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TOXIC RISKS ASSOCIATED WITH APITHERAPY PRODUCTS

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ABSTRACT

The history of honeybee products utilization for medicinal applications dates back thousands of years. Today, the benefits attributed to these products by traditional medicine are confirmed by scientists, research data revealing antibacterial, antifungal, anti-inflammatory, cytotoxic and antihepatotoxic activities for honey, propolis, royal jelly and bees' pollen. The paper addresses the problem of toxicological risk assessment of honey and related products. Although there is substantial scientific data to sustain the use of apitherapy as a prophylactic tool, as well as treatment for several medical conditions, the quality and safety of these products needs to be carefully assessed. Several contaminants and toxic compounds have been identified in honeybee products (phytotoxins, heavy metals, pesticides, antibiotics, 5-hydroxymethylfurfural, mycotoxins), and, in some cases, the presence of these compounds was associated with severe outcomes.

1. Introduction

Alternative medical therapies include a broad spectrum of practices and beliefs. Biologic-based practices (dietary therapy, herbal medicine, and dietary supplements – nutraceuticals) are one of the broadest categories, relying on the use of chemical substances or dietary alterations to promote healing. Apitherapy is a form of Complementary and Alternative Medicine that uses honeybee products, such as bees' pollen, honey, royal jelly, propolis, beeswax, and bee venom, for therapeutic purposes (Diehl and Eisenberg, 2000). The history of honeybee products use for medicinal applications dates back thousands of years. Today, honey is classified as a functional food. Scientific research demonstrated the antimicrobial, anti-inflammatory, and antioxidant potential of the product, investigating its efficiency in wound healing (Oryan *et al.,* 2016), hepatic and renal protection against different aggressive agents (eq. CCl_4) (El-Haskoury *et al.,* 2018), gastrointestinal protection (Mundo *et al.,* 2004; Nasuti *et al.,* 2006) and immunostimulatory effect (Ota *et al.,* 2019). Propolis is a complex resinous substance collected by bees, also containing salivary secretions and enzymes, and it is used for protection against invading insects and microorganisms and in beehives repair. It is a rich source of essential elements (Ca, Mg, Fe, Cu, Zn, Mn, Ni), vitamins, and phenolic compounds (caffeic acid phenethyl ester being one of the most studied compounds found in propolis), but the composition varies according to specific flora at the site of collection (Rufatto *et al.,* 2017). Scientific data revealed that propolis exhibits antibacterial, antifungal, anti-inflammatory, and cytotoxic activities (Rufatto *et al.,* 2017; Dobrowolski *et al.,* 1991). Bee pollen is a product that results from the agglutination of flower pollens with nectar, combined with salivary bees' secretions. It represents a good source of bioactive substances and energy and also possesses many therapeutic and protective effects: antimicrobial, antifungal, antioxidant, anti-inflammatory, anti-carcinogenic, anti-allergic, hepatoprotective, improving the cardiovascular and digestive systems, immunity booster, and aging delaying (Pascoal *et al.,* 2014; Huang *et al.,* 2017; Li *et al.,* 2018). Royal jelly is a honeybee secretion product used to feed the larvae and adult queens. Studies have indicated antioxidant, anti-inflammatory, anti-hepatotoxic, and anticancer activities for royal jelly (Pasupuleti *et al.,* 2017). There is substantial scientific data to sustain the use of apitherapy as a prophylactic tool, as well as treatment for several medical conditions, but one very important aspect that needs to be assessed is the safety of these products. Quality parameters must be imposed for all nutraceuticals and dietary supplements.

2. Contaminants and toxic compounds in honeybee products

2.1. Phytotoxins

The composition of honeybee products varies greatly depending on the flora at the site of collection. Some secondary plant metabolites (pyrrolizidine alkaloids, grayanotoxins, hyoscyamine, hyoscine, saponin, strychnine, gelsemine, tutin, hyenanchin, oleandrin, and oleandrigenin) can be transferred to honey and related products, leading to toxic effects in humans (Figure 1) (Grigoryan, 2016).

Pyrrolizidine alkaloids are one of the most common natural toxins, being identified in over 6000 plants. They possess genotoxic and hepatotoxic effects. Contaminated honey is a possible source of intoxication. The ingested dose is usually not high enough to cause acute poisoning, but a long-time consumption of low doses of pyrrolizidine alkaloids can cause liver fibrosis, pulmonary arterial hypertension, somatic mutation, and liver cancer. Fetuses and neonates are more susceptible to pyrrolizidine alkaloids poisoning, even at extremely low levels (Zhu *et al.,* 2018).

Tutin is a plant-derived neurotoxin, responsible for many intoxication cases associated with honey consumption; clinical signs include nausea, headache, vomiting, dizziness, and in severe cases seizures and coma. These cases are common in New Zealand, where *Coriaria arborea* (tutu), which is known to contain tutin, grows (Fields *et al.,* 2014).

Grayanotoxins are often found in "mad honey", produced by bees from the nectar of *Rhododendron ponticum*, a member of the *Ericaceae* family, which is used in indigenous medicine, especially in the treatment of hypertension and sexual dysfunctions. This phenomenon was known from ancient times (Xenophon recorded the intoxication of Greek soldiers stationed on the Black Sea coast), but its prevalence is still high, especially in Turkey, where "mad honey" can be purchased in local markets. The common symptoms of intoxication are dizziness, bradycardia, nausea, vomiting, presyncope and syncope, blurred vision, hypotension, and fainting (Silici *et al.,* 2015; Demircan *et al.,* 2009). Besides "mad honey poisoning" described in Turkey, Nepal, and Korea, and "Tutin honey poisoning" described in New Zealand, there is another type of honey poisoning caused by *Tripterygium wilfordii* Hook F. It occurs mainly in southwestern China, and it is characterized by multiple-organ damage and high mortality. The toxic potential of the plant is mainly related to the presence of triptolide – a highly toxic substance – whose major target is the kidney, acute renal failure being the main cause of death (Zhang *et al.,* 2016; Zhang *et al.,* 2017).

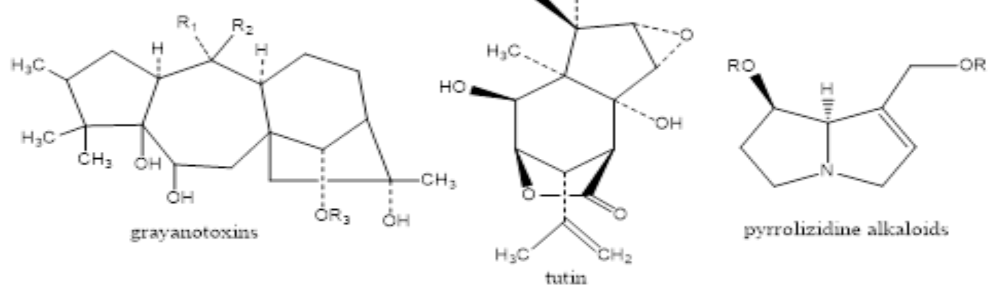

Figure 1. Phytotoxins commonly found in honeybee products

2.2. Toxic elements – Heavy metals and metalloids

Heavy metals pollution is a serious problem nowadays around the world, affecting the quality of the atmosphere and waters and also posing a threat to the health and life of human beings and animals via the food chain (Aghamirlou *et al*., 2015).

The content of toxic elements (heavy metals and metalloids – Table 1) in honeybee products depends on many factors: floral source (some plant species can selectively accumulate toxic elements), environmental contamination and conditions (geo-climatic conditions, geochemical characteristics of the soil, anthropogenic activities – eq. chemical industries in the vicinity) and production methods. Therefore, bees and their products can often serve as bio-indicators for heavy metal contamination. Many studies on this matter were conducted and the results showed significant differences in element concentrations between honey products of different botanical origins and from different geographic areas (Czipa *et al.,* 2015; Bilandžić *et al.,* 2017). Two of the most frequently studied metals are lead and cadmium. Lead originates mainly from motor traffic, contaminates the air, and then nectar, and honeydew. It is not generally transported by plants, unlike cadmium, which is transported from the soil to plants, also contaminating nectar and honeydew. Lead pollution is expected to diminish, due to the reduction of toxic car emissions worldwide, associated with the introduction of car-engine catalysts (Bogdanov, 2006).

The quantities of heavy metals accumulated in different apiculture products can vary. Honey usually has a lower degree of contamination than other products, probably due to bees' "filtering" capacity, but lead residues found in propolis are often high, indicating that the harvest area should not be placed near heavy traffic roads (Bogdanov, 2006).

Table 1. Toxic elements identified in honeybee products

Toxic element	Toxic effects	References
Pb	• neurotoxicity • gastrointestinal and renal dysfunctions	Aldgini *et al.,* 2019; Ru *et al.,* 2013; Aljedani, 2017; Talk Gajger *et al.,* 2016; Kieliszek *et al.,* 2018
Cd	• gastrointestinal and renal dysfunctions • osteomalacia and osteoporosis • carcinogenic effects	Aldgini *et al.,* 2019; Ru *et al.,* 2013; Aljedani, 2017; Kieliszek *et al.,* 2018
Hg	• gastrointestinal, hepatic and renal damage • neurotoxicity	Aghamirlou *et al*., 2015; Ru *et al.*, 2013; Talk Gajger *et al.,* 2016; Kieliszek *et al.,* 2018
Al	• toxic effects on the central nervous, skeletal and hematopoietic systems	Bilandžić *et al*., 2017
Cr	• carcinogenic and teratogenic effects • nephrotoxic and hepatotoxic effects	Harmanescu *et al.,* 2007
Ni	• sensitization and allergic contact dermatitis • hepatotoxic and nephrotoxic	Bilandžić et al., 2017; Aldgini *et al.,* 2019
As	• carcinogen (skin, kidney, lung, bladder, and liver cancers)	Aldgini *et al.,* 2019; Talk Gajger *et al.,* 2016; Kieliszek *et al.,* 2018; Fiorentini *et al.,* 2019
Ba	• acute toxicity: low potassium levels, cardiac arrhythmia, gastrointestinal dysfunction or paralysis, muscle twitching, and high blood pressure • chronic exposure: kidney damage, respiratory failure, the development of neurodegenerative diseases, including multiple sclerosis	Bilandžić *et al*., 2017
Be	• carcinogen to humans	Bilandžić *et al*., 2017
Sb	• acute cardiac toxicity and myocarditis • prolonged skin contact – dermatitis kidney and liver damage, vomiting	Bilandžić *et al*., 2017

2.3. Pesticides

Pesticides are indispensable for today's agriculture, increasing crop productivity and minimizing losses due to uncontrollable pests, but exposure to pesticides has several negative consequences for all living beings, including humans. Pesticide residues present in the environment, but mostly in food products, can cause skin rashes, respiratory disorders (asthma attacks); chronic exposure is often associated with cancer, neurological and reproductive dysfunctions, and birth defects (Gil *et al.,* 2016).

Bee products can also be a source of pesticide exposure, due to both environmental pollution (honeybees are exposed by consumption of contaminated pollen and water or by contact with plants and soil) and wrong beekeeping practices (administration of pesticides and antibiotics, in order to control hive infestations).

Organohalogens, organophosphates, organonitrogens, pyrethroids, carbamates are examples of pesticide residues most frequently reported in honey and related products (Figure 2), in countries like Brazil, Turkey, Spain, Colombia, China, France, Portugal, and India (López *et al.,* 2014). Organophosphates and organohalogens occupy the first positions in terms of detection frequency. Although organochlorine pesticides (eq. lindane) have been prohibited by law for decades in most countries, their residues are still present as pollutants in water, soil, air, and food products, due to their high persistence. Organochlorine pesticides are lipophilic substances, soluble and stable in beeswax, and an amount of these substances gradually migrates from wax into the stored honey (Gaweł *et al.,* 2019). Bee pollen samples are also a good indicator for environmental monitoring, many studies being focused on quantifying pesticide residues in pollen samples (de Oliveira *et al.,* 2016). However, the distribution of pesticides in different apiculture products is heterogeneous. There are studies indicating that, in some cases, pesticides, especially herbicides, can contaminate bees and pollen and rarely appear in honey. This effect probably appears due to the filtering capacity of bees (Fléché *et al.,* 1997). Similar results were obtained when pesticide levels in wax, pollen, and honey were compared. Beeswax was the most contaminated hive compartment regarding quantities of pesticides detected (Jan *et al.,* 1993; Calatayud-Vernich *et al.*, 2018). Some authors also argued whether honey consumption represents an important source of pesticide exposure and a threat to human health, contributing substantially to the daily intake of pesticides, based on the consumed quantities and the degree of contamination, which is generally very low. However, different national regulations have established maximum concentrations of pesticide residues permitted in honey and related products, but the lack of homogeneity causes problems in international trade. The maximum limits of pesticide residues in honey are not included in the Codex Alimentarius (Grigoryan, 2016; Al-Waili *et al.,* 2012). Maximum residue limits (MRL) were also established in the European Union for several pesticides used in agricultural and beekeeping practices (Table 2). In the EU, an action level of 0.01 mg/kg is often considered for pesticides with no fixed MRL (***, 2005).

It is important to control bees' exposure to pesticides because bees end up inhabiting a toxic hive, exposed to different pesticides cocktails, and their health is seriously affected. Another concern is related to the safety of bee products consumers. In this context, Yuan *et al.* investigated the photodegradation phenomenon of organophosphorus pesticides in honey medium, concluding that photodegradation could become an accepted method for organophosphorus pesticides removal from honey (Yuan *et al.,* 2014).

Table 2. Maximum levels of pesticide residues for honey and other apiculture products – Regulation (EC) No 396/2005

No	**Pesticide**	**MRL (mg/kg)**	**No**	**Pesticide**	**MRL (mg/kg)**
1	Asulam	0.05*	20	Fenpyroximate	0.01*
2	Azoxystrobin	0.05*	21	Fipronil	0.01
3	Bicyclopyrone	0.05*	22	Fluopyram	0.05*
4	Boscalid	0.5	23	Fluoxastrobin	0.01*
5	Bromopropylate	0.1	24	Flutolamil	0.02*
6	Cabendazin + Benonyl	1	25	Fosetyl	0.5*
7	Chlordane	0.01	26	Fosetyl-Al	0.5*
8	Chlormequat	0.05*	27	Gibberellic acid	0.1
9	Cyprodinil	0.05*	28	Haloxyfop	0.05
10	DDT	0.05	29	Heptachlor	0.01
11	Diclofop	0.01*	30	Isoprothiolane	0.05*
12	Difenoconazole	0.05*	31	Isopyrazam	0.05*
13	Endosulfan	0.01*	32	Lindane	0.01*
14	Endrin	0.01	33	Mepiquat	0.05*
15	Epoxiconazole	0.05	34	Oxamyl	0.05*
16	Etofenprox	0.05	35	Prothioconazole	0.05*
17	Fenoxaprop-P	0.05	36	Spinetoram	0.05*
18	Fenpropidin	0.02*	37	Trifloxystrobin	0.05*
19	Fenpropimorph	0.05*	38	Triflumezopyrim	0.05*

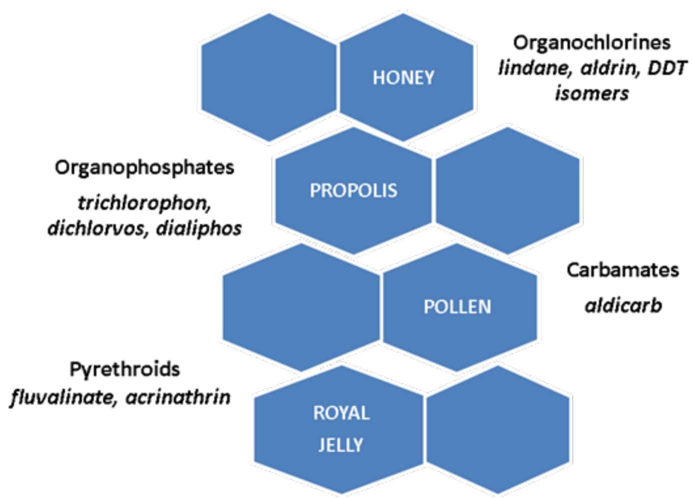

Figure 2. Common pesticides found in bee products

2.4. Residues of veterinary medicinal products – Antibiotic residues

Exposure of the general population to antibiotics can have negative effects, like allergenic reactions, or even contributing to the expansion of the increased bacterial resistance phenomenon. Therefore, the use of antibiotics is forbidden in beekeeping practice in the EU, due to the risk of antibiotic residues in honey. There are many studies regarding the monitoring of antibiotic residues in honey. Although EU directive 2377/90 states that honey should be free of antibiotic contamination, research in this domain revealed that many analyzed samples of honey contained traces of antibiotics, generally used against bacterial plant pests. Typically found antibiotics residues include streptomycin, sulphonamides, chloramphenicol, macrolides, tetracycline, streptomycin, and nitrofurans (Grigoryan, 2016; Al-Waili *et al*., 2012).

2.5. 5-Hydroxymethylfurfural

5-Hydroxymethylfurfural is an indicator of the poor quality of food products, and it is usually formed during the heating or preservation of honey. There are several factors that favor the formation of 5-hydroxymethylfurfural: use of metallic containers for storage, physicochemical properties of honey (eq. acidity), humidity, and thermal and photochemical stress. Due to the mutagenic, carcinogenic, and cytotoxic potential, the amount of 5-hydroxymethylfurfural is limited by EU regulations to 40 mg/kg (exceptions: 80 mg/kg in honey from regions with tropical temperatures, and 15 mg/kg in honey with low enzyme levels) (***, 2001). Ample research was performed in this direction, investigating the level of 5-hydroxymethylfurfural in honey samples from different countries (like Spain or The Czech Republic), the results indicating that honey is unlikely to exceed the 40 mg/kg limit unless it is mishandled, commercial honey-processing methods (eq. heating above 15°C) being usually incriminated for the appearance of undesirable compounds, including 5-hydroxymethylfurfural (Grigoryan, 2016).

2.6. Genetically modified organisms (GMOs)

The appearance of genetically modified plants, grown in some countries, has raised new concerns about the impact of this phenomenon on apiculture, in terms of the marketability of bee products. In the European Union, it is compulsory to notify the consumers if the GMO content in food is above 1%. Pollen is the most affected bee product, because it contains genetic material, while honey contains only a small percentage of pollen (less than 0.1% pollen, if the honey is sieved) and probably will not require any specific appellations (Grigoryan, 2016; Bogdanov, 2006).

2.7. Microbiological contaminants and mycotoxins

In terms of microbiological contaminants, bacterial risks associated with honey consumption are usually low, but honey has been identified as a dietary risk factor for infant botulism. *Clostridium botulinum* is a Gram-positive, anaerobic, spore-forming bacterium that produces a neurotoxin. Honey samples can contain *Clostridium botulinum* spores, but botulinum toxin is not found in honey, because the natural antimicrobial potential and the high osmotic pressure prevent spores' germination. However, the spores can colonize the undeveloped gut of infants, leading to infant botulism, a rare neuroparalytic disease that can occur among babies under 1 year of age (Grigoryan, 2016).

Aside from *C. botulinum*, mold, yeasts, and other spore-forming bacteria can be found in honey. The main sources of contamination are the environment and not respecting good manufacturing practices, contamination with fungi and bacteria usually indicates inadequate hygiene conditions during collection, processing, and storage (Grigoryan, 2016; Bogdanov, 2006). Mycotoxins are toxic compounds produced by fungi that colonize different nutritional substrates. Bee products represent an adequate medium for the development of fungi, thus being subjected to the risk of accumulating mycotoxins. Among mycotoxins, aflatoxins and ochratoxin A are the most common, being involved in both acute and chronic intoxications (González *et al.,* 2005).

Aflatoxins, produced by species of *Aspergillus*, are hepatotoxic, teratogenic, mutagenic, and carcinogenic mycotoxins. Ochratoxin A, also produced by species of *Aspergillus* (eq. *Aspergillus ochraceus*), is nephrotoxic, hepatotoxic, teratogenic, and immunotoxic, being associated with fatal endemic human nephropathies (González *et al.,* 2005). Unprocessed honey is a poor medium for synthesis of mycotoxins, and it is relatively safe, from this point of view (Martins *et al.,* 2003;

Eissa *et al.*, 2014), but bee pollen was found to be a substrate that stimulates ochratoxin A production by *Aspergillus ochraceus*. The levels of mycotoxin found in the incubation medium containing bee pollen was significantly higher than in corn, wheat, and rice grains (Medina *et al.,* 2004). González G *et al*. analyzed the presence of mycotoxins and mycotoxin-producing fungi in bee pollen and stressed the importance of application of good manufacturing practices, sanitization procedures, and analysis of risks and critical control points to honeybee products (González *et al.,* 2005).

3. Conclusions

The benefits associated with the consumption of honey and other related bee products are unquestionable. As highlighted above, scientific research revealed antimicrobial, anti-inflammatory, antioxidant, immunostimulatory activities for these products, promoting general health and well-being. Despite these considerations, it is also important to point out the possibility of contamination with several toxic compounds, which can lead to grave outcomes in some cases. If for honey, the most popular bee product, intensely consumed around the world, quality criteria are usually clearly specified, when it comes to other related products, many quality regulation gaps can be found. Another problematic issue is represented by the existence of different national standards for honey produced and commercialized in different parts of the world (European countries, the United States, Canada, Australia, and India have separate standards), making difficult the elaboration of general guidelines for quality assessment.

4. References

*** (2001). EC Council directive 2001/110/EC of 20 December 2001 relating honey. Official Journal of the European Communities 12.1.2002 L10/47-52. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2002:010:FULL&from=EN.

***. (2005). Regulation (EC) 396/2005 of the European Parliament and of the Council on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0552&from=EN EC-396/2005.

Aghamirlou, H.M., Khadem, M., Rahmani, A. Sadeghian, M., Mahvi, A.H., Akbarzadeh, A., Nazmara, S. (2015). Heavy metals determination in honey samples using inductively coupled plasma-optical emission spectrometry. *Journal of Environmental Health Science & Engineering*, 13, 39-47.

Aldgini, H.M.M., Abdullah Al-Abbadi, A., Abu-Nameh, E.S.M., Alghazeer, R.O. (2019). Determination of metals as bio indicators in some selected bee pollen samples from Jordan. *Saudi Journal of Biological Sciences*, 26(7), 1418-22.

Aljedani, D.M. (2017). Determination of Some Heavy Metals and Elements in Honeybee and Honey Samples from Saudi Arabia. *Entomology and Applied Science Letters*, 4(3), 1-11.

Al-Waili. N., Salom, K., Al-Ghamdi, A., Ansari, M.J. (2012). Antibiotic, pesticide, and microbial contaminants of honey: human health hazards. *The Scientific World Journal*, 2012, 930849.

Bilandžić, N., Tlak Gajger, I., Kosanović, M., Čalopek, B., Sedak, M., Solomun Kolanović, B., Varenina, I., Luburić, Đ.B., Varga, I., Đokić, M. (2017). Essential and toxic element concentrations in monofloral honeys from southern Croatia. *Food Chemistry*, 234, 245-53.

Bogdanov, S. (2006). Contaminants of bee products. *Apidologie*, 37(1), 1-18.

Calatayud-Vernich, P., Calatayud, F., Simó, E., Picó, Y. (2018). Pesticide residues in honeybees, pollen, and beeswax: Assessing beehive exposure. *Environmental Pollution*, 241, 106-14.

Czipa, N., Andrási, D., Kovács, B. (2015). Determination of essential and toxic elements in Hungarian honeys. *Food Chemistry*, 175, 536-42.

de Oliveira, R.C., Queiroz, S.C.D.N., da Luz, C.F.P., Porto, R.S., Rath, S. (2016). Bee pollen as a bioindicator of environmental pesticide contamination. *Chemosphere*, 163, 525-34.

Demircan, A., Keleş, A., Bildik, F., Aygencel, G., Doğan, N.O., Gómez, H.F. (2009). Mad honey sex: therapeutic misadventures from an ancient biological weapon. *Annals of Emergency Medicine*, 54(6), 824-829.

Diehl, D.L., Eisenberg, D. (2000). Complementary and alternative medicine (CAM): epidemiology and implications for research. *Progress in Brain Research*, 122, 445-55.

Dobrowolski, J., Vohora, S., Sharma, K., Shah, S.A., Naqvi, S.A., Dandiya, P.C. (1991). Antibacterial, antifungal, antiamoebic, antiinflammatory and antipyretic studies on propolis bee products. *Journal of Ethnopharmacology*, 35(1), 77-82.

Eissa, A.A., Hassan, A.M., El-Rahman, T.A. (2014). Determination of total aflatoxins and carbamate pesticide residues in some bee honey samples using QuEChERS method and high performance liquid chromatography. *Food and Public Health*, 4, 209-13.

El-Haskoury, R., Al-Waili, N., Kamoun, Z., Makni, M., Al-Waili, H., Lyoussi, B. (2018). Antioxidant Activity and Protective Effect of Carob Honey in CCl4-induced Kidney and Liver Injury. *Archives of Medical Research*, 49(5), 306-13.

Fields, B.A., Reeve, J., Bartholomaeus, A., Mueller, U. (2014). Human pharmacokinetic study of tutin in honey; a plant-derived neurotoxin. *Food and Chemical Toxicology*, 72, 234-41.

Fiorentini, E.F., Canizo, B.V., Wuilloud, R.G. (2019). Determination of As in honey samples by magnetic ionic liquid-based dispersive liquid-liquid microextraction and electrothermal atomic absorption spectrometry. *Talanta*, 198, 146-53.

Fléché, C., Clément, M., Zeggane, S., Faucon, J. (1997). Contamination des produits de la ruche et risques pour la santé humaine: situation en France. *Revue scientifique et technique (International Office of Epizootics)*, 16(2), 609–19.

Gaweł, M., Kiljanek, T., Niewiadowska, A., Semeniuk, S., Goliszek, M., Burek, O., Posyniak, A. (2019). Determination of neonicotinoids and 199 other pesticide residues in honey by liquid and gas chromatography coupled with tandem mass spectrometry. *Food Chemistry*, 282, 36-47.

Gil, F., Hernández, A.F., Martín-Domingo, C.M. (2016). Toxic Contamination of Nutraceuticals and Food Ingredients. In: Gupta RC (ed). Nutraceuticals: Efficacy, Safety and Toxicity. San Diego: Academic Press, 825-837.

González, G., Hinojo, M.J., Mateo, R., Medina, A., Jiménez, M. (2005). Occurrence of mycotoxin producing fungi in bee pollen. *International Journal of Food Microbiology*, 105(1), 1-9.

Grigoryan, K. (2016). Honey Safety. In: Prakash V, Martin-Belloso O, Keener L, Astley S, Braun S, McMahon H, Lelieveld H (eds.). Regulating Safety of Traditional and Ethnic Foods. San Diego: Academic Press, 217-246.

Harmanescu, M., Bordean, D., Gergen, I. (2007). Heavy metals contents of bee's pollen from different locations of Romania. *Lucrari Stiintifice - Universitatea de Stiinte Agricole a Banatului Timisoara, Medicina Veterinara*, 40, 253-60.

Huang, H., Shen, Z., Geng, Q., Wu, Z., Shi, P., Miao, X. (2017). Protective effect of Schisandra chinensis bee pollen extract on liver and kidney injury induced by cisplatin in rats. *Biomedicine & Pharmacotherapy*, 95, 1765-76.

Jan, J., Cerne, K. (1993). Distribution of some organochlorine compounds (PCB, CBz, and DDE) in beeswax and honey. *The Bulletin of Environmental Contamination and Toxicology*, 51(5), 640-646.

Kieliszek, M, Chlebowska-Śmigiel, A., Kot, A.M., Błażejak, S., Chlebowska-Śmigiel, A., Wolska, I. (2018) Pollen and bee bread as new health-oriented products: A review.

Trends in Food Science & Technology, 71, 170-80.

Li, Q.Q., Wang, K., Marcucci, M.C., Frankland Sawaya, A.C.H., Hu, L., Xue, X-F., Wu, L-M., Hu, F-L. (2018). Nutrient-rich bee pollen: A treasure trove of active natural metabolites. *Journal of Functional Foods*, 49, 472-84.

López, D.R., Ahumada, D.A., Díaz, A.C., Guerrero, J.A. (2014). Evaluation of pesticide residues in honey from different geographic regions of Colombia. *Food Control*, 37, 33-40.

Martins, H.M., Martins, M.L., Bernardo, F.M.A. (2003). Bacillaceae spores, fungi and aflatoxins determined in honey Esporos de Bacillaceae, fungos e aflatoxinas em mel. *Revista portuguesa de ciências veterinárias*, 98, 85-8.

Medina, A., González, G., Sáez, J.M., Mateo, R., Jiménez, M. (2004). Bee pollen, a substrate that stimulates ochratoxin A production by Aspergillus ochraceus Wilh. *Systematic and Applied Microbiology*, 27(2), 261-7.

Mundo, M.A., Padilla-Zakour, O.I., Worobo, R.W. (2004). Growth inhibition of foodborne pathogens and food spoilage organisms by select raw honeys. *International Journal of Food Microbiology*, 97(1), 1-8.

Nasuti, C., Gabbianelli, R., Falcioni, G., Cantalamessa, F. (2006). Antioxidative and gastroprotective activities of anti-inflammatory formulations derived from chestnut honey in rats. *Nutrition Research*, 26(3), 130-7.

Oryan, A., Alemzadeh, E., Moshiri, A. (2016). Biological properties and therapeutic activities of honey in wound healing: A narrative review and meta-analysis. *Journal of Tissue Viability*, 25(2), 98-118.

Ota, M., Ishiuchi, K., Xu, X., Minami, M., Nagachi, Y., Yagi-Utsumi, M., Tabuchi, Y., Cai, S-Q., Makino, T. (2019). The immunostimulatory effects and chemical characteristics of heated honey. *Journal of Ethnopharmacology*, 228, 11-7.

Pascoal, A., Rodrigues, S., Teixeira, A., Feás, X., Estevinho, L.M. (2014). Biological activities of commercial bee pollens: antimicrobial, antimutagenic, antioxidant and anti-inflammatory. *Food and Chemical Toxicology*, 63, 233-9.

Pasupuleti, V. R., Sammugam, L., Ramesh, N., Gan, S. H. (2017). Honey, Propolis, and Royal Jelly: A Comprehensive Review of Their Biological Actions and Health Benefits. *Oxidative medicine and cellular longevity*, 1259510. https://doi.org/10.1155/2017/1259510.

Ru, Q.M., Feng, Q., He, J.Z. (2013). Risk assessment of heavy metals in honey consumed in Zhejiang province, southeastern China. *Food and Chemical Toxicology*, 53, 256-62.

Rufatto, L.C., dos Santos, D.A., Marinho, F., Henriques, J.A.P., Ely, M.R., Moura, S. (2017). Red propolis: Chemical composition and pharmacological activity. *Asian Pacific Journal of Tropical Biomedicine*, 7(7), 591-8.

Silici, S., Atayoglu, A.T. (2015). Mad honey intoxication: A systematic review on the 1199 cases. *Food and Chemical Toxicology*, 86, 282-90.

Tlak Gajger, I., Kosanović, M., Bilandžić, N., Sedak, M., Čalopek, B. (2016). Variations in lead, cadmium, arsenic, and mercury concentrations during honeybee wax processing using casting technology. *Arhiv za Higijenu Rada i Toksikologiju*, 67(3), 223-8.

Yuan, Z., Yao, J., Liu, H., Han, J., Trebše, P. (2014). Photodegradation of organophosphorus pesticides in honey medium. *Ecotoxicology and Environmental Safety*, 108, 84-8.

Zhang, Q.; Chen, X.; Chen, S.; Ye, Y.; Luo, J.; Li, J.; Yu, S.; Liu, H.; Liu, Z., (2017). Fatal honey poisoning in southwest China: a case series of 31 cases. *The Southeast Asian Journal of Tropical Medicine and Public Health*, 48(1), 189-96.

Zhang, Q., Chen, X., Chen, S., Liu, Z., Wan, R., Li, J. (2016). Fatal Honey Poisoning Caused by Tripterygium wilfordii Hook F in

Southwest China: A Case Series. *Wilderness & Environmental Medicine*, 27(2), 271-3.

Zhu, L., Wang, Z., Wong, L., He, Y., Zhao, Z., Ye, Y., Fu, P.P., Lin, G. (2018). Contamination of hepatotoxic pyrrolizidine alkaloids in retail honey in China. *Food control*, 48, 484-94.