activities, and also displaying antimicrobial properties by binding to the surfaces of fungi and bacteria (Lee *et al.,* 2016). Inhibitor cysteine knot (ICK) peptide and a Kazal-type serine protease inhibitor isolated from *A. cerana* venom, have been shown to act as antibacterial, antifungal and insecticidal venom toxins (Kim *et al.,* 2013; Park *et al.,* 2014).

Tertiapin is a 21 amino acid neurotoxin blocking inward rectifier K+ channels expressed in epithelial cells, heart, and central nervous system. In the heart, tertiapin contrasts G-protein-gated, acetylcholine-activated K+ current that mediate parasympathetic heart rate decrease and K+ channel modulation (Drici *et al.,* 2000).

Mast cell degranulating (MCD) peptide is a 22-amino acid peptide similar to apamin with two disulfide bridges, with different mechanisms of action.MCD at low concentrations induces mast cell degranulation through histamine release, while at higher concentrations it can produce anti-inflammatory effects (Buku, 1999). MCD also acts as a neurotoxin by blocking fast-inactivating (A-type) and slow-inactivating (delayed rectifier) K+ channels, thereby increasing neuronal excitability (Mourre *et al.,* 1997).

Bee pollen

Pollen is often regarded as "the world's best food product" (Bobis *et al.,* 2010). Global production of the pollen is around 1500 tons per year. The largest producers are China, Australia, and Argentina (Estevinho *et al.,* 2011). Foraging bees collect pollen from flowers bring pollen back to the hive where it is packed into pellets and stored. During this process, the pollen mixed with nectar and bee salivary secretions becomes the "bee bread," representing a main food reserve for the hive colony (Almeida-Muradian *et al.,* 2005).

Bee pollen consist of carbohydrates, proteins and amino acids, lipids and fatty acids, phenolics, enzymes and coenzymes, vitamins and minerals (Komosinska-Vassev *et al.,* 2015). Chemical composition of bee pollen is highly variable, depending on plant source, geographical region, and climatic conditions, thus deeply affecting biological properties and therapeutic virtues (Denisow and Denisow-Pietrzyk, 2016).Bee pollen is widely used as an energy food in humans diet supplement and for the conditioning of athletes. The high content of protein, fat, and minerals (particularly Ca, Mg, Fe, and P) gives bee pollen a nutritional value identical to, or higher than, that of dried legumes. Among vitamins, the levels of pantothenic and nicotinic acids are close to those of beef, ascorbic acid is similar to that of vegetables, such as lettuce and tomatoes, and riboflavin is comparable to that of skimmed milk power (Linskens and Jorde, 1997).

Bee pollen is used in complementary and alternative medicine to cure prostatitis, stomach ulcers, infectious diseases, and for the prevention and treatment of high altitude-sickness syndrome (Linskens and Jorde, 1997).Bee pollen shows a wide range of therapeutic properties, including antimicrobic, antioxidant, hepatoprotective, chemopreventive and anticarcinogenic, antiatherosclerotic, anti-inflammatory, antiallergenic, and immunomodulatory activities (Komosinska-Vassev *et al.,* 2015; Denisow and Denisow-Pietrzyk, 2016).

Antioxidant activity

The antioxidant activity of bee pollen seems to be mainly due to phenolic acids (vanillic, protocatechuic, gallic, and p-coumaric acids) and to flavonoids (hesperidin, rutin, kaempferol, apigenin, luteolin, quercetin, and isorhamnetin). These compounds are thought to inactivate electrophiles and scavenge free radicals and reactive oxygen species (Bonvehí *et al.*, 2001; Pascoal *et al.*, 2014).

Antimicrobial activity

Antimicrobial effects of bee pollen, possibly mediated by glucose oxidase activity, deriving from honeybee secretion, as well as plant phenolics and flavonoids (Denisow and Denisow-Pietrzyk, 2016; Fatrcova-Sramkova *et al.*, 2016). Phenolic compounds from bee pollen extracts is effective against Gram-positive and Gram-negative pathogenic bacteria, microscopic fungi and yeasts (Baltrušaityte *et al.*, 2007; Kacániová *et al.*, 2012).

Anti-inflammatory activity

Bee pollen exerts anti-inflammatory effects that have been compared to those of common non-steroidal anti-inflammatory drugs due to the activity of flavonoids, phenolic acids, phytosterols, and flavoring substances like anethole, an inhibitor of the NF-KB pathway (Middleton, 1998; Choi, 2007). Specific effects include the capability of removing swellings caused by cardiovascular and renal pathologies (Yakusheva, 2010), protect the liver from carbon tetrachloride-induced damages (Yildiz *et al.*, 2013), and of alleviating prostate inflammation and hyperplasia (Yakusheva, 2010). Positive effects on prostatic conditions have been also ascribed to antiandrogen actions (Rzepecka-Stojko *et al.*, 2012).

Anticancer activity

Studies showed potential anticancer activity of bee pollen, probably associated with antioxidant and antimutagenic potentials (Denisow and Denisow-Pietrzyk, 2016). The steroid fraction of chloroform extract from *Brassica campestris* bee pollen showed strong cytotoxicity on human prostate cancer PC-3 cells, associated to stimulation of TNF-α secretion and apoptosis induction (Wu and Lou, 2007).

Honey bee products possesses numerous biological, biochemical and physiological activities in animals as well as in humans. The efficacy and properties depends on the types of phenolic com-pounds present in these bee products. Honey bee products have been investigated for their antimicrobial, anticancer, antidiabetic, anti-hypercholesterolemic, anti-inflammatory, antioxidant, and wound healing properties. Beebread and pollen contain the nutrients well absorbed by humans. Thus, they allow in supplementing nutritional deficiencies, as well as better adaptation of an organism to adverse environmental conditions, improving the physical and mental state. Given the importance of drug discovery from natural sources and present Covid-19 pandemic situation, this review is aimed at providing an exhaustive screening of the bioactive compounds detected in honeybee products and of their curative or adverse biological effects.

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