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Revisión | Review

Composition, biological activity and toxicity of bee pollen: State of the art

[Composición, actividad biológica y toxicidad del polen apícola: Estado-del-arte]

Louise CF Saraiva[1], Francisco VM Cunha[2], Daniel ROD Léllis[3] & Lívio CC Nunes[1]

[1]*Programa de Pós-Graduação em Ciências Farmacêuticas, Universidade Federal do Piauí (UFPI), Teresina, PI, Brasil*
[2]*Rede Nordeste de Biotecnologia, Universidade Federal do Piauí (UFPI), Teresina, PI, Brasil*
[3]*Departamento de Farmácia, Universidade Federal do Piauí (UFPI), Teresina, PI, Brasil*
Contactos | Contacts: **Louise CF SARAIVA** - ***E-mail address:*** **louise_fsaraiva@hotmail.com**

Abstract: A research was conducted in scientific databases using keywords related to the composition, biological activity and toxicity of bee pollen from 2007 to July 2017. It was verified that this product is rich in carbohydrates, proteins and lipids, as well as various minerals and phenolic compounds. Its functional biological properties can be attributed mainly to the high content of flavonoids and polyphenols and a considerable antioxidant capacity has been reported, also highlighting antimicrobial activity and against cancer. However, current research still lacks deeper experimental evidence to justify the use of bee pollen for these purposes. The potential risks of their consumption can be attributed to contamination by pesticides, heavy metals and due to their allergenicity. A search of patents executed in technological databases with respect to the main properties of bee pollen has demonstrated a high interest in the development of technological products based on its many applications. The number of articles and patents found with this theme highlights the importance of this natural product in the scientific-technological advance, focusing on the development of natural supplements.

Keywords: Bee pollen; Composition; Biological activity; Toxicity; Patents.

Resumen: Há sido realizada una investigación en bases de datos científicas utilizando palabras clave relacionadas a la composición, actividad biológica y toxicidad del polen apícola en el período de 2007 a julio de 2017. Se ha verificado que este producto es rico en carbohidratos, proteínas y lípidos, además de diversos minerales y compuestos fenólicos. Sus propiedades biológicas funcionales pueden ser atribuidas principalmente al alto contenido de flavonoides y polifenoles y se ha reportado una considerable capacidad antioxidante, con destaque también para la actividad antimicrobiana y contra el cáncer. Sin embargo, las investigaciones actuales todavía carecen de evidencias experimentales más profundas para justificar el uso del polen apícola para estos propositos. Los riesgos potenciales de su consumo pueden ser atribuidos en gran parte a la contaminación por pesticidas, metales pesados y debido a su alergenicidad. Una búsqueda de patentes realizada en bases de datos tecnológicas con relación a las principales propiedades del polen apícola ha revelado un alto interés en el desarrollo de productos tecnológicos con base en sus diversas aplicaciones. La cantidad de artículos y patentes encontrados con ese tema evidencia la importancia de ese producto natural en el avance científico y tecnológico, con enfoque para el desarrollo de suplementos naturales.

Palabras clave: Polen apícola; Composición; Actividad biológica; Toxicidad; Patentes.

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INTRODUCTION

Natural products and preparations for food and nutritional supplementation or for dietetic purposes have gained more attention in recent years, including bee products. Honey is the most common beehive product, however, there are other products, such as bee pollen, royal jelly, propolis and beeswax. Although they have been applied for centuries in traditional medicine, the increase in the demand for these natural products by consumers is justified by their nutritional and physiological properties, given their healthy effects on the human organism (Feás *et al.*, 2012).

The pollen grains are tiny structures contained in the anthers of flowering plants and represent the male reproductive element of plants. Each pollen grain carries a variety of nutrients needed for its survival and fusion with the female gamete. Besides playing an essential role in the sexual propagation of plants, pollen is also the most important source of nutrients for bee survival (Edlund *et al.*, 2004). Pollen derived from bees is defined as "the result of the pollen agglutination of flowers by worker bees using nectar and its salivary substances, which is collected at the entrance of the beehive" (ANVISA-Brasil, 2001).

Each bee pollen has specific characteristics according to the flower species visited by the bees. When there is a single botanical origin maintaining its organoleptic and biochemical properties, the bee pollen is called monofloral. Heterofloral bee pollen has varied biochemical properties, due to the great variability of pollen types (different floral species visited) (Almeida-Muradian *et al.*, 2005; Gabriele *et al.*, 2015). Thus, the chemical composition of bee pollen depends strongly on vegetal origin, along with other factors such as geographic origin, environmental conditions, collection season, soil type and bees race (Avni *et al.*, 2014; Negrão *et al.*, 2014; Sattler *et al.*, 2015).

Ancient Egyptians described pollen as "life-giving dust". Some of the "Fathers of Western Medicine" (Hippocrates, Pliny and Pythagoras) relied on the healing properties of bee pollen and often prescribed it to their patients. The word pollen comes from Latin and means fine flour or dust. It was first used in 1686 by John Ray in *Historia plantarum*. The pollen collected from bees began to be used for human nutrition in large scale only after Second World War, when pollen traps were developed and became available (Campos *et al.*, 2010).

In the scientific field, the oldest publications focus on approaches based mainly on the characterization of flavonoids and phenolic compounds (Campos *et al.*, 1990; Tomás-Lorente *et al.*, 1992; Campos *et al.*, 1997). Biological activity studies generally focused on the presence of the antioxidant effects of bee pollen extracts (Campos *et al.*, 2003). Regarding to the toxicity, Cohen *et al.* (1979) and Lin *et al.* (1989) already reported the occurrence of allergic reaction (acute or not) after ingestion of bee pollen.

According to Barreto *et al.* (2005), the production of bee pollen in Brazil began to emerge in the late 1980s. Nowadays, the product is commercialized in natural food stores, supermarkets and drugstores. The consumption is mainly *in natura* or dehydrated, and may also be accompanied by other foods such as yogurt, honey and juice. In addition to Brazil, some countries such as Switzerland and Argentina have established official quality standards and limits by legally recognizing bee pollen as a food additive. In Brazil, bee pollen needs to be certified and registered in health surveillance organs in order to be commercialized (SEBRAE, 2015).

This study aimed to perform a bibliographic survey of the composition, biological activity and toxicity of bee pollen from 2007 to July 2017, as well as a search of patents related to their properties, analyzing patent applications filed in national and international banks of innovation and technology.

REVIEW METHODOLOGY

The literature review was executed during the months of May to July of 2017 based on scientific articles published from 2007 until the date of the research. The research was based on the search of articles that approached experimental studies which objective was to evaluate the physicochemical composition, biological activity and toxicity of bee pollen. The search was conducted in the databases PubMed, Science Direct, Scopus and Scientific Electronic Library Online (SciELO). The following search terms were used: "bee pollen and composition", "bee pollen and biological activity", "bee pollen and toxicity" and their correspondents in Portuguese: "pólen apícola e composição", "pólen apícola e atividade biológica" and "pólen apícola e toxicidade". Review articles and book chapters were excluded, as well as articles in cases of duplication in another database and articles that from the reading of titles and abstracts did not fit the research theme.

The databases used to search of patents were: National Institute of Industrial Property of Brazil (INPI), World Intellectual Property Organization (WIPO), European Patent Office (EPO) and United States Patent and Trademark Office (USPTO), using the search terms: "bee pollen", "bee pollen and antioxidant", "bee pollen and antimicrobial", "bee pollen and antibacterial", "bee pollen and

anticarcinogenic", "bee pollen and anticancer", "bee pollen and antitumor" and their correspondents in Portuguese: "pólen apícola", "pólen apícola e antioxidante", "pólen apícola e antimicrobiano", "pólen apícola e antibacteriano", "pólen apícola e anticarcinogênico", "pólen apícola e anticâncer" and "pólen apícola e antitumoral". An exploratory reading of the titles and abstracts was performed, being selected and analyzed integrally those patents that were related to the purpose of the study.

RESULTS AND DISCUSSION

The search in the scientific databases resulted in a total of 595 articles published between 2007 and 2017. Among these, 289 articles were found from the PubMed search, 160 in Science Direct, 114 in Scopus and 32 in SciELO (Table No. 1). After the screening, applying the inclusion and exclusion criteria, 122 articles were selected for analysis.

Table No. 1
Number of scientific articles published in the PubMed, Science Direct, Scopus and SciELO databases by keyword between 2007 and 2017

KEYWORDS	PubMed	Science Direct	Scopus	SciELO
"bee pollen and composition" or "pólen apícola e composição"	103	49	87	32
"bee pollen and biological activity" or "pólen apícola e atividade biológica"	65	100	11	0
"bee pollen and toxicity" or "pólen apícola e toxicidade"	121	11	16	0

Composition of bee pollen

According to data found in the articles, carbohydrates constitute the main fraction of bee pollen and represent an important component from the nutritional and energy aspect. We can exemplify through the data reported by Modro *et al.* (2009) and Kostic *et al.* (2015), which found levels of 68,10% and 75,51%, respectively. Proteins were the second most abundant component in bee pollen and their content varied between 19,44% and 23,80% in the selected articles (Fuenmayor *et al.*, 2014; Kostic *et al.*, 2015).

The lipid content is variable and depends on the amount of fatty acids, carotenoids and vitamins and ranged from 2,66% to 7,34% in the selected articles (Fuenmayor *et al.*, 2014; Kostic *et al.*, 2015; Costa *et al.*, 2017). Conte *et al.* (2016) and Araújo *et al.* (2017), in their experiments, highlighted the presence of two polyunsaturated fatty acids, linoleic acid and α-linolenic acid, which were the most prevalent in the samples analyzed. In addition, the polyunsaturated fatty acids were those found in greater quantity in relation to the saturated and monounsaturated ones in Xu *et al.* (2009), Conte *et al.* (2016), Araújo *et al.* (2017) and Ghosh & Jung (2017).

Linoleic and α-linolenic acids play important roles in the human body since they are part of the cell membrane and have antithrombotic and anti-inflammatory activities, besides being related to the reduction of coronary heart disease and its risk factors (Chiarello *et al.*, 2005).

In a study accomplished by Ghosh & Jung (2017), the main minerals found in bee pollen were potassium and phosphorus. The sodium content was considered very low. This data is in disagreement with the results reported by Kalaycioglu *et al.* (2017), which sodium was the most abundant macroelement. The latter also reported the presence of other essential minerals such as potassium, calcium, magnesium, iron, zinc, manganese, copper and chromium. Fuenmayor *et al.* (2014) found almost the same minerals, varying only in the order relative to their concentration in the analyzed samples. Sattler *et al.* (2016) found significant differences in the mineral content studied, even in samples of the same apiary, demonstrating that bee pollen of the same apiary can have different botanical origins within the same period.

Also with regard to the substances that make up the bee pollen, the presence of the phenolic compounds stands out. Phenolic compounds are a class of substances with a high capacity to neutralize reactive oxygen species and this is strongly associated with their structure: the conjugated double bonds and the number of hydroxyl groups in the aromatic ring attributed mainly to cinnamic acid derivatives and flavonoids (Pascoal *et al.*, 2014). The total phenolic content in bee pollen can vary depending on the type and concentration of the solvent used in its extraction and, especially, according to the floral origin of the bee pollen

(Kroyer & Hegedus, 2001; Carpes *et al.*, 2007; Mărghitaş *et al.*, 2009).

The phenolic profile consists of the analysis of the samples using reference standards of known phenolic compounds. From this methodology, it was possible to identify and quantify different phenolic compounds in bee pollen, among which we can highlight kaempferol, quercetin, isoramnetin, catechin, rutin, chrysin and pinocembrin, among others (Graikou *et al.*, 2011; Aygul *et al.*, 2016). Previously, Tomás-Lorente *et al.* (1992), when conducting studies of this type, detected the presence of basically the same flavonoids (myricetin, quercetin, kaempferol and isoramnetin), however presented in their glycosidic form.

High amounts of tocopherols, carotenoids, sterols, vitamin B and vitamin C were detected in bee pollen (Xu *et al.*, 2011; Xu *et al.*, 2012; Arruda *et al.*, 2013; Sattler *et al.*, 2015; Conte *et al.*, 2016). Montenegro *et al.* (2013) emphasized the presence of β-carotene and lycopene pigments in bee pollen, finding values that can be compared with values reported in other foods, such as fruits and shellfish, so that bee pollen can be classified as a natural source of these substances and can be included in the human diet. It should be noted that the presence of these pigments also contributes to the antioxidant activity, which is largely determined by the phenolic compounds.

According to Zu *et al.* (2014) dietary intake of lycopene is associated with reduced risk of lethal prostate cancer and in tumor angiogenesis. Assar *et al.* (2016) have found that the anticancer properties of lycopene may be related to the inhibition of the NF-κB signaling pathway and its effects on cancer cells have been observed at concentrations that are relevant and achievable in vivo.

Biological activity of bee pollen

Regarding to the biological activity of bee pollen, 56 articles were found that referred some type of biological action. Turkey, China and Brazil were the countries with the most articles according to the geographical origin of bee pollen studied.

Most of the biological activities reported for bee pollen were in relation to its antioxidant capacity, as mentioned in 30 articles. Except for one article, all the others that reported antioxidant activity for the bee pollen studied also aimed to evaluate the presence of phenolic compounds. Table No. 2 below presents some of these studies.

The articles published previously to this review also had main focus on the antioxidant activity and free radical scavenging capacity, as can be verified by Campos *et al.* (2003) and Almaraz-Abarca *et al.* (2004). Kroyer & Hegedus (2001) found that bee pollen extracts can be considered as effective natural and functional food supplements. These properties are due to their remarkable content of polyphenolic substances and their significant capacity to remove radicals. In addition, they have other benefits such as their nutritional and physiological implications and their health promoting effect.

The content of total phenolics and flavonoids in bee pollen samples generally illustrates a positive correlation regarding to their antioxidant capacity, as evidenced in the experiments of Aloisi & Ruppel (2014), Grosso *et al.* (2015) and Kalaycioglu *et al.* (2017). On the other hand, Carpes *et al.* (2008) found a variable correlation between the antioxidant activity and the content of phenolic compounds and flavonoids, which was attributed in this study to different methods used to evaluate the antioxidant activity. According to Mărghitaş *et al.* (2009), the antioxidant activity is not necessarily correlated with high amounts of phenolic compounds and suggests that the antioxidant activity in bee pollen extracts is not limited only to phenolic compounds.

Another prominent biological action of bee pollen is the antimicrobial activity, demonstrated in Table No. 3. As reported in the articles, it was found that bacteria are more sensitive to the action of bee pollen than fungi, especially *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In general, gram-positive bacteria have been demonstrated to be more sensitive than gram-negative bacteria. In relation to fungi, stands out the activity against *Candida* sp. and *Aspergillus* sp.

Table No. 2
Bee pollen and antioxidant activity

Reference (Geographical origin)	Study model of action	Chemical compound studied / involved	Botanical origin	Form / presentation
Almaraz-Abarca *et al.*, 2007 (Mexico)	Evaluation of inhibition of lipid peroxidation on mouse hepatic microsomal preparations and in liver homogenate of	Flavonoids	*Prosopis juliflora*	Maceration with ethanol-water solution for 60 min followed by centrifugation for 10 min and the supernatant

	bromobenzene-intoxicated mice by quantification of TBARS			was subjected to evaporation of the solvent to dryness at low-pressure
Šarić *et al.*, 2009 (Croatia)	Evaluation of the effect of food supplementation with bee pollen on TBARS levels in the mice liver and brain, in modulating of antioxidant enzymes activity (SOD, CAT and GPx) in the mice liver, brain and lysate of erythrocytes and the reduction of hepatic lipid peroxidation	Phenolic compounds	*Cystus incanus* L., *Quercus ilex*, *Quercus* spp., *Asphodelus* spp. and Brassicaceae	Bee pollen was dehydrated at 8-10% moisture, then was pulverized (no chemical refinement)
Tohamy *et al.*, 2014 (Egypt)	Measurement of TBARS, GSH and CAT activity in the mice livers, kidneys and testis homogenates	No specific chemical compound has been studied	Not informed	Suspension in water by vigorous stirring, followed by standing overnight and centrifugation at 10.000 rpm at 10°C for 45 min. The supernatant was filtered and stored at -20°C until use
Araújo *et al.*, 2017 (Brazil)	DPPH, ABTS, FRAP and β-carotene bleaching assays	Fatty acids, total phenols and flavonoids	*Cocos nucifera*, *Miconia* spp., *Spondias* spp., *Eucalyptus* spp. and multifloral	Extraction with methanol, followed by evaporation of the solvent

Note: TBARS = thiobarbituric acid reactive substances; SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; GSH: glutathione reduced; DPPH = 2,2-diphenyl-1-picrylhydrazyl; ABTS = 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); FRAP = ferric reducing antioxidant power

Antimicrobial activity can be attributed mainly to the high content of flavonoids, such as quercetin and kaempferol glycosides, which are known to have antibacterial activity (Hong *et al.*, 2014; Djouossi *et al.*, 2015). It has also been reported that certain fatty acids, such as linoleic, linolenic and palmitic acids (all present in bee pollen) have activity against microorganisms that are pathogenic to humans (Huang *et al.*, 2010; Jubie & Dhanabal, 2012).

The goal of many researchers has been discovery of natural and synthetic compounds to be used in the prevention and/or treatment of cancer. In this context, different studies have presented potential anticarcinogenic and/or anticancer activity of bee pollen, probably associated with antioxidant and antimutagenic effects (Table No. 4).

A study performed by Tohamy *et al.* (2014) revealed that the chemoprotective potential of bee pollen with regard to chromosomal and histological damages in bone marrow, liver, kidney and testis tissues of mice seems to depend on the antioxidant effect related to the attenuation of lipid peroxidation and elevation of catalase and glutathione concentration. Therefore, many phenolic compounds, in addition to antioxidant activity, also appear to exert anticarcinogenic activity.

Bee pollen has also been proposed as a valuable food supplement because it increases the growth rate and the feed conversion ratio, and can be used to increase physical capacity and even strengthen the immune system. These properties may be related to a complex of active substances, including amino acids, vitamins, polyphenols, carotenoids and minerals (Li *et al.*, 2009; Attia *et al.*, 2014).

Table No. 3
Bee pollen and antimicrobial activity

Reference (Geographical origin)	Study model of action	Chemical compound studied / involved	Botanical origin	Form / presentation
Pascoal *et al.*, 2014 (Portugal and Spain)	Minimum inhibitory concentration test	Total phenols and flavonoids	Fabaceae, Cistaceae, Ericaceae and Boraginaceae	Extraction with methanol, followed by evaporation of the solvent
Graikou *et al.*, 2011 (Greece)	Minimum inhibitory concentration test	Flavonoids, sugars, fatty acids, fatty acid esters, phenolic acids and total phenols	*Papaver rhoeas*, *Chamomila recutita*, *Sinapis arvensis*, *Cistus* sp., *Trifolium* sp., *Dorycnium* sp., *Cichorium* sp., *Convolvulus* sp., *Circium* sp., *Malva sylvestris*, *Fumaria* sp., *Eucalyptus camaldulensis*, *Anemone* sp., *Ononis* sp., *Asphodelus* sp. and *Quercus ilex*	Extraction with solvents dichloromethane, methanol and water
Carpes *et al.*, 2007 (Brazil)	Disk diffusion assay	Total phenols	Not informed	Extraction with ethanol (40 to 90%) at 70°C for 30 min with constant agitation
Fatrcová-Šramková *et al.*, 2013 (Slovakia)	Agar diffusion method	Total phenols	*Papaver somniferum* L., *Brassica napus* subsp. *napus* L. and *Helianthus annuus* L.	Extraction with 90% ethanol in a water bath at 70°C for 30 min, followed by filtration

Table No. 4
Bee pollen and anticarcinogenic activity

Reference (Geographical origin)	Specific activity	Study model of action	Chemical compound studied / involved	Botanical origin	Form / presentation
Wang *et al*, 2013 (China)	Anti-proliferative (anticancer)	*In vitro* anti-proliferative activity assay in HT-29 and HCT116 cell lines (MTT assay)	Polysaccharides	*Rosa rugosa*	Extraction with hot water followed by precipitation by the addition of ethanol 95%
Sun *et al*, 2017 (China)	Anti-tyrosinase / inhibition of melanogenesis (anticancer and anticarcinogenic)	Determination of *in vitro* inhibitory activity for mushroom tyrosinase, measurement of melanin content and inhibition of tyrosinase in B16 cells, evaluation of melanin synthesis reduction by increasing the GSH/GSSG ratio in B16 cells, determination of intracellular levels of cAMP	Total phenols, total flavonoids, phenolic profile	Not informed	Extraction of free phenols: extraction with 70% methanol after removal of lipids using hexane / Extraction of bound phenols: was executed from the hydrolysis of the residue from the extraction of free phenolics

		in B16 cells			
Wu & Lou, 2007 (China)	Inducer of apoptosis in human prostate cancer PC-3 cells (anticancer)	Determination of cell viability by trypan blue exclusion assay, verification of apoptosis by flow cytometry by determination of propidium iodide, staining with acridine orange and ethidium bromide followed by fluorescence microscopy, caspase-3 activity assay, expression of Bcl-2 in PC-3 cells by western blot analysis	Steroid fraction	*Brassica campestris* L.	Chloroform extraction
Šarić *et al*, 2009 (Croatia)	Anti-estrogenic (anticancer and anticarcinogenic)	Assay of *Saccharomyces cerevisiae* containing the human estrogen receptor α (hERα) and a *Xenopus laevis* vitellogenin ERE sequence linked to the reporter gene lacZ encoding for the enzyme β-galactosidase	Phenolic compounds	*Cystus incanus* L., *Quercus ilex*, *Quercus* spp., *Asphodelus* spp. and Brassicaceae	Bee pollen was dehydrated at 8-10% moisture, then was pulverized (no chemical refinement)

Note: MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; GSH = glutathione reduced; GSSG = glutathione disulfide; cAMP = cyclic adenine monophosphate; Bcl-2 = B-cell lymphoma 2

The antioxidant effect of bee pollen may also be related to the protective activity against damage induced by toxic chemicals, especially pesticides such as carbon tetrachloride, propoxur and carbaryl. It was observed an improvement in oxidative stress markers when bee pollen was administered after exposure or associated with the toxic agent. Therefore, it is suggested that bee pollen can be used as a food additive for prophylactic purposes and in combination with other medicinal products to support treatment against pesticide intoxications (Eraslan *et al.*, 2009a; Eraslan *et al.*, 2009b; Saral *et al.*, 2016).

With regard to the range of beneficial properties attributed to bee pollen, it is necessary to accomplish more complete and in-depth studies, since the analyzed articles used, in their entirety, *in vitro* and/or animal study models.

Toxicity of bee pollen

In contrast to its important nutritional and biological value, bee pollen may also contain toxic elements. Health risks associated with the use of bee pollen may result from the occasional presence of contaminants, such as heavy metals, pesticides, mycotoxins and bacteria (Table No. 5).

Table No. 5
Contaminants found in bee pollen

Reference (Geographical origin)	Contaminants found
Altunatmaz *et al.*, 2017 (Turkey)	Lead, cadmium and arsenic
Sattler *et al.*, 2016 (Brazil)	Barium, cadmium, lithium, lead and vanadium
Oliveira *et al.*, 2016 (Brazil)	Trifluralin, bioallethrin, aldrin, alpha endosulfan, fempropatrim, alachlor and permethrin
Codling *et al.*, 2016 (Canada)	Clothianidin and nitenpyram
Dübecke *et al.*, 2011 (Different origins)	Pyrrolizidine alkaloids
Kačániová *et al.*, 2011 (Slovakia)	Fungi and mycotoxins

Contaminants can be present in air, soil, water and plants and spread to bee pollen through these routes. The indiscriminate use of pesticides in crops and industrial contamination inserts some heavy metals, harmful to living organisms, into agricultural ecosystems (Bogdanov, 2006; Morgano *et al.*, 2010).

Careful handling and frequent monitoring of levels of pesticides, fertilizers and other chemicals in agriculture are essential to ensure food safety for bee pollen. The researchers also state that it can be used as a bioindicator of environmental contamination by pesticides (Oliveira *et al.*, 2016).

In addition, bee pollen derived from flowers of the genus *Echium*, *Senecio* and *Eupatorium* may contain dangerous levels of pyrrolizidine alkaloids (Dübecke *et al.*, 2011). In 2011, the European Food Safety Authority published a scientific opinion about pyrrolizidine alkaloids in food. It was reported that exposure to pyrrolizidine alkaloids in pollen and dietary herbal supplements may potentially be far superior to dietary exposure of honey and is known to have caused disease in humans. Reports of pyrrolizidine alkaloid intoxication in humans, including deaths, have shown that their toxicity predominantly affects liver and lungs.

It has been reported that bee pollen can also be allergenic and should be avoided in patients with allergic predisposition and asthmatic individuals because it increases the risk of allergic reactions after ingestion. Martín-Muñoz *et al.* (2010) reported the case of a four-year-old boy who developed allergic rhinitis and two months later, when he ingested a small spoon of bee pollen for the first time, immediately developed intense itching in his mouth, tongue and pharynx with uvula edema, difficulty swallowing and respiratory symptoms. An allergy skin test with bee pollen was positive.

The cases of allergic reactions to bee pollen are not so recent. Lin *et al.* (1989) reported the case of a patient who developed hypereosinophilia with concomitant pathophysiological disorders six weeks after beginning the ingestion of bee pollen. This shows that the public and health professionals should be aware of the risk of allergic reactions that appear after ingestion of certain bee products. Warning labels that indicate possible adverse reactions should be found on the packaging of these products to protect the costumers from this danger.

Patents search

The patents search was conducted at INPI, USPTO, WIPO and EPO bases through search terms that related the use of bee pollen in its main biological activities, as illustrated in Table No. 6.

Table No. 6
Number of patents found per search term in each technological database

SEARCH TERMS	INPI	USPTO	WIPO	EPO
"*bee pollen*" or "pólen apícola"	6	17	874	1310
"*bee pollen and antioxidant*" or "pólen apícola e antioxidante"	0	2	6	11
"*bee pollen and antimicrobial / antibacterial*" or "pólen apícola e antimicrobiano / antibacteriano"	0	0	14	19
"*bee pollen and anticarcinogenic / anticancer / antitumor*" or "pólen apícola e anticarcinogênico / anticâncer / antitumoral"	0	0	5	5

The search carried out at the INPI base presented six patents with the descriptor "pólen apícola" filed between 2007 and 2015. Among them, three were selected (Table No. 7), since they were those that aimed at a product containing bee pollen. It is observed the prominent participation of the universities in the patent applications filed in the Brazilian base.

Table No. 7
Patents reporting the technological applications of bee pollen filed at the National Institute of Industrial Property (INPI)

Patent Nº. (Classification)	Main claims	Filing date / Inventor (Applicant)
BR 10 2015 031440 0 A2 (A23P)	Process and formulation of soft gelatin capsule containing coconut monofloral bee pollen and coconut oil for use as functional food	2015 / Tania M. S. Silva, Werslandia B. Silva, Girliane R. Silva, Celso A. Câmara (Federal Rural University of Pernambuco)
BR 10 2014 031986 7 A2 (A23L)	Food bar with bee pollen and sesame as protein source	2014 / Maria C. P. Rodrigues, Afra M. C. B. Nascimento (Federal University of Ceará)
PI 1107450-7 A2 (A23L)	Light bee pollen and process of obtaining	2011 / Edilson D. Araújo, Maria A. A. P. Silva, Yara R. R. Santos, Narendra Narain, Yzila L. F. M. Araújo (Federal University of Sergipe)

The search in the USPTO database, in terms of patent applications, returned a total of 19 results. Table 8 presents the main patents found after the selection of those that involved a final product with some type of biological function. With regard to the countries of origin of the patents, they all originate in the United States. In contrast to the Brazilian technological base, in USPTO predominates patents filed by companies or autonomous researchers.

Table No. 8
Patents reporting the technological applications of bee pollen filed at the United States Patent and Trademark Office (USPTO)

Patent Nº. (Classification)	Main claims	Filing date / Inventor (Applicant)
US 20150374759 A1 (A61K)	A composition for the topical treatment of sores, lesions, ulcers and other disorders of skin, which includes a combination of a bee product (bee pollen, propolis, honey or royal jelly) and caffeine	2015 / Gilbert Clinton Gee
US 20070141168 A1 (A61K)	A composition for burn treatment containing sweet almond oil, bitter almond oil, lavender oil, beeswax, bee pollen, purified honey, propolis and water	2005 / Wafa Alkazemi
US 6287567 B1 (A23F and A23L)	Drink to relieve symptoms of fatigue, congestion, fever and asthma, formed by water and a combination of equal portions of rosehip, goldenseal, comfrey leaf, bee pollen, spearmint, chickweed, comfrey root, chamomile flower, catnip, mullein, pennyroyal, eucalyptus, and licorice root	2000 / Dorothy J. Blount
US 4426397 A (A23L, A23C and A23K)	A process for the production of a dry, stable bee product composition and its use, comprising bee pollen, bee bread, propolis, honey or mixtures thereof, said bee product containing 0-10%	1981 / Rudolf Schanze
US 20130287855 A1 (A23V, A23L and A61K)	Compositions based on clay and bee pollen, method for preparing the same, and nutritional and therapeutic uses thereof	2011 / Alexandra Fregonese (Alexandra Fregonese, Laboratoire Beepratte)
US 20060172022 A1 (A61K)	A topical treatment composition added of bee pollen to treat dry or damaged skin and to maintain healthy skin	2005 / Sharon Szanzer
US 20140134705 A1 (A62D)	Oil spill containment system and method using as suitable organic bacterial nutrient the bee pollen	2012 / James Jackson Milham Henry (Rok Investment Group Ltd)
US 20150093494 A1	A bioactive additive consisting of bee pollen, water and	2014 / Konstantine

(A23L and A23V)	alcohol, which when added to products such as bread and bread-like products, enriches them with amino acids, vitamins and minerals	George Chakhunashvili, David Konstantine Chakhunashvili, Irakli Artemon Kalandia (Apipuri, Inc.)

The search in the WIPO and EPO databases through the descriptor "bee pollen" returned a very large number of patents. Therefore, it was opted to analysis only patent applications referring to the biological activities in question.

The patents selected from the WIPO search are presented in Table No. 9. Regarding the antioxidant activity of bee pollen, only CN 103463134 A was excluded from selection because it was a method to extract the antioxidant substances from bee pollen. Regarding the antimicrobial/antibacterial activity, although the WIPO base has recovered 14 patents, after reading, it was verified that the majority of the patents did not focus on the activity in question, besides that in most patents, as in CN 102160573 B, it is not specified whether the antibacterial action of the composition is in fact related to bee pollen. Similarly, patents such as CN 102260617 B, which involve anticancer products containing bee pollen, specify that this activity is attributed to another component of the formulation and not to bee pollen.

Table No. 9
Patents reporting the technological applications of bee pollen filed in the World Intellectual Property Organization (WIPO)

Patent Nº. (Classification)	**Main claims**	**Filing date / Inventor (Applicant)**
WO 2017014375 A1 (A61K)	A bee pollen composition which may be used as a cosmetic material or pharmaceutical composition	2015 / Hwa Jin Suh, Se Gie Kim, Yun Sik Choi, Il Kyung Chung (Nsb Co., Ltd.)
KR 1020150103720 B1 (A61K)	A bee pollen composition which may increase the antioxidant effects and increase the polyphenol content to allow it to be used as a cosmetic ingredient or a pharmaceutical composition	2015 / Hwa Jin Suh, Se Gie Kim, Yun Sik Choi, Il Kyung Chung
RU 0002522339 C1 (A23K)	Natural biologically active veterinary feed supplement Vita-forze M	2013 / Иванов Аркадий Васильевич
CN 101284024 A (A61K)	Bee pollen capsules that can be used as a health product for daily administration	2008 / Ding Xuefeng
CN 101978864 B (A23L)	A rapeseed bee pollen extract with anti-inflammatory, analgesic and antibacterial properties	2010 / Sun Liping, Xu Xiang, An Zhongyao, Dong Jie, Li Chunyan (Bee Research Institute of Chinese Academy of Agricultural Sciences)
CN 1350861 A (A61P)	Process for preparing an oral liquid to prevent cancer	2000 / Chen Ping, Guo Yuerong (Oral Liquid Factory, Inst of Bio-Engineering, Fujian Agricultural Univ.)
CN 1806574 C (A23C)	Method of preparing an anticancer yogurt for achieving the functions of resistance to cancer mutation, expulsion of toxins and enhancement of the immunity of the human body	2005 / Yu Neixun, Yu Qianliang

Table No. 10 presents the patents found in the EPO after the exclusion of those with duplication in the databases and patents in which the final product has the activity investigated, but it is not attributed to the presence of the bee pollen in the formulation. Patent applications resulting from

antimicrobial/antibacterial and anticarcinogenic /anticancer/antitumor activity search were not exposed because the patents selected after reading the documents found were the same as those from the WIPO database.

Table No. 10
Patents reporting the technological applications of bee pollen filed in the European Patent Office (EPO)

Patent Nº. (Classification)	Main claims	Filing date / Inventor (Applicant)
CN 105433327 A (A23L)	Antioxidant milk prepared from bee pollen	2015 / Cheng Ni, Cao Wei, Gao Hui (Northwestern University)
CN 105193893 A (A61K)	Extract of *Carthamus tinctorius* L. bee pollen with antioxidant capacity to be used as a cosmetic additive	2015 / Yang Lixin, Xu Gang, Liu Aizhong, Pei Shengji (Kunming Institute of Botany, Chinese Academy of Sciences)
CN 105010927 A (A23L)	Method of preparation of lyophilized bee pollen with antioxidant activity	2015 / Lai Ye, Lai Qiuping, Zhang Fangzhen, Qiu Aifang, Liu Gongliang (Guangdong Guiling Apiculture Technology Co., Ltd)
CN 104644462 A (A61K)	Emulsion containing bee pollen with antioxidant effect for external use on the skin	2015 / Chen Guang, Ao Jianfang, Han Rui (Shenzhen Aesthetic Biolog Technology Co Ltd; Aesthetic Internat Holdingschain Group)

With respect to the International Patent Classification (IPC), in which patents are classified according to the application, it was observed in this survey that the largest proportion of patent applications is within the area of human needs and distributed mainly between categories A23 (food or foodstuffs, their treatment not covered by other classes) and A61 (medical or veterinary science, hygiene).

It was observed that the countries with the largest number of patent applications were China and the United States. Although Brazil is rich in biodiversity and develops a lot of research with natural products, the research in the patent bases revealed a low interest for the development of technologies related to bee pollen. With regard to the filing year of the patents, it has been found that patent applications have accumulated especially in recent years, revealing a trend in increasing concern to develop products obtained from natural sources, such as bee pollen.

CONCLUSION

Bee pollen is a promising natural product for food supplements development due to its nutritional and therapeutic properties. Its functional biological properties may be related to the high content of flavonoids and polyphenols and may be affected by the chemical composition of bee pollen, which is highly variable and depends on factors such as floral and geographic origin. The potential risks of bee pollen consumption can be largely attributed to contamination by pesticides, heavy metals and due to their allergenicity.

The information revealed during 2007-2017 agrees with the information previously reported to this period. However, there is now a greater range of information, resulting from the deepening and improvement of research related to bee pollen.

Pollen composition is not constant because it is produced from highly variable exogenous sources. Therefore it is expected that its pharmacological properties also change. There are no clinical trials that support the biological activities reported in the article and in general in the literature; in many cases it is only about in vitro tests.

This important bee product has been used since the beginning by traditional medicine in its *in natura* or dehydrated form. However, it is observed that currently there is a high interest in developing technological products based on its various applications, as observed in the search of patents. The amount of articles and patents found with this theme highlights the importance of this natural product in the scientific-technological advance, focusing on the development of natural supplements.

REFERENCES

Almaraz-Abarca N, Campos MG, Ávila-Reyes JA, Naranjo-Jiménez N, Herrera-Corral J, González-Valdez LS. 2004. Variability of antioxidant activity among honeybee-collected pollen of different botanical origin. **Interciencia** 29: 574 - 578.

Almaraz-Abarca N, Campos MG, Ávila-Reyes JA, Naranjo-Jiménez N, Herrera-Corral J, González-Valdez LS. 2007. Antioxidant activity of polyphenolic extract of monofloral honeybee-collected pollen from mesquite (*Prosopis juliflora*, Leguminosae). **J Food Compost Anal** 20: 119 - 124.

Almeida-Muradian LB, Pamplona LC, Coimbra S, Barth OM. 2005. Chemical composition and botanical evaluation of dried bee pollen pellets. **J Food Compost Anal** 18: 105 - 111.

Aloisi PV, Ruppel, S. 2014. Propiedades bioactivas y nutricionales del polen apícola de la provincia del Chubut, Argentina. **Rev Investig Agropecu** 40: 296 - 302.

Altunatmaz SS, Tarhan D, Aksu F, Barutçu UB, Or ME. 2017. Mineral element and heavy metal (cadmium, lead and arsenic) levels of bee pollen in Turkey. **Food Sci Technol** Epub March 09, 2017.

ANVISA-Brasil. 2001. Agência Nacional de Vigilância Sanitária. **Instrução Normativa No. 3,** de 19 de janeiro de 2001. Aprova os Regulamentos Técnicos de Identidade e Qualidade de Apitoxina, Cera de Abelha, Geleia Real, Geleia Real Liofilizada, Pólen Apícola, Própolis e Extrato de Própolis. **http://extranet.agricultura.gov.br/sislegis-consulta/consultarLegislacao.do?operacao=visualizar&id=1798**

Araújo JC, Chambó ED, Costa MAPC, Silva SMPC, Carvalho CAL, Estevinho LM. 2017. Chemical composition and biological activities of mono- and heterofloral bee pollen of different geographical origins. **Int J Mol Sci** 18: 921.

Arruda VAS, Pereira AAS, Freitas AS, Barth OM, Almeida-Muradian LB. 2013. Dried bee pollen: B complex vitamins, physicochemical and botanical composition. **J Food Compost Anal** 29: 100 - 105.

Assar EA, Vidalle MC, Chopra M, Hafizim S. 2016. Lycopene acts through inhibition of IκB kinase to suppress NF-κB signaling in human prostate and breast cancer cells. **Tumour Biol** 37: 9375 - 9385.

Attia YA, El-Hanoun AM, Bovera F, Monastra G, El-Tahawy WS. Habiba HI. 2014. Growth performance, carcass quality, biochemical and haematological traits and immune response of growing rabbits as affected by different growth promoters. **J Anim Physiol Anim Nutr** 98: 128 - 139.

Avni D, Hendriksma HP, Dag A, Uni Z, Shafir S. 2014. Nutritional aspects of honey bee-collected pollen and constraints on colony development in the eastern Mediterranean. **J Insect Physiol** 69: 65 - 73.

Aygul I, Karahalil FY, Supuran CT. 2016. Investigation of the inhibitory properties of some phenolic standards and bee products against human carbonic anhydrase I and II. **J Enzyme Inhib Med Chem** 31: 119 - 124.

Barreto LMRC, Funari SRC, Orsi RO. 2005. Composição e qualidade do pólen apícola proveniente de sete estados brasileiros e do Distrito Federal. **B Indústr Anim** 62: 167 - 175.

Bogdanov S. 2006. Contaminants of bee products. **Apidologie** 37: 1 - 18.

Campos MGR, Sabatier S, Amiot MJ, Aubert S. 1990. Characterization of flavonoids in three hive products: bee pollen, propolis, and honey. **Planta Med** 56: 580 - 581.

Campos MGR, Markham KR, Mitchell KA, Cunha AP. 1997. An approach to the characterization of bee pollens via their flavonoid/phenolic profiles. **Phytochem Anal** 8: 181 - 185.

Campos MGR, Webby RF, Markham KR, Mitchell KA, Cunha AP. 2003. Age-induced diminution of free radical scavenging capacity in bee pollens and the contribution of constituent flavonoids. **J Agric Food Chem** 51: 742 - 745.

Campos MGR, Frigerio C, Lopes J, Bogdanov, S. 2010. What is the future of bee-pollen? **J ApiProduct & ApiMedical Sci** 2: 131 - 144.

Carpes ST, Begnini R, Alencar SM, Masson ML. 2007. Study of preparations of bee pollens extracts, antioxidant and antibacterial activity. **Ciênc Agrotec** 31: 1818 - 1825.

Carpes ST, Prado A, Moreno IAM, Mourão GB, Alencar SM, Masson ML. 2008. Avaliação do potencial antioxidante do pólen apícola produzido na região sul do Brasil. **Quím Nova** 31: 1660 - 1664.

Chiarello RJ, Rios CE, Pereira SE. 2005. Avaliação subjetiva global de crianças de 1 a 4 anos de idade durante suplementação diária com fonte alimentar vegetal de ômega-3. **Rev Inst Ciênc Saúde** 23: 25 - 34.

Codling G, Naggar YA, Giesy JP, Robertson AJ. 2016. Concentrations of neonicotinoid insecticides in honey, pollen and honey bees (*Apis mellifera* L.) in central Saskatchewan, Canada. **Chemosphere** 144: 2321 - 2328.

Cohen SH, Yunginger JW, Rosenberg N, Fink JN. 1979. Acute allergic reaction after composite pollen ingestion. **J Allergy Clin Immunol** 64: 270 - 274.

Conte G, Benelli G, Serra A, Signorini F, Bientinesi

M, Nicolella C, Mele M, Canale A. 2016. Lipid characterization of chestnut and willow honeybee-collected pollen: Impact of freeze-drying and microwave-assisted drying. **J Food Compos Anal** 55: 12 - 19.

Costa MCA, Morgano MA, Ferreira MMC, Milani RF. 2017. Analysis of bee pollen constituents from different Brazilian regions: Quantification by NIR spectroscopy and PLS regression. **LWT - Food Sci Technol** 80: 76 - 83.

Djouossi MG, Tamokou JD, Ngnokam D, Kuiate JR, Tapondjou LA, Harakat D, Voutquenne-Nazabadioko, L. 2015. Antimicrobial and antioxidant flavonoids from the leaves of *Oncoba spinosa* Forssk. (Salicaceae). **BMC Complement Altern Med** 15: 134.

Dübecke A, Beckh G, Lüllmann C. 2011. Pyrrolizidine alkaloids in honey and bee pollen. **Food Addit Contam Part A Chem Anal Control Expo Risk Assess** 28: 348 - 358.

Edlund AF, Swanson R, Preuss D. 2004. Pollen and stigma structure and function: The role of diversity in pollination. **Plant Cell** 16: S84 - S97.

EFSA Panel on Contaminants in the Food Chain (CONTAM). 2011. Scientific opinion on pyrrolizidine alkaloids in food and feed. **EFSA Journal** 9: 2406.

Eraslan G, Kanbur M, Silici S. 2009a. Effect of carbaryl on some biochemical changes in rats: The ameliorative effect of bee pollen. **Food Chem Toxicol** 47: 86 - 91.

Eraslan G, Kanbur M, Silici S, Liman BC, Altinordulu S, Sarica ZS. 2009b. Evaluation of protective effect of bee pollen against propoxur toxicity in rat. **Ecotoxicol Environ Saf** 72: 931 - 937.

Fatrcová-Šramková K, Nôžková J, Kačániová M, Máriássyová M, Rovná K, Stričík M. 2013. Antioxidant and antimicrobial properties of monofloral bee pollen. **J Environ Sci Health B** 48: 133 - 138.

Feás X, Vázquez-Tato MP, Estevinho L, Seijas JA, Iglesias A. 2012. Organic bee pollen: Botanical origin, nutritional value, bioactive compounds, antioxidant activity and microbiological quality. **Molecules** 17: 8359 - 8377.

Fuenmayor C, Zuluaga C, Díaz C, Quicazán D, Cosio M, Mannino S. 2014. Evaluation of the physicochemical and functional properties of Colombian bee pollen. **Rev MVZ Cordoba** 19: 4003 - 4014.

Gabriele M, Parri E, Felicioli A, Sagona A, Pozzo L, Biondi C, Domenici V, Pucci L. 2015. Phytochemical composition and antioxidant activity os Tuscan bee pollen of different botanic origins. **Ital J Food Sci** 27: 248 - 259.

Ghosh S, Jung C. 2017. Nutritional value of bee-collected pollens of hardy kiwi, *Actinidia arguta* (Actinidiaceae) and oak, *Quercus* sp. (Fagaceae). **J Asia-Pac Entomol** 20: 245 - 251.

Graikou K, Kapeta S, Aligiannis N, Sotiroudis G, Chondrogianni N, Gonos E, Chinou I. 2011. Chemical analysis of Greek pollen - Antioxidant, antimicrobial and proteasome activation properties. **Chem Cent J** 5: 33.

Grosso GS, López JAH, Tangarife MPO. 2015. Fracción fenólica y flavonoides totales del polen corbicular colombiano: actividad antioxidante y capacidad antirradicalaria. **Zootecnia Trop** 33: 351 - 374.

Hong J, Hu JY, Liu JH, Zhou Z, Zhao AF. 2014. *In vitro* antioxidant and antimicrobial activities of flavonoids from *Panax notoginseng* flowers. **Nat Prod Res** 28: 1260 - 1266.

Huang CB, George B, Ebersole JL. 2010. Antimicrobial activity of n-6, n-7 and n-9 fatty acids and their esters for oral microorganisms. **Arch Oral Biol** 55: 555 - 560.

Jubie S, Dhanabal SP. 2012. Gas chromatography-mass spectrometry analysis and antibacterial activity of fatty acid mixture of *Spirulina platensis*. **J Pharm Sci & Res** 4: 1836 - 1838.

Kačániová M, Juráček M, Chlebo R, Kňazovická V, Kadasi-Horáková M, Kunová S, Lejková J, Haščík P, Mareček J, Simko M. 2011. Mycobiota and mycotoxins in bee pollen collected from different areas of Slovakia. **J Environ Sci Health B** 46: 623 - 629.

Kalaycioglu Z, Kaygusuz H, Döker S, Kolayli S, Erim FB. 2017. Characterization of Turkish honeybee pollens by principal component analysis based on their individual organic acids, sugars, minerals, and antioxidant activities. **LWT - Food Sci Technol** 84: 402 - 408.

Kostic AZ, Barac MB, Stanojevic SP, Milojkovic-Opsenica DM, Tesic ZL, Sikoparija B, Radisic P, Prentovic M, Pesic MB. 2015. Physicochemical composition and techno-functional properties of bee pollen collected in Serbia. **LWT - Food Sci Technol** 62: 301 - 309.

Kroyer G, Hegedus N. 2001. Evaluation of bioactive properties of pollen extracts as functional dietary food supplement. **Innov Food Sci Emerg Technol** 2: 171 - 174.

Li F, Yuan Q, Rashid F. 2009. Isolation, purification and immunobiological activity of a new water-soluble bee pollen polysaccharide from *Crataegus pinnatifida* Bge. **Carbohyd Polym** 78: 80 - 88.

Lin FL, Vaughan TR, Vandewalker ML, Weber RW. 1989. Hypereosinophilia, neurologic, and gastrointestinal symptoms after bee-pollen ingestion. **J Allergy Clin Immunol** 83: 793 - 796.

Mărghitaş LA, Stanciu OG, Dezmirean DS, Bobiş O, Popescu O, Bogdanov S, Campos MG. 2009. *In vitro* antioxidant capacity of honeybee-collected pollen of selected floral origin harvested from Romania. **Food Chem** 115: 878 - 883.

Martín-Muñoz MF, Bartolome B, Caminoa M, Bobolea I, Garcia Ara MC, Quirce S. 2010. Bee pollen: a dangerous food for allergic children. Identification of responsible allergens. **Allergol Immunopathol** 38: 263 - 265.

Modro AFH, Silva IC, Luz CFP, Message D. 2009. Analysis of pollen load based on color, physicochemical composition and botanical source. **An Acad Bras Cienc** 81: 281 - 285.

Montenegro G, Pizarro R, Mejías E, Rodríguez S. 2013. Evaluación biológica de polen apícola de plantas nativas de Chile. **Phyton** 82: 7 - 14.

Morgano MA, Martins MCT, Rabonato LC, Milani RF, Yotsuyanagi K, Rodriguez-Amaya DB. 2010. Inorganic contaminants in bee pollen from southeastern Brazil. **J Agric Food Chem** 58: 6876 - 6883.

Negrão AF, Barreto LMRC, Orsi RO. 2014. Influence of the collection season on production, size, and chemical composition of bee pollen produced by *Apis mellifera* L.. **J Apic Sci** 58: 5 - 10.

Oliveira RC, Queiroz SCN, Luz CFP, Porto RS, Rath S. 2016. Bee pollen as a bioindicator of environmental pesticide contamination. **Chemosphere** 163: 525 - 534.

Pascoal A, Rodrigues S, Teixeira A, Feás X, Estevinho LM. 2014. Biological activities of commercial bee pollens: Antimicrobial, antimutagenic, antioxidant and anti-inflammatory. **Food Chem Toxicol** 63: 233 - 239.

Saral Ö, Yildiz O, Aliyazicioğlu R, Yuluğ E, Canpolat S, Öztürk F, Kolayli S. 2016. Apitherapy products enhances the recovery of CCL_4-induced hepatic damages in rats. **Turk J Med Sci** 46: 194 - 202.

Šarić A, Balog T, Sobocanec S, Kusic B, Sverko V, Rusak G, Likic S, Bubalo D, Pinto D, Marotti T. 2009. Antioxidant effects of flavonoid from Croatian *Cystus incanus* L. rich bee pollen. **Food Chem Toxicol** 47: 547 - 554.

Sattler JAG, De-Melo AAM, Nascimento KS, Melo ILP, Mancini-Filho J, Sattler A, Almeida-Muradian LB. 2016. Essential minerals and inorganic contaminants (barium, cadmium, lithium, lead and vanadium) in dried bee pollen produced in Rio Grande do Sul State, Brazil. **Food Sci Technol** 36: 505 - 509.

Sattler JAG, Melo ILP, Granato D, Araújo E, Freitas AS, Barth OM, Sattler A, Almeida-Muradian LB. 2015. Impact of origin on bioactive compounds and nutritional composition of bee pollen from southern Brazil: A screening study. **Food Res Int** 77: 82 - 91.

SEBRAE - Serviço Brasileiro de Apoio às Micro e Pequenas Empresas. **Técnicas de manejo para produção de pólen.** Portal Sebrae, 2015. **https://www.sebrae.com.br/sites/PortalSebrae/artigos/tecnicas-de-manejo-para-producao-do-polen,3f58fa2da4c72410VgnVCM100000b272010aRCRD#**

Sun L, Guo Y, Zhang Y, Zhuang Y. 2017. Antioxidant and anti-tyrosinase activities of phenolic extracts from rape bee pollen and inhibitory melanogenesis by cAMP/MITF/TYR pathway in B16 mouse melanoma cells. **Front Pharmacol** 8: 104.

Tohamy AA, Abdella EM, Ahmed RR, Ahmed YK. 2014. Assessment of anti-mutagenic, anti-histopathologic and antioxidant capacities of Egyptian bee pollen and propolis extracts. **Cytotechnology** 66: 283 - 297.

Tomás-Lorente F, Garcia-Grau MM, Nieto JL, Tomás-Barberán FA. 1992. Flavonoids from *Cistus ladanifer* bee pollen. **Phytochemistry** 31: 2027 - 2029.

Wang B, Diao Q, Zhang Z, Liu Y, Gao Q, Zhou Y, Li S. 2013. Antitumor activity of bee pollen polysaccharides from *Rosa rugosa*. **Mol Med Rep** 7: 1555 - 1558.

Wu Y, Lou Y. 2007. A steroid fraction of chloroform extract from bee pollen of *Brassica campestris* induces apoptosis in human prostate cancer PC-3 cells. **Phytother Res** 21: 1087 - 1091.

Xu X, Sun L, Dong J, Zhang H. 2009. Breaking the cells of rape bee pollen and consecutive

extraction of functional oil with supercritical carbon dioxide. **Innov Food Sci Emerg Technol** 10: 42 - 46.

Xu X, Dong J, Mu X, Sun L. 2011. Supercritical CO_2 extraction of oil, carotenoids, squalene and sterols from lotus (*Nelumbo nucifera* Gaertn) bee pollen. **Food Bioprod Process** 89: 47 - 52.

Xu X, Gao Y, Sun L. 2012. Free and esterified triterpene alcohol composition of bee pollen from different botanical origins. **Food Res Int** 48: 650 - 656.

Zu K, Mucci L, Rosner BA, Clinton SK, Loda M, Stampfer MJ, Giovannucci E. 2014. Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. **J Natl Cancer Inst** 106: djt430.