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Nutrient-rich bee pollen: A treasure trove of active natural metabolites

Qiang-Qiang Li[a], Kai Wang[a,*], Maria Cristina Marcucci[b], Alexandra Christine Helena Frankland Sawaya[c], Lin Hu[d], Xiao-Feng Xue[a], Li-Ming Wu[a,*], Fu-Liang Hu[e]

[a] Institute of Apicultural Research, Chinese Academy of Agricultural Sciences, Beijing, China
[b] Laboratory of Natural Products, Pharmacy and Biotechnology Department, University Anhanguera of São Paulo, SP, Brazil
[c] Faculty of Pharmaceutical Science, Universidade Estadual de Campinas, UNICAMP, Campinas, Brazil
[d] Institutes of Biology and Medical Sciences, Soochow University, Suzhou, China
[e] College of Animal Sciences, Zhejiang University, Hangzhou, China

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ABSTRACT

Bee pollen is a mixture of plant pollen pellet with nectar and honeybee secretions. Due to its active natural metabolites with extensive nutritional and therapeutic properties, it is recommended as a treasure trove of human nutrition. The nutritional components in bee pollen include carbohydrates, proteins, lipids, vitamins, minerals, polyphenols, and a small percentage of other components. Previous studies demonstrated that bee pollen exhibit antioxidant, antibacterial, anti-inflammatory, anticarcinogenic, and antiallergic properties. This comprehensive review focused on the nutritional properties and potentially active phytometabolites (polyphenolic acids and flavonoids) of bee pollen and its therapeutic health benefits. We also covered the food safety and guidelines for the consumption with future industrial challenges of bee pollen.

1. Introduction

Honey bees collect the pollen and agglutinate to fill their baskets from the flowers using their hind legs to make bee pollen. This process involves the moistening of flowers with bee oral secretions and allows forming the pellet and sticking to the specific baskets (corbiculae) (Fig. 1A) (Campos et al., 2008). Beekeepers use pollen traps at the entrance of their hives to collect raw bee pollen, which makes easy to collect bee pollen for commercial uses possible (Fig. 1B and C). The different nutritional components of bee pollen confer to various valuable therapeutic properties (Denisow and Denisow-Pietrzyk, 2016; Kieliszek et al., 2017). Bee pollen is widely recognized as the potential for medical or nutritional applications since early times. Previous literature showed women who had bee pollen in their diet in ancient time's maintained health, beauty, and strong human body (Graham, 2015 (Chapter 23)). The chemical composition of bee pollen differs based on the variety of factors, including botanical origins, bee species, and geographic origins. The palynology analysis is the most representative method for identifying the botanical origins of bee pollen (Almaraz et al., 2004; Da Silva, da Natividade, Camara, da Silva, & Silva, 2014; Nogueira, Iglesias, Feás, & Estevinho, 2012; Saa-Otero, Díaz-Losada, & Fernández-Gómez, 2000; Szczesna, 2006; Yang et al., 2013). Recent days, a wide variety of bee pollen products have been formulated as granules, tablets, candy bars, oral liquids, and tonics for

Abbreviations: GC–MS, gas chromatography-mass spectrometry; LC-ESI/MS, liquid chromatography-electrospray ionization mass spectrometry; TLC, thin layer chromatography; HPLC-DAD-ESI/MS, high-performance liquid chromatography-diode array detection-electrospray ionization mass spectrometry; HPLC-DAD-APCI/MS, high-performance liquid chromatography-diode array detection-atmospheric pressure chemical ionization mass spectrometry; UHPLC-LTQ-orbitrap/MS, ultra-performance liquid chromatography with a linear ion trap high-resolution orbitrap mass spectrometry system; UPLC-Q-Exactive orbitrap/MS, ultra-performance liquid chromatography in tandem with hybrid quadrupole-orbitrap mass spectrometry system; NMR, nuclear magnetic resonance; ICP-OES, inductively coupled plasma-optical emission spectrometry; TXRF, total reflection X-ray fluorescence; ICP-AES, inductively coupled argon plasma-atomic emission spectrometry; ASS, atomic absorption spectrometry; SGLT1, sodium-dependent glucose transporter 1; MRP2, multidrug resistance-associated protein 2; BSβG, broad-specific-β-glucosidase; LPH, lactase phlorizin hydrolase; UGT, UDP-glucuronosyltransferase; ROS, reactive oxygen species; MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; ABTS, 1, 2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); DPPH, 1-diphenyl-2-picrylhydrazyl radical; COX-2, cyclooxygenase-2; NO, nitric oxide; PGs, prostaglandins; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; IgE, immunoglobulin E; IgG1, immunoglobulin G1; MRL, maximum residue limits; ELISA, enzyme-linked immune-sorbent assay

* Corresponding authors.
E-mail address: kaiwang628@gmail.com (K. Wang).

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Fig. 1. Bee pollen raw materials collection process, including gathering pollen by bees (A), intercepting pollen grains by pollen traps (B), collecting the intercepted bee pollen grains (C), drying bee pollen (D), and packaging bee pollen (E). F shows the micromorphology of the bee pollen grains, using Scanning Electron Microscope (SEM) technology. The bee pollen shown in A, B, C is from *Camellia sinensis* L. in Zhejiang province of China, and the bee pollen shown in D, E, F comes from coconut palms (*Cocos nucifera* L.) in the province of Sergipe, Brazil. Figures A, B and C were provided by Prof. Zhongyin Zhang, from Henan Institute of Science and Technology, Xinxiang, China. Figures D and E were taken by Dr. Kátia Peres Gramacho from Universidade Federal Rural do Semi-Árido, Mossoró, RN, Brazil. Figure F were taken by Dr. Maria de Fatima Brito Souza Sundin, Department of Analytical Chemistry, Chemical Institute of Campinas State University (UNICAMP), Campinas, SP, Brazil.

human consumption (Bogdanov, 2012 (Chapter 2); Campos, Markham, Mitchell, & Cunha, 2015).

Improved techniques and methods for comprehensive composition profiling of bee pollen from various origins are necessary for understanding their variety of nutrients varying from different origins, as well as the potential bioactivities that are beneficial to human health. Recently, specific techniques like gas chromatography (GC), liquid chromatography (LC), gas chromatography-mass spectrometry (GC–MS), liquid chromatography in tandem with mass spectrometry (LC-MS), and high-resolution mass spectrometry have been used to analyze the composition of bee pollen to facilitate the quality control, nutrient profiling, as well as metabolism and bioactivity mechanisms investigations (Campos et al., 2008). According to previously published reviews, Puerto, Prieto, and Castro (2015) summarized the chemical composition of bee pollen, and some phenolic compounds that cause its antioxidant activity; Denisow and Denisow-Pietrzyk (2016) mainly introduced its biological and therapeutic properties; Ares, Valverde, Bernal, Nozal, and Bernal (2017) reported the extraction and determination techniques of some nutrients (carbohydrates, proteins, amino acids, lipids, phenolic compounds, vitamins and minerals) in bee pollen. However, the nutrient profile of samples of bee pollen with different botanical and geographic origins has been insufficiently studied. Although the studies on compositional profiling, a systematic classification of bee pollen lacks traceability of sample sources. Moreover, the studies on the metabolism of active natural plant metabolites from bee pollen after consumption, as well as the food safety of bee pollen are both unsatisfactory.

Therefore, the purpose of this review is to provide a comprehensive overview of recent studies regarding the nutrient profile of bee pollen with various botanical and geographic origins, as well as to give recent updates on nutritional properties of bee pollen and its potential bioactivities for human health. Additionally, the *in vivo* metabolic pathways of various potential active natural plant metabolites (mainly phenolic acids and flavonoids) from the different origin of bee pollen are highlighted. Moreover, this review also covers the food safety, essential guidance for the consumption of bee pollen, as well as a brief overview of several challenges and the future outcomes, which can facilitate its industrial development and wide-ranging applications.

2. Nutrients and nutritional properties

2.1. Essential nutrients

2.1.1. Carbohydrates

Carbohydrates are the major class of components and comprised of approximately 40–85% (W/W) of dry bee pollen (Table 1). Fructose is abundant, followed by glucose and sucrose compared to other carbohydrate components of bee pollen (Table 2). Oligosaccharides and polysaccharides are also very important ingredients in bee pollen which help to regulate various biological functions. Moreover, these compounds are regarded as characteristic markers for discriminating the botanical origin of bee pollen. However, it's difficult to detect them both by GC and high-performance liquid chromatography (HPLC) due to their highly hydrophilic nature, high molecular weight, and very similar polarity among these sugars (Martins, Morgano, Vicente, Baggio, & Rodriguez-Amaya, 2011; Qian, Khan, Watson, & Fearnley, 2008; Serra & Jorda, 1997). Therefore, it needs an attention to develop proper, innovative and effective methods for oligosaccharide and polysaccharide detection in bee pollen.

2.1.2. Protein and amino acids

The second most abundant components are protein, making up approximately 14–30% (W/W) with the total of 20 essential amino acids in dry bee pollens (Da Silva et al., 2014; González-Paramás, Bárez, Marcos, García-Villanova, and Sánchez, 2006; Serra & Jorda, 1997; Szczesna, 2006; Yang et al., 2013). HPLC and ion exchange

Table 1
The general nutrients in different species of bee pollen.

Components	g/100 g of dry bee pollen	Methods	Flora origins	Geographic origins	References
Protein	17.0–25.0	Kjeldahl method	*Arecaceae*, *Asteraceae*, *Myrtaceae* etc.	Southern Brazil	Almeida-Muradian, Pamplona, Coimbra, & Barth (2005)
	25.5–28.7		*Castanea*, *Cistus*, *Rubus*	Tuscany, Italy	Domenici et al. (2015)
	14.6–19.5		*Cucurbita pepo Thunb, Phoenix dactylifera* L., *Helianthus annuus* L., *Brassica napus* L., *Medicago sativa* L.	Saudi Arabia	Taha (2015)
	14.8–27.3		*Brassicaceae*, *Fabaceae*, *Ranunculaceae*, etc.	Serbia	Kostić, Barać et al. (2015)
Lipids	5.0–9.0	Soxhlet extraction; Folch method	*Arecaceae*, *Asteraceae*, *Myrtaceae* etc.	Southern Brazil	Almeida-Muradian et al. (2005)
	1.7–3.0		*Castanea*, *Cistus*, *Rubus*	Tuscany, Italy	Domenici et al. (2015)
	1.8–5.4		*Cucurbita pepo Thunb, Phoenix dactylifera* L., *Helianthus annuus* L., *Brassica napus* L., *Medicago sativa* L.	Saudi Arabia	Taha (2015)
	1.31–6.78		*Brassicaceae*, *Fabaceae*, *Ranunculaceae*, etc.	Serbia	Kostić, Barać et al. (2015)
Carbohydrates	41.1–60.4	Ultraviolet spectrophotometry	–	Southern Brazil	Carpes et al. (2009)
	67.6–84.8		–	Portugal and Spain	Nogueira et al. (2012)
	52.7–59.9		*Castanea*, *Cistus*, *Rubus*	Tuscany, Italy	Domenici et al. (2015)
	64.4–81.8		*Brassicaceae*, *Fabaceae*, *Ranunculaceae*, etc.	Serbia	Kostić, Barać et al. (2015)

chromatography are the two major techniques for the amino acid analysis. The amino acid such as proline, glutamic acid, and aspartic acid are the chief amino acids, although the composition and contents of amino acids differ among bee pollen samples from different botanical and geographic origins (Table 3). The high levels of proteins and amino acids make bee pollen an excellent animal feed and human food nutrition enhancer.

2.1.3. Lipids

Previous studies on the total lipid content of bee-collected pollen showed 1–10% (W/W) in dry bee pollen, and GC and GC–MS methods were used for the analysis of fatty acids (FAs) (Table 3) (Bárbara et al., 2015; Campos et al., 2008; Domenici et al., 2015; Feás, Vázqueztato, Estevinho, Seijas, & Iglesias, 2012; Saa-Otero et al., 2000; Serra & Jorda, 1997; Yang et al., 2013). A total of 20 FAs have been found in bee pollen; FA(C18:3) and FA(C16:0) are the major FAs. In addition, Mărgăoan et al. (2014) and Kostić, Pešić et al. (2017) proved the correlation between the distribution of FAs and the botanical origin of bee pollen based on PCA analysis. However, due to the complex lipid structures and numerous lipid isomers, it is difficult to identify various other classes of lipids, including phospholipids and sphingolipids, using current methods. In our recent research, a system of ultra-performance liquid chromatography in tandem with hybrid quadrupole-orbitrap mass spectrometry (UPLC-Q-Exactive orbitrap/MS) profiled various lipids in bee pollen including phosphatidylcholine (41 types), phosphatidylethanolamine (43 types), phosphatidylglycerol (9 types), phosphatidylserine (10 types), lysophosphatidylcholine (12 types), ceramide (8 types), diglyceride (27 types), triglyceride (137 types), and fatty acids (47 types) (Li et al., 2017). This method might be useful for understanding the physiological role of different lipids and be helpful for explaining the pharmacological mechanisms of active lipids.

2.1.4. Vitamins

Bee pollen is rich in vitamins, especially group-B vitamins. The vitamin B3 with nicotinamide and niacin, is the major component among other group-B vitamins, which suggests a good supplement against pellagra (Table 4) (Arruda, Pereira, Freitas, Barth, & Almeida-Muradian, 2013). Moreover, vitamin A, as an excellent antioxidant, accounts for approximately 1.5 mg per 100 g dry bee pollen. Bee pollen also contains vitamin E (α-tocopherol - 6.2 mg/100 g dry bee pollen from *Zea mays* L.) and trace amounts of vitamin C (Chantarudee et al., 2012). Additionally, the variation in vitamin contents between different pollen species may provide indications of the botanical origins of bee pollen.

2.1.5. Minerals

Bee pollen contains rich micronutrients such as potassium (K), sodium (Na), calcium (Ca), magnesium (Mg), phosphorus (P), zinc (Zn), iron (Fe), copper (Cu), and manganese (Mn); and it is the best supplement for respective deficiencies in human nutrition (Table 4). Various techniques, such as inductively coupled plasma-optical emission spectrometry (ICP-OES) (Kostić, Pešić et al., 2015; Serra & Jorda, 1997), total refection X-ray fluorescence (TXRF) (Mărgăoan, Mărghitaş, Dezmirean, Mihai, & Bobis, 2010), inductively coupled argon plasma-atomic emission spectrometry (ICP-AES) (Yang et al., 2013), and atomic absorption spectrometry (ASS) (Carpes, Mourão, Alencar, & Masson, 2009; Da Silva et al., 2014; Formicki, Greń, Stawarz, Zyśk, & Gał, 2013), provide reliable mineral detection methods for bee pollen. Taha (2015) found that bee pollen from different botanical origins was classified according to their different types and contents of minerals. The composition of pollen loads contains maximum contents of Mg, P, and Mn for *Phoenix dactylifera* L., Ca and Zn for *Medicago sativa* L., Na and K for *Brassica napus* L., Cu for *Helianthus annuus* L., and Fe for *Cucurbita pepo* Thunb. Thus, the minerals in bee pollen may not only be used as food supplements in the diet but also as the characteristic markers for identifying plant origins and monitoring bee pollen quality.

2.1.6. Carotenoids

Carotenoids are a very diverse group of yellow-to-red-color polyenes and are responsible for colors in many plant-derived agro-products, and play important roles in human health. β-carotene converts into vitamin A, which offers to lower the risk of cancer and cardiovascular diseases (Kritchevsky, 1999). Mărgăoan et al. (2014) identified several carotenoids from Romanian bee pollen, such as lutein (57.04–476.30 μg/g dry bee pollen), β-cryptoxanthin (1.31–35.43 μg/g dry bee pollen), β-carotene (trace-18.18 μg/g dry bee pollen) using HPLC method. They also found that the β-carotene content was significantly lower in Romanian samples compared with Brazilian samples. According to Muniategui, Sancho, Lopez, Huicobro, and Simal (1990), the total carotene contents are varied widely due to climatic differences and botanical origin of the pollen.

Table 2
The sugars in different species of bee pollen.

Components	Abbr.	g/100 g of dry bee pollen	Methods	Flora origins	Geographic origins	References
Fructose	Fru	15.2–22.4	Gas chromatography (GC)	–	Western Spain	Serra and Jorda (1997)
		7.2	Thin layer chromatography (TLC)	*Zea mays* L.	Thailand	Chantarudee et al. (2012)
		17.0–21.4	High Performance Liquid Chromatography (HPLC)	*Cucurbita pepo Thunb, Phoenix dactylifera* L., *Helianthus annuus* L., *Brassica napus* L., *Medicago sativa* L.	Tuscany, Italy	Taha (2015)
Glucose	Glc	7.0–21.9	HPLC	–	Brazil	Martins et al. (2011)
		6.4	TLC	*Zea mays* L.	Thailand	Chantarudee et al. (2012)
		15.3–17.1	HPLC	*Cucurbita pepo Thunb, Phoenix dactylifera* L., *Helianthus annuus* L., *Brassica napus* L., *Medicago sativa* L.	Tuscany, Italy	Taha (2015)
Sucrose	S	14–19.8	HPLC	–	Spain, Israel, China and Romania	Qian et al. (2008)
		0.6	TLC	*Zea mays* L.	Thailand	Chantarudee et al. (2012)
Maltose	Mal	0.8–3.2	GC	–	Western Spain	Serra and Jorda (1997)
Isomaltose	Iso	0.1–0.6				
Melezitose	Mel	0.1–0.3				
Raffinose	Raf	0.1–0.2				
Trehalose	Tre	0.1–0.4				
Erlose	Erl	0.1–0.3				

2.2. The potentially active natural plant metabolites and the associated in vivo metabolic pathways from bee pollen

2.2.1. Polyphenols

Polyphenols are secondary metabolites of plants and generally involved in defense against ultraviolet radiation (UV) or aggression by pathogens. There are specific plant enzymes participating in the polyphenol biosynthetic pathway. Some polyphenols present in pollen play an important role during the pollen germination and promote the growth of the pollen tube and also vary from the palynological origins (Karioti et al., 2008). According to their chemical structures, polyphenols have been divided into flavonoids (i.e., non-glycosylated and glycosylated flavonoids) and phenolic acids. There are 14 different phenolic acids such as gallic acid, ferulic acid, caffeic acid, vanillic acid, syringic acid, benzoic acid, chlorogenic acid, protocatechuic acid, tert-cinnamic acid, and *p*-coumaric acid; 20 flavonoids, including 13 non-glycosylated flavonoids such as quercetin, isorhamnetin, naringenin, hesperetin, kaempferol, catechin, epicatechin, luteolin, and apigenin; and 7 glycosylated flavonoids, have been identified and quantified in diverse samples of bee pollen varying from different botanic and geographic origins (Table 5). Additionally, approximately 30 glycosylated flavonoids have been identified, however not quantified, in several pollen samples collected by honeybees (Campos et al., 2015; Ferreres, Pereira, Valentão, & Andrade, 2010; Paola-Naranjo, Sánchez-Sánchez, González-Paramás, & Rivas-Gonzalo, 2004; Tomás-Barberán, Tomás-Lorente, Ferreres, & Garcia-Viguera, 2010). The advanced techniques such as high-performance liquid chromatography-diode array detection (HPLC-DAD) (Freire et al., 2012), high-performance liquid chromatography-diode array detection-electrospray ionization mass spectrometry (HPLC-DAD-ESI/MS) (Lv, Wang, He, Wang, & Suo, 2015), liquid chromatography-electrospray ionization mass spectrometry (LC-ESI/MS) (Ares et al., 2015), high performance liquid chromatography-diode array detection-atmospheric pressure chemical ionization mass spectrometry (HPLC-DAD-APCI/MS), ultra-performance liquid chromatography with a linear ion trap-high resolution orbitrap mass spectrometry system (UHPLC-LTQ-orbitrap/MS) (Zhang, Yang, Jamali, & Peng, 2016) and nuclear magnetic resonance (NMR) (Li et al., 2015; Zhou et al., 2015), have been applied to the identification and quantification of polyphenols. However, the different types of polyphenols in different bee pollens remain unknown and need to be studied in the future.

2.2.2. Metabolic pathways of polyphenols in vivo

As mentioned above, 60 types of polyphenols such as phenolic acids, glycosylated and non-glycosylated flavonoids have been found in bee pollens of varied botanical origins. Several polyphenols, like quercetin, kaempferol, quercetin-3-O-glucoside, and kaempferol-3-O-glucoside (from *Brassica campestris* L.) are distributed abundantly in the *B. campestris* L. bee pollen (Fig. 2). Additionally, intake of raw bee pollen or bee pollen related products (capsules, tablets, powder) in human, the polyphenols undergo a series of the complex digestive, absorptive, and other metabolisms *in vivo*. The metabolized polyphenols then exert their various bioactivities, such as antioxidant, anti-inflammatory, anticancer, etc. (Rzepecka-Stojko et al., 2015; Walle, 2004). Future studies are needed to understand the exact underlying mechanisms *in vivo*, to identify the bioactive mechanisms.

The metabolic pathways of specific flavonoids are presented in Fig. 2, oligomeric flavonoids are first digested to monomeric units in the stomach. However, Hollman, De Vries, Van Leeuwen, Mengelers, and Katan (1995) have suggested that some flavonoid glycosides could be absorbed intact by the sodium-dependent glucose transporter 1 (SGLT1) in the small intestine. Furthermore, Walgren, Karnaky, Lindenmayer, and Walle (2000) demonstrated that the absorption efficiency of some flavonoid glycosides was dramatically suppressed by the apical transporter multidrug resistance-associated protein 2 (MRP2). Most of the flavonoid metabolisms occur in the small intestine where a variety of flavonoid metabolism-related enzymes exist, such as

Table 3
The amino acids and fatty acids in different species of bee pollen.

Components	Abbr.	Content mg/g of dry bee pollen	Methods	Flora origins	Geographic origins	References
Total amino acids						
Threonine	Thr	0.04–12.5	HPLC	*Cistaceae, Boraginaceae, Papilonaceae, Asteraceae, Fagaceae, Rosaceae, Ericaceae*	Spain	González-Paramás et al. (2006)
Valine	Val	0.06–11.9	Ion exchange chromatography (using Amino acid analyzer)	*Melipona subnitida*	Brazil	Da Silva et al. (2014)
Methionine	Met	0.02–5.6		*Onagraceae, Caryophyllaceae, Artemisia, Agrimonia, Rheum, Cornus, Fragaria, Syringa, Ranunculus, Majorana* type, *Brassica, Sinapis alba, Sinapis arvensis, Campanula patula, Chelidonium maius, Polygonum bistorta*	Poland	Szczesna (2006)
Isoleucine	Ile	0.05–10.2			12 regions of China	Yang et al. (2013)
Leucine	Leu	0.07–23.1	Ion exchange chromatography (using Amino acid analyzer)			
Phenylalanine	Phe	0.04–11.8				
Lysine	Lys	0.07–21.1				
Tryptophan	Trp	0.07–0.5				
Aspartic acid	Asp	0.1–30.2		*Brassica napus* L., *Citrullus lanatus* L., *Camellia japonica* L., *Dendranthema indicum* L., *Fagopyrum esculentum* L., *Helianthus annuus* L., *Nelumbo nucifera Gaertn.*, *Papaver rhoeas* L., *Rosa rugosa*, *Schisandra chinensis*, *Vicia faba* L., *Zea mays* L.		
Asparagine	Asn	0.03–4.9				
Serine	Ser	0.05–13.3				
Glutamic acid	Glu	0.1–31.2				
Glutamine	Gln	0.05–8.4				
Proline	Pro	0.1–42.7				
Glycine	Gly	0.05–12.8				
Alanine	Ala	0.07–12.9				
Cystine	Cys	0.01–3.1				
Tyrosine	Tyr	0.02–10.6				
Histidine	His	0.04–6.2				
Arginine	Arg	0.07–11.3				
Fatty acids		Percentage of total fatty acids				
Caproic acid	C6:0	Trace-0.15%	GC	*Castanea Sativa, Cytisus, Erica, Eucalyptus, Halimium alyssoides, Quercus robur, Raphanus raphanistrum, Rubus*	NW Iberian Peninsula within Galicia	Saa-Otero et al. (2000)
Caprylic acid	C8:0	Trace-4.8%	GC/MS			Feás et al. (2012)
Capric acid	C10:0	Trace-15.8%			Portugal	Yang et al. (2013)
Lauric acid	C12:0	Trace-27.9%		*Cistaceae, Boraginaceae, Rosaceae, Fagaceae, Asteraceae, Fabaceae, Ericaceae, Mimosaceae, Myrtaceae*	12 regions of China	Mărgăoan et al. (2014)
Myristic acid	C14:0	Trace-21.8%			Romania	
–	C14:1	Trace-1.7%				
Pentadecylic acid	C15:0	Trace-2.4%		*Brassica napus* L., *Citrullus lanatus* L., *Camellia japonica* L., *Dendranthema indicum* L., *Fagopyrum esculentum* L., *Helianthus annuus* L., *Nelumbo nucifera* Gaertn., *Papaver rhoeas* L., *Rosa rugosa*, *Schisandra chinensis*, *Vicia faba* L., *Zea mays* L.	João Dourado and Uibaí	Bárbara et al. (2015)
Palmitic acid	C16:0	Trace-67.6%				
palmitoleic acid	C16:1	Trace-5.1%			Serbian	Kostić, Pešić et al. (2017)
Margaric acid	C17:0	Trace-0.7%				
Stearic acid	C18:0	Trace-9.1%				
Oleic acid	C18:1	Trace-36.0%		*Rosaceae, Fabaceae, Asteraceae, Brasicaceae, Ericaceae, Salicaceae*		
Linoleic acid	C18:2	Trace-49.7%				
α-Linolenic acid	C18:3	Trace-63.4%		*Mellipona mandacaia* Smith		
Arachidic acid	C20:0	Trace-42.7%		*Fraxinus sp.*, *Zea mays*, *Fabaceae, Brassicaceae*		
Gadoleic acid	C20:1	Trace-3.4%				
Eicosatrienoic acid	C20:3	Trace-0.5%				
Behenic acid	C22:0	Trace-18.1%				
Erucic acid	C22:1	Trace-1.7%				
Lignoceric acid	C24:0	Trace-1.5%				
Nervonic acid	C24:1	Trace-0.2%				

'Trace' means that the content is less than the limit of quantification (LOQ).

broad-specific-β-glucosidase (BSβG) and lactase phlorizin hydrolase (LPH) for flavonoid glycosides deglycosylation and hydrolysis (Day et al., 2000), and UDP-glucuronosyl transferase (UGT) for glucuronidation (Boersma et al., 2002). In the small intestine, metabolites such as glucuronides, sulfates, and O-methylated aglycones like quercetin, luteolin, naringenin, hesperetin, and epicatechin are transferred across the small intestine membranes and arrive the liver, which exhibits beneficial bioactivities in our body (Spencer et al., 1999). Further absorption occurs in the colon where the enzymes stemming from gut microflora could degrade flavonoids into phenolic acids. Phenolic acids with the simple structures could be easily absorbed or metabolized in the liver (Spencer, Abd-El-Mohsen, & Rice-Evans, 2004). Flavonoids usually degrade to form desaminotyrosine (DAT) in the gut microflora. DAT may be able to modulate the immune response to influenza infection (Steed et al., 2017).

Previous studies provide little information on the metabolism of bee pollen in the human. However, studies related to the dietary polyphenols metabolisms are still unclear, further studies are needed to be focused on the circulation of these active natural plant metabolites and the potential *in vivo* metabolisms.

2.3. Nutritional properties

Bee pollen is recommended as a best dietary supplement and exhibits beneficial effects to human health. It has good nutritional values which are associated with metabolism at the molecular level and regulates certain biochemical functions (Iversen, Fiirgaard, Schriver, Rasmussen, & Andreasen, 1997). A diet with nutrient-rich bee pollen is attractive for the children with loss of appetite and the patients of malnutrition (Denisow & Denisow-Pietrzyk, 2016). Regular intake of bee pollen is ameliorative to the adverse reactions during chemotherapy and radiotherapy (Yakusheva, 2010). Besides, bee pollen also benefits the people undertaking strenuous mental/physical work (Attia, Alhanoun, Eldin, Bovera, & Shewika, 2011; Nakajima, Tsuruma, Shimazawa, Mishima, & Hara, 2009). Studies showed that a diet supplemented with bee pollen strengthens muscle and improve the body condition in humans (Salles et al., 2014).

3. Biological activities of bee pollen on human health

Bee pollen contains a variety of primary and secondary metabolites which possesses potential therapeutic properties such as antioxidant,

Table 4
The vitamins and minerals in different species of bee pollen.

Compounds	Common name	Content	Methods	Flora origins	Geographic origins	References
Vitamins		mg/100 g of dry bee pollen				
Vitamin A	β-Carotene	Trace-1.5	AOAC microfluorimetry	*Zea mays* L.	Thailand	Chantarudee et al. (2012)
Vitamin B1	–	0.2–0.9	LC		Brazil	Arruda et al. (2013)
Vitamin B2	–	0.5–2.4				
Vitamin B3	Nicotinic acid	0.2–3.8				
	Nicotinamide	0.5–12.1				
	Niacin	0.7–13.0				
Vitamin B5	–	Trace-0.4				
Vitamin B6	Pyridoxol	Trace-0.1				
	Pyridoxal	Trace-0.4				
	Pyridoxamine	Trace-0.6				
	Pyridoxine	Trace-0.7				
Vitamin B9	Folic acid	Trace				
Vitamin B12	–	Trace				
Vitamin C	Ascorbic acid	Trace				
Vitamin E	α-Tocopherol	Trace-6.21				
Minerals	Abbr.	mg/g of dry bee pollen				
Potassium	K	2.5–20.0	Inductively coupled argon plasma-atomic emission spectrometry (ICP-AES)	*Brassica napus* L., *Citrullus lanatus* L., *Camellia japonica* L., *Dendranthema indicum* L., *Fagopyrum esculentum* L., *Helianthus annuus* L., *Nelumbo nucifera Gaertn.*, *Papaver rhoeas* L., *Rosa rugosa*, *Schisandra chinensis*, *Vicia faba* L., *Zea mays* L. *Melipona subnitida* *Fraxinus*, *Brassicaceae*, *Fabaceae*, *Helianthus*, *Salix*, *Plantago*, *Ambrosia*, *Apiaceae*, *Rosaceae*, *Asteraceae*, *Sophora*, *Ranunculaceae* *Cucurbita pepo Thunb*, *Phoenix dactylifera* L., *Helianthus annuus* L., *Brassica napus* L., *Medicago sativa* L.	12 regions of China	Yang et al. (2013)
Magnesium	Mg	0.2–4.7			Brazil	Da Silva et al. (2014)
Calcium	Ca	0.2–5.8			Serbia	Kostić, Pešić et al. (2015)
Sodium	Na	Trace-8.4	Atomic absorption spectrophotometry (AAS)		Saudi Arabia	Taha (2015)
Phosphorus	P	0.8–9.6				
Iron	Fe	0.01–0.6	Inductively coupled plasma-optical emission spectrometry (ICP-OES)			
Zinc	Zn	0.02–0.1				
Copper	Cu	Trace-0.02				
Strontium	Sr	Trace-0.004	AAS			
Manganese	Mn	0.01–0.1				
Aluminum	Al	0.01–0.3				

'Trace' means that the content is less than the limit of quantification (LOQ).

antibacterial, anti-inflammatory, anticarcinogenic, and antiallergic activities which capable of regulating body functions (Fig. 3).

3.1. Antioxidant activity

Reactive oxygen species (ROS), such as $O_2^{\cdot-}$, $HO^{\cdot}$, $ROO^{\cdot}$, H_2O_2 most frequently found in biological systems are involved in stress response, aging, and cancer (Campos, Webby, Markham, Mitchell, & Da Cunha, 2003). Excessive free radicals effortlessly cause cell damage or apoptosis and lead to many diseases, such as cardiovascular and cerebrovascular diseases, Parkinson's disease, and cancer (Heim, Tagliaferro, & Bobilya, 2002). The *in vitro* antioxidant studies of ethanoic or methanolic extracts of bee pollen showed the lipid peroxidation inhibiting and free radicals scavenging activities (Fatrcová-Šramková, Nôžková, Máriássyová, & Kačániová, 2016; Khider, Elbanna, Mahmoud, & Owayss, 2013; Rzepecka-Stojko, Pilawa, Ramos, & Stojko, 2012; Silva et al., 2009; Zhang et al., 2016). Thus, bee pollen with excellent antioxidant activity is awfully important for human health.

Flavonoids block the oxidation by scavenging free radical chain from the hydrogen atoms of phenolic hydroxyl groups. Besides, toxic metals also can be eradicated from the body by binding metal ions with the flavonoids (Campos et al., 2008; Münstedt & Bogdanov, 2008; Nogueira et al., 2012). Thus, flavonoids have been proved as an effective agent against genotoxic and carcinogenic substances (Campos et al., 2003; Chen et al., 2002; Rzepecka-Stojko et al., 2012). Moreover, the flavonoids such as kaempferol-3-O-(2-O-p coumaroyl)-α-L-arabinopyranoside isolated from Brazilian bee pollen, exerted strong antioxidant activity evaluated by scavenging 1, 2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 1-diphenyl-2-picrylhydrazyl (DPPH), and ROS (Abouda, Zerdani, Kalalou, Faid, & Ahami, 2011; LeBlanc, Davis, Boue, Delucca, & Deeby, 2009; Ohta et al., 2007).

The *in vivo* antioxidant effects of bee pollen were also investigated from the *Cistaceae* bee pollen which modulated the expression of antioxidant enzymes in mice (liver, brain, and lysate of erythrocytes), and reduced hepatic lipid peroxidation (Šarić et al., 2009). Bee pollen originating from Cairo and Egypt, led to a significant decrease of malondialdehyde (MDA), as well as a notable increase of superoxide dismutase (SOD) and glutathione (GSH) levels in blood and brain, which enhanced the antioxidant system against sodium fluoride-induced toxicity in rats (Khalil & Elsheikh, 2010). Chestnut bee pollen protected hepatocytes against oxidative stress and promoted the restoration of the liver in CCl_4-induced rats (Yıldız et al., 2013). The previous date showed bee pollen also modulated the catalase (CAT), glutathione peroxidase (GSH-Px) and SOD levels in thioacetamide-induced hyperammonemia of rats (Omnia, Hatem, & Rania, 2014). These *in vitro* and *in vivo* studies demonstrated the effective antioxidant activities of bee pollen, and it can be used as a dietary antioxidant for human health.

3.2. Antimicrobial activity

The previous antimicrobial studies of ethanoic and methanolic extracts of bee pollen exerted strong antimicrobial activities on several bacterial strains (*Escherichia coli*, *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella enteritidis*, *Listeria monocytogenes*, and *Pseudomonas aeruginosa*) (Abouda et al., 2011; Fatrcová-Šramková, et al., 2016; Khider et al., 2013; Pascoal, Rodrigues, Teixeira, Feás, & Estevinho, 2014). Additionally, these extracts also exhibited antifungal effects on different strains of microscopic fungi and yeasts, such as *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Geotrichum candidum*, and *Rhodotorula mucilaginosa* (Kačániová et al., 2012). Moreover, Barbosa, Silvestre, Simões, and

Table 5
The polyphenols in different species of bee pollen.

Components	μg/g of bee pollen	Methods	Flora origins	Geographic origins	References
Gallic acid	Trace-32	HPLC; HPLC with electrochemical detection	*Zea mays*	Anzer Plateau; Latvia, Lithuania, Spain, China; Fayoum, Egypt	Ulusoy and Kolayli (2014); Kaškonienė, Ruočkuvienė, Kaškonas, Akuneca, and Maruška (2015), Mohdaly, Mahmoud, Roby, Smetanska, and Ramadan (2015)
Epicatechin	Trace-5	HPLC	*Zea mays*	Anzer Plateau; Fayoum, Egypt	Ulusoy and Kolayli (2014), Mohdaly et al. (2015)
Catechin	Trace				
Quercetin	Trace-530	HPLC-DAD; Nano-LC-UV; HPLC; HPLC with electrochemical detection; HPLC-DAD-APCI/MS; UHPLC-LTQ-orbitrap/MS	*Cecropia*, *Eucalyptus*, *Elaeis*, *Mimosa pudica*, *Eupatorium*, and *Scoparia*; *Brassica campestris* L.; *Zea mays*; *Brassica campestris* L.	Canavieiras municipality (northeastern Brazil); Viannos (Crete); Anzer Plateau; Latvia, Lithuania, Spain, China; Qinghai-Tibetan Plateau, northwest China; Fayoum, Egypt; Nanjing, Jiangsu province, China	Freire et al. (2012), Fanali, Dugo, and Rocco (2013), Ulusoy and Kolayli (2014), Kaškonienė et al. (2015), Lv et al. (2015), Mohdaly et al. (2015), Zhang et al. (2016)
Naringenin	Trace-118	HPLC-DAD; Nano-LC-UV; HPLC with electrochemical detection; HPLC; UHPLC-LTQ-orbitrap/MS	*Cecropia*, *Eucalyptus*, *Elaeis*, *Mimosa pudica*, *Eupatorium*, and *Scoparia*; *Zea mays*; *Brassica campestris* L.	Canavieiras municipality (northeastern Brazil); Viannos (Crete); Latvia, Lithuania, Spain, China; Fayoum, Egypt; Nanjing, Jiangsu province, China	Freire et al. (2012), Fanali et al. (2013), Kaškonienė et al. (2015), Mohdaly et al. (2015), Zhang et al. (2016)
Kaempferol	Trace-8	HPLC-DAD; Nano-LC-UV; HPLC-DAD-APCI/MS; HPLC; UHPLC-LTQ-orbitrap/MS	*Cecropia*, *Eucalyptus*, *Elaeis*, *Mimosa pudica*, *Eupatorium*, and *Scoparia*; *Brassica campestris* L.; Zea mays; *Brassica campestris* L.	Canavieiras municipality (northeastern Brazil); Viannos (Crete); Qinghai-Tibetan Plateau, northwest China; Fayoum, Egypt; Nanjing, Jiangsu province, China	Freire et al. (2012), Fanali et al. (2013), Lv et al. (2015), Mohdaly et al. (2015), Zhang et al. (2016)
Luteolin	Trace	HPLC-DAD; HPLC	*Cecropia*, *Eucalyptus*, *Elaeis*, *Mimosa pudica*, *Eupatorium*, and *Scoparia*; *Zea mays*	Canavieiras municipality (northeastern Brazil); Fayoum, Egypt	Freire et al. (2012), Mohdaly et al. (2015)
Hesperetin	Trace-3	Nano-LC-UV	–	Viannos (Crete)	Fanali et al. (2013)
tert-Cinnamic acid	0.07–6	Nano-LC-UV; HPLC	–	Viannos (Crete); Anzer Plateau	Fanali et al. (2013), Ulusoy and Kolayli (2014)
o-Coumaric acid	Trace-37				
Protocatechuic acid	Trace-0.2				
Ferulic acid	Trace-149	Nano-LC-UV; HPLC; HPLC with electrochemical detection	*Zea mays*	Viannos (Crete); Anzer Plateau; Latvia, Lithuania, Spain, China; Fayoum, Egypt	Fanali et al. (2013), Ulusoy and Kolayli (2014), Kaškonienė et al. (2015), Mohdaly et al. (2015)
Benzoic acid	Trace-11	HPLC	–	Anzer Plateau	Ulusoy and Kolayli (2014)
p-OH benzoic acid	Trace-1.2				
Chlorogenic acid	Trace-0.8				
Rutin	Trace-956	HPLC; HPLC with electrochemical detection; HPLC-DAD-APCI/MS; UHPLC-LTQ-orbitrap/MS	*Brassica campestris* L.; *Zea mays*; *Brassica campestris* L.	Anzer Plateau; Latvia, Lithuania, Spain, China; Qinghai-Tibetan Plateau, northwest China; Fayoum, Egypt; Nanjing, Jiangsu province, China	Ulusoy and Kolayli (2014), Kaškonienė et al. (2015), Lv et al. (2015), Mohdaly et al. (2015), Zhang et al. (2016)
Caffeic acid	Trace-21	HPLC; HPLC with electrochemical detection	*Zea mays*	Anzer Plateau; Latvia, Lithuania, Spain, China; Fayoum, Egypt	Ulusoy and Kolayli (2014), Kaškonienė et al. (2015), Mohdaly et al. (2015)
p-Coumaric acid	0.3–1.8	HPLC	*Zea mays*	Anzer Plateau; Fayoum, Egypt	Ulusoy and Kolayli (2014), Mohdaly et al. (2015)
Vanillic acid	0.2–0.9				
Syringic acid	0.1–2.6				
2-Hydroxycinnamic acid	43–180	HPLC with electrochemical detection	–	Latvia, Lithuania, Spain, China	Kaškonienė et al. (2015)
Apigenin	–	HPLC	*Zea mays*	Fayoum, Egypt	Mohdaly et al. (2015)
3,4-Dimethoxycinnamic acid	–				
Quercetin-3-O-*β*-D-glucosyl-(2 → l)- *β*-glucoside	0.65–5108	HPLC-DAD-ESI-MS; NMR	*Brassica napus* L.	China	Li et al. (2015), Zhou et al. (2015)
Kaempferol-3,4′-di-O-*β*-D-glucoside	1.89–895				
Kaempferol-3-O-*β*-D-glucosyl-(2 → l)-*β*-D-glucoside	0.2–4243				
	mg/g of extracts [a]				
Isorhamnetin	Trace-3	HPLC-DAD; HPLC-DAD-APCI/MS; UHPLC-LTQ-orbitrap/MS	*Cecropia*, *Eucalyptus*, *Elaeis*, *Mimosa pudica*, *Eupatorium*, and *Scoparia*; *Brassica campestris* L.	Canavieiras municipality (northeastern Brazil); Qinghai-Tibetan Plateau, northwest China; Nanjing, Jiangsu province, China	Freire et al. (2012), Lv et al. (2015), Zhang et al. (2016)

(*continued on next page*)

Table 5 (*continued*)

Components	μg/g of bee pollen	Methods	Flora origins	Geographic origins	References
Quercitrin	21	UHPLC-LTQ-orbitrap/MS	*Brassica campestris* L.	Nanjing, Jiangsu province, China	Zhang et al. (2016)
Quercetin 3-O-glucoside	20				
Kaempferol 3-O-glucoside	19				
	μg/kg of bee pollen				
trans-Piceid	Trace	LC-ESI-MS	–	Spain	Ares et al. (2015)
cis-Piceid	Trace-70				
trans-Resveratrol	Trace-9100				
cis-Resveratrol	Trace-115				

'Trace' means that the content is less than the limit of quantification (LOQ).
[a] it means the ethanol extracts from bee pollen.

Estevinho (2010) found that the lipophilic fractions of bee pollen originating from three different floras could resist the growth of several *Gram*-positive bacteria. The antimicrobial and antifungal properties of bee pollen help in the prevention and aid in the management of bacterial and fungal infections respectively.

3.3. Anti-inflammatory activity

Previous studies indicate that bee pollen possesses anti-inflammatory activity due to its abundant polyphenolic compounds (Al-Salem, Bhat, Al-Ayadhi, & El-Ansary, 2016; Maruyama, Sakamoto, Araki, & Hara, 2010; Moita et al., 2013), especially the ethanol extracts of bee pollen from different plant species rich in polyphenols. Maruyama et al. (2010) revealed that the ethanol extracts of *Cistus* sp. bee pollen, collected from Spain, resisted carrageenan-induced rat hind paw edema through inhibition on cyclooxygenase-2 (COX-2) and nitric oxide (NO) production. Moita et al. (2013) demonstrated that the ethanol extracts of *Echium plantagineum* L. bee pollen exerted anti-inflammatory activity by reducing NO and prostaglandins (PGs) production in lipopolysaccharide (LPS)-challenged murine macrophages. Al-Salem et al. (2016) also showed the bee pollen anti-inflammatory effects on propionic acid (PA)-intoxicated rats by regulating interferon-γ (IFN-γ), nor-adrenaline, 5-hydroxytryptamine, dopamine, and caspase-3. Previous studies also demonstrated the anti-inflammatory activities of fatty acids, phytosterols, and phospholipids of bee pollen (Choi, 2010; Li et al, 2017; Pascoal et al., 2014).

3.4. Anticarcinogenic activity

Previous studies demonstrated the anticarcinogenic activities of bee pollen. According to Gao, Hu, Zhu, and Li (2003) and Wang et al., 2013, the polysaccharides isolated from *Brassica napus* L. bee pollen inhibited tumor growth in Sarcoma 180 and B16 melanoma-bearing mice, as well as the polysaccharides extracted from *Rosa rugosa* bee pollen exhibited significant anti-proliferative effects on colon cancer cells including HT-29 and HCT116 cell lines. Additionally, Wu and Lou (2007) purified the steroid fraction from chloroform extracts of *Brassica campestris* bee pollen which showed anticarcinogenic properties against prostate cancer. Murakami et al. (2008) also reported that intake of bee pollen reduced prostatic hyperplasia.

3.5. Antiallergic activity and immune response

As previously described, treatment with extracts rich in phenolic compounds of bee pollen can prevent allergy. Medeiros et al. (2008) found that phenolic extracts of bee pollen inhibited allergic reactions in the rats induced by ovalbumin, with decreased serum immunoglobulin E (IgE) and immunoglobulin G1 (IgG1) levels as well as the inhibition of leukocyte migration into the bronchoalveolar lavage. Ishikawa et al. (2008) reported that the bee pollen from alfalfa and red clover reduced the degranulation in mast cells, by inhibiting phosphorylation of protein tyrosine. They further demonstrated that the lipid-soluble fraction of bee pollen exerted antiallergic activity by inhibiting the IgE binding to FcεRI in cutaneous cells (Ishikawa et al., 2009). Moita et al. (2014) revealed that the hydromethanolic extracts of *Echium plantagineum* L. bee pollen (containing flavonoids, fatty acids, and organic acids) inhibited β-hexosaminidase expression in rat basophilic leukemic cells. These studies suggest a great potential of bee pollen to prevent allergy and regulate the immune system. However, the bee pollen extracts and their underlying mechanisms between antiallergic activity and immune responses need to be clearer further.

3.6. Cardioprotective effects

Bee pollen possesses the hypolipidemic activity by reducing the content of cholesterol, triacylglycerol, and total lipids in the body,

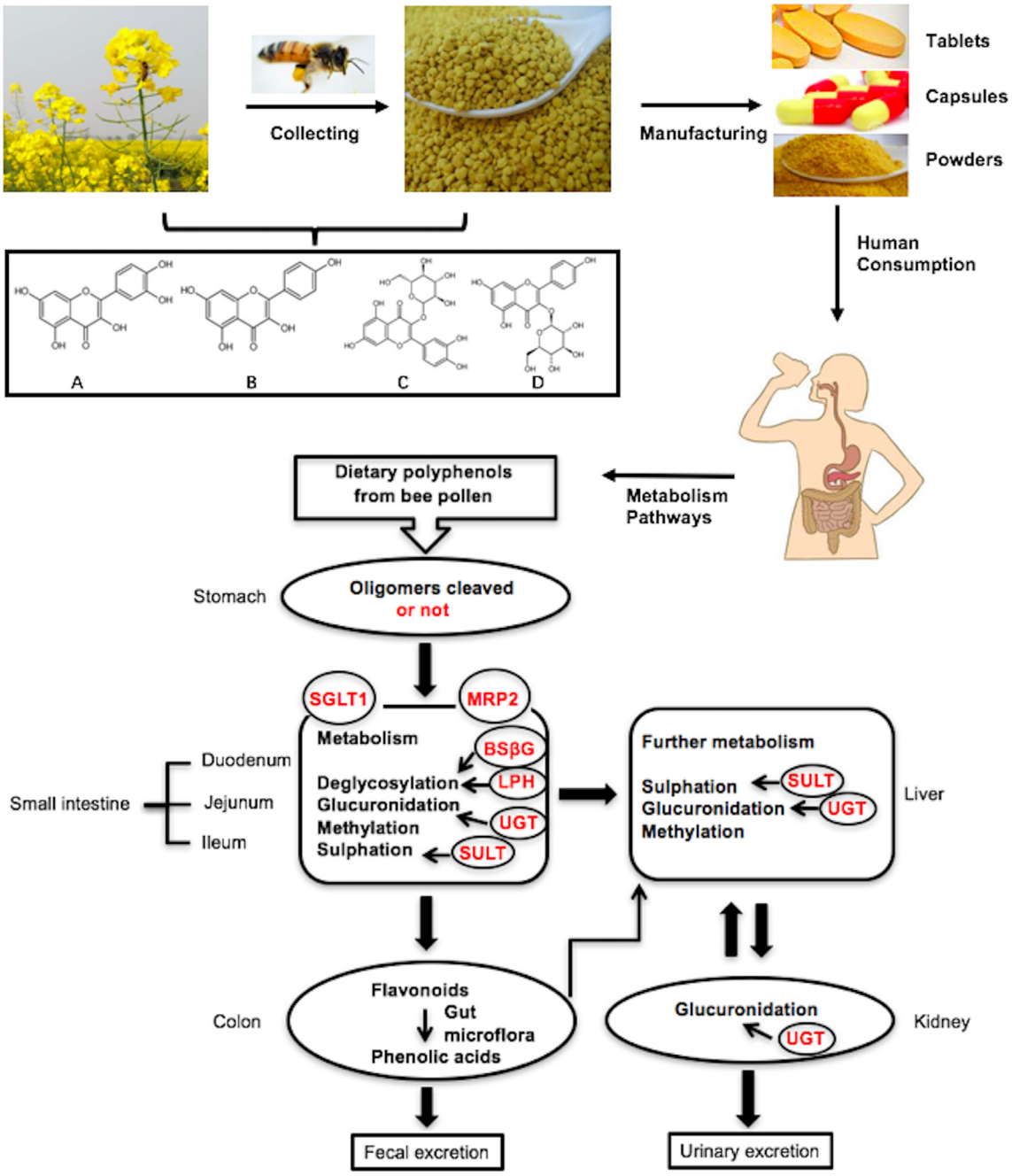

Fig. 2. The metabolic pathways of specific polyphenols. The first photo shows that bee is collecting pollen from the flower of *Brassica campestris* L.; The second one displays the *B. campestris* L. pollen collected by honeybees as a dietary supplement for human consumption. The representative flavonoids in the bee pollen including, quercetin (A), kaempferol (B), quercetin-3-O-glucoside (C), and kaempferol-3-O-glucoside (D) stemming from *B. campestris* L. are still present in *B. campestris* L. bee pollen as dietary flavonoids involved in the body metabolism. SGLT1, sodium-dependent glucose transporter 1; MRP2, multidrug resistance-associated proteins 2; BSβG, broad-specific-β-glucosidase; LPH, lactase phloridzin hydrolase; UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase.

which is beneficial for the treatment of cardiovascular diseases (Komosinska-Vassev, Olczyk, Kaźmierczak, Mencner, & Olczyk, 2015; Polański, Okoń, Przybyło, & Frasik, 1998). The regular intake of bee pollen significantly inhibits the platelet aggregation and atherosclerotic plaque formation (Pascoal et al., 2014; Rzepecka-Stojko, Stojko, Jasik, & Buszman, 2017; Yakusheva, 2010). Yakusheva (2010) demonstrated that the activities of bee pollen are relative to the ω-3 fatty acids levels, such as α-linolenic acid, acting as a prostaglandin-3 precursor and an inhibitor against platelet aggregation.

3.7. Hepatoprotective effects

In vivo studies showed that bee pollen enhanced the hepatic functions and the consumption also detoxified the liver by lowering the marker enzymes (such as alanine transaminase, aspartate transaminase, and acid phosphatase) and bilirubin in the blood (Uzbekova, Makarova, Khvoynitskaya, & Slepnev, 2003; Yıldız et al., 2013). Cheng et al. (2013) also reported that the methanol extracts from *Schisandra chinensis* L. bee pollen showed hepatoprotective effects by decreasing the level of MDA in the liver of mice of CCl_4-induced liver acute damage. The hepatoprotective activity of bee pollen is due to the presence of polyphenols (phenolic acids and flavonoids) (Eraslan et al., 2009).

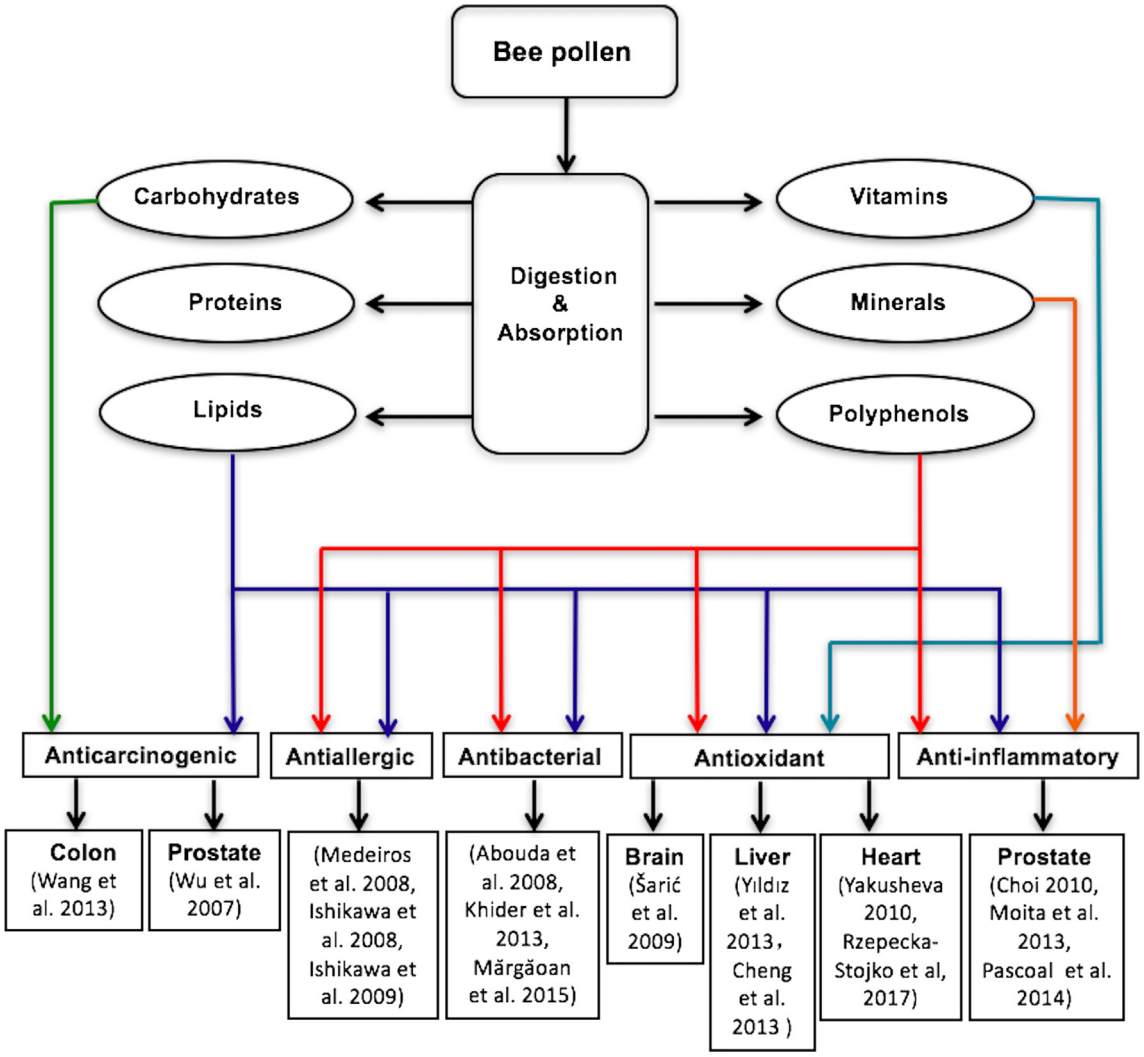

Fig. 3. Potential therapeutic properties of bee pollen.

Therefore, bee pollen has been recommended as an agent against acute and chronic liver diseases.

4. Safety

Although, a few previous studies focused and found serious public concerns about the safety of the bee pollen ingestion. Does the bee pollen cause human allergic responses? To clarify the question, many allergy studies have investigated the bee pollen. Choi, Jang, Oh, Kim, and Hyun (2015) found that the bee pollen containing some anemophilous pollen grains (from *Compositae* or *Chenopodiaceae*) showed a few allergic reactions in atopic patients. Martín-Muñoz et al. (2010) demonstrated that *Asteraceae* pollen as the most likely allergen source might induce the adverse reactions after ingestion. Shahali (2015) also reported that some airborne pollen allergens from birch, olive, cypress, grasses, and several weeds which caused the risk of anaphylactic reactions. Based on these studies, the interfusion of airborne pollen allergens in bee pollen is the main allergy risk factor. Thus, it is necessary to strengthen quality monitoring for bee pollen safety. Cifuentes (2015) proved that there was no direct relationship between honeybee venom allergy and bee products allergy, although, the patients allergic to honeybee venom might also be sensitive to some of the bee products. Therefore, it is not a reason to prevent consuming bee products by the patients with bee venom allergy (though not all bee pollen products are allergic).

Additionally, some contaminants such as toxic heavy metals, fungi, and mycotoxins, have been detected in bee pollen, which causes serious risks to human health. Bee pollen collected from plants is exposed to the environment, such as soil, water, and anthropogenic pollution sedimentation, in plant growth areas. The levels of accumulation of toxic heavy metals in bee pollen depend mainly on the environmental pollution. Previous studies reported the presence of heavy metals (such as arsenic (As), plumbum (Pb), cadmium (Cd), and mercury (Hg)) in bee pollen from different regions by ICP-AES and AAS methods (Dinkov & Stratev, 2016; Roman, 2009). In addition, strontium (Sr) was firstly detected in Serbia bee pollen based on ICP-OES method by Kostić, Pešić et al. (2015). In order to control the safety of bee pollen, bee products need to maintain Maximum Residue Limits (MRL). The suggested values of Pb and Cd in bee pollen must be below 0.5 and 0.03 mg/kg, respectively (Campos et al., 2008). Moreover, due to nutrient-rich quality of bee pollen may cause a growth of a variety of microorganisms, certain processes, including collection, transportation, and storage, are typical factors to control the growth of fungi (such as yeasts and molds of *Penicillium* spp.). The exposure to high humidity increases fungal growth (molds produce mycotoxins, such as ochratoxins and aflatoxins) during the collection of bee pollen in flowering seasons. Kostić, Petrović, et al. (2017) found aflatoxin B1 contamination in all samples (26) of bee pollen while only 10 samples were contaminated with some fungi genus or species. That is why authors emphasize that, beside microbiological, it should be include micotoxicological tests as

mandatory for bee pollen analysis. The ingestion of contaminated bee pollen causes acute or chronic poisoning to humans. To prevent the contaminations, we should use quality measures by drying (with moisture 10–11%), freezing at −18 to −20 °C, and UV exposure which can protect the quality (Kačániová et al., 2011). It is also necessary to set up maximum limits (CFU/g) before the manufacturing of bee products to decrease the number of microorganisms, especially toxic fungi. Furthermore, the biological technologies like enzyme-linked immunesorbent assay (ELISA), as well as the chemical methods like TLC and HPLC, have been developed for mycotoxin detection to control the safety of bee pollen (González, Hinojo, Mateo, Medina, & Jiménez, 2005; Kačániová et al., 2011).

5. Concluding remarks

In summary, we conclude the bee pollen is the nutrient-rich treasure trove of active natural metabolites and benefits human health. To expand the consumption and application for humankind, the following key points should be addressed in the future. First, to establish novel techniques with higher sensitivity, resolution, and accuracy will be necessary for the comprehensive compositional analysis of bee pollen. Second, species identification, including botanical and geographic origins, is essential to further strengthen the database of different species of bee pollen, and also for better control of its quality and safety. Third, research on metabolic pathways and mechanisms of the many biological interactions are necessary to determine the bioactivity of bee pollen in regulating body functions and resisting specific diseases. Finally, accelerating the transformation of scientific insights into clinical practice and enriching the diversity of bee pollen products play important roles in promoting future industrial developments of bee pollen.

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7. Conflicts of interest

The authors declare no conflict of interest.

8. Ethics statements

This is a review article which did not include any human subjects and animal experiments.

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