Review

An Overview of the Hazards and Management Strategies for Antibiotic Residue in Honey

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Abstract: Humans have kept bees for the production and harvest of honey since 4000 BC. In past societies, honey was of great importance, particularly for its medicinal purposes. Honey has the image of being a natural and healthy product. However, today honey is produced in an environment, polluted by different sources of contamination. The contamination sources can be environmental and apicultural ones. Antibiotics are found in honey largely because they are used in apiculture for treatment of bacterial diseases. Antibiotics such as oxytetracycline, erythromycin, lincomycin, monensin, streptomycin, and enrofloxacin are also reportedly used in beekeeping. The extensive use of antibiotics leads to an accumulation of residues in honey decreasing their quality and making their marketing more difficult. Antibiotic residues show a relatively long half-life and they may have direct toxic effects on consumer’s e.g., allergic reactions in hypersensitive individuals and disorder of the haemopoietic system, or cause problems indirectly through induction of resistant strains of bacteria. The European Union (EU) regulates honey under the Council Directive 2001/110/EC, and the standard for antibiotics in food is listed in Regulation (EU) No. 37/2010.

Keywords: honey; antibiotic residue; hazards; management strategy.
1. Introduction

Honey is the natural sweet substance produced by honeybees from the nectar of plants or from secretions of living parts of plants or excretions of plant sucking insects on the living parts of plants, which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store and leave in the honey comb to ripen and mature. Humans have kept bees for the production and harvest of honey since 4000 BC. Annual world honey production is estimated at about 1.4 million tones. Asia is the largest producer of honey, accounting for about 40% of the global production. The main uses of honey are in cooking, baking, as a spread on breads, and as an addition to various beverages such as tea and as a sweetener in some commercial beverages. Honey can be used as instant energizer as it contains sugars which are quickly absorbed by our digestive system and converted into energy. In past societies, honey was of great importance, particularly for its medicinal purposes (Bogdanov, 2006; Subramanian et al., 2007; FAO/WHO, 2008; Mahmoudi et al., 2014). It was believed to be a powerful aphrodisiac and a valuable antibacterial wound dressing. The use of honey as a dietary supplement could be benefit in treatment of gastroenteritis, gastric ulcers, and diabetes (Jeffrey and Echazarreta, 1997). Today, honey is produced in almost every country of the world, with 90% being eaten directly as table honey. The remaining 10% is used as an ingredient in a diverse range of products.

2. Antibiotics and Honey Contamination

Honeybees are affected by protozoan, bacterial, viral and acarine diseases. Beekeepers use antibiotics at relatively high doses, as therapeutic agents to treat clinical infections (bacterial brood diseases), or they may be administered at low, sub therapeutic doses as “growth promoters”. Beekeeping with the use of antibiotics is less labor intensive and more profitable (Mutinelli, 2003).

Antibiotics are found in honey largely because they are used in apiculture for treatment of bacterial diseases. Oxytetracycline is commonly used to treat European foulbrood disease (EFB) and American foulbrood diseases (AFB) caused by Paenibacillus (Bacillus) larvae and Streptococcus pluton bacteria, respectively. However, there are reports of tetracycline resistance in these bacteria because of its widespread use. Other antibiotics such as erythromycin, lincomycin, monensin, streptomycin, and enrofloxacin are also reportedly used in beekeeping (Williams, 2000; Mahmoudi et al., 2013; Mahmoudi et al., 2014).

3. Antibiotic Residue in Honey

Antibiotic residues in honey have recently become a major consumer concern. Research shows
that residues of antibiotics in honey originate mostly, not from the environment, but from improper beekeeping practices (Reybroeck, 2003). There are several international reports of antibiotic residues in honey samples (Wang, 2004; Hammel et al., 2008; Lopez et al., 2008).

In the period 2000–2001, 248 samples of locally produced and imported honey were monitored for the presence of residues of veterinary drug residues. Streptomycin was detected in 4 out of 248, tetracycline in 2 out of 72, and sulfonamides in 3 out of 72 samples. No residues of β-lactam antibiotics and chloramphenicol were found. In imported honey samples streptomycin was detected in 51 out of 102 samples, tetracyclines in 29 out of 98 samples, sulfonamides in 31 out of 98 samples, and chloramphenicol 40 out of 85 samples. For the streptomycin and tetracycline contamination, most cases involved the beekeeper admitting to having added foreign honey to his production (Reybroeck, 2003). Of the 75 samples of honey obtained commercially in Switzerland, 34 which originated from Asian countries, 13 samples (17%) contained chloramphenicol residues. The concentration of chloramphenicol in honey was between 0.4 and 6.0 μg/kg, with six samples containing approximately 0.8–0.9 μg/kg (just below the Swiss limit) and two containing approximately 5 μg/kg (Ortelli et al., 2004).

In another study, 251 honey samples produced across Greece were analyzed by liquid chromatography to detect tetracycline-derived residues. Twenty-nine percent of the samples had tetracycline residues. Majority of samples contained residues from 0.018–0.055 mg/kg of honey while some others had residues in excess of 0.100 mg/kg (Saridaki-Papakonstadinou et al., 2006). Centre for Food Safety (CFS) found that two of the 19 samples of honey collected for examination for antibiotics contained trace amounts of chloramphenicol, one brand of honey produced in Jiangxi and another brand produced in Zhuhai. Other antibiotics found in the honey samples in trace amount, namely streptomycin, sulfamethoxazole (a kind of sulfonamides) and ciprofloxacin (a kind of quinolone), they can normally be used in food animals (CFS, 2006).

In China, five antibiotics compounds, tetracycline, oxytetracycline, doxycycline, chlorotetracycline, and chloramphenicol, were successfully separated and determined in honey samples. The detection limits were 10 μg/L for chloramphenicol, 20 μg/L for tetracycline, oxytetracycline, and doxycycline, and 40 μg/L for chloramphenicol (Chen et al., 2001).

In India, high levels of antibiotics in honey exported from India to EU and US have been reported by Agricultural Processed Food Product Export Development Agency from 2005 onwards (Al-Waili et al., 2012). In 2006, about 14% samples were contaminated with tetracycline and in 2007–2008 about 28% samples were contaminated with same antibiotic. In 2009–2010, of the 362 honey samples tested, 29.2% samples had more than the prescribed limit of antibiotics. In 2000–2001, streptomycin was detected in 4/248, tetracycline in 2/72, and sulfonamides in 1/72 samples. Nectar and honey samples collected from bee hives during the peak flowering seasons of rubber (March to April)
and banana (December to January) plantation crops in southern part of Tamil Nadu were analyzed for antibiotic residues. These samples showed 4–17 and 11–29 ng/kg of streptomycin, 2–29 and 3–44 ng/kg of ampicillin, and 17–34 and 26–48 ng/kg of kanamycin, respectively (Solomon et al., 2006).

Mahmoudi et al. (2014) investigated the occurrence of oxytetracycline residue in 145 honey samples (collected from Ardabil provinces, Northwest region of Iran) by using ELISA and HPLC methods. The ELISA assay showed that out of 145 samples, 34 samples were positive for oxytetracycline residue (Mahmoudi et al., 2014). ELISA analyses demonstrated that the minimum and maximum levels of oxytetracycline residue were 5.32 and 369.1 ng/g, respectively. HPLC analyses confirmed the ELISA findings, although the level of oxytetracycline detected in honey samples using HPLC method was remarkably (P < 0.05) lower than that detected by ELISA. Considering the relatively high contamination level of foods of animal origin with oxytetracycline and their high levels of consumption, it is likely that consumers experience a high risk of exposure to drug residues, especially through honey bees (Mahmoudi et al., 2014).

Out of the 3855 honey samples tested, 1.7% samples were non-compliant with EU4 standards, and the antibiotics were detected in the honey samples in the range: streptomycin 3–10.8 μg/kg, sulfonamides 5–4.6 μg/kg, tetracyclines 5–2.1 μg/kg, chloramphenicol 0.1–169 μg/kg, nitrofurans 0.3–24.7 μg/kg, tylosine 2–18 μg/kg, and quinolones < 1–504 μg/kg (Gunes et al., 2008).

Fifty honey samples comprised of chestnut, pine, linden, and multiflower honeys collected from the hives in Southern Maramar region of Turkey were analyzed for erythromycin residues by liquid chromatography-mass spectrometry using electrospray ionization in the positive ion mode (LC-ESI-MS). Four of the honey samples were contaminated with erythromycin residues at the concentrations ranging from 50 to 1776 ng/g. An erythromycin-fortified cake feeding assay was also performed in a defined hive to test the transfer of erythromycin residue to the honey matrix. In this test hive, the residue level in the honey, three months after dosing, was approximately 28 ng/g (Diserens, 2007).

Another study aimed to assess oxytetracycline (OTC) residue levels in honey after treatment of honeybee colonies with two methods of application (in liquid sucrose and in powdered icing sugar). The samples of honey were extracted up to 12 weeks after treatment and following metal chelation and analyzed by HPLC, which showed that the current method of application of oxytetracyclin (terramycin) in liquid form results in very high residue levels in honey with residues of 3.7 mg/kg, eight weeks after application (Thompson et al., 2005).

Recently researchers have developed a method to simultaneously detect the presence of 17 antibiotics (macrolides, tetracyclines, quinolones, and sulfonamides) in honey samples taken from supermarkets while five were collected from various private beekeepers throughout Granada and Almeria. The results of the study show that one of the commercial honey samples contained 8.6 μg/kg,
while another contained traces of sarafloxacin, and residues of tylosin, sulfadimidine and sulfachlorpyridazine were found in the honey from one bee farm (Vidal et al., 2002).

A total of 57 real royal jelly samples collected from beekeepers and supermarkets were analyzed for seven fluoroquinolones used in beekeeping, viz. ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, danofloxacin, enrofloxacin, and difloxacin, which were analyzed by high performance liquid chromatography with fluorescence detection. Ofloxacin, ciprofloxacin, and norfloxacin were detected in concentrations ranging from 11.9 to 55.6 ng/g in some royal jelly samples, and difloxacin was found at concentration of about 46.8 ng/g in one sample though it is rarely used in beekeeping (Zhou et al., 2002).

The result of antibiotic residues investigation (including enrofloxacin, penicillin, chloramphenicol, gentamicin, tylosin, tetracycline, and sulfonamide) in 135 honey samples collected randomly from Qazvin Province (Iran) showed that the range of antibiotic residues value was 0.0–72.1 ng/g, besides, the highest percentage of antibiotic residues in honey samples was the enrofloxacin (20.7%). The highest mean contamination (ng/g) was enrofloxacin (10.8 ± 1.6) followed by penicillin (4.4 ± 2.9), and the lowest was chloramphenicol (0.1 ± 0.1). The highest level of antibiotic residues (71.85%) was found in honey samples collected during the autumn season (Mahmoudi et al., 2014).

4. Antibiotic Residue in Honey and Health Impact

The extensive use of antibiotics leads to an accumulation of the residues in honey decreasing their quality and making their marketing more difficult (Fuselli et al., 2005).

The WHO has identified antibiotic resistance as “one of the three greatest threats to human health”. The primary cause is long-term exposure to antibiotics through their use as medicines in humans and animals, horticulture and for food preservation. The types of antibiotics used in animals are frequently similar to those used in humans. In December 2003, workshop convened by the Food and Agriculture Organization of the United Nations, the World Organization for Animal Health and the WHO concluded that “there is clear evidence of adverse human health consequences due to resistant organisms resulting from nonhuman usage of antimicrobials”. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures, and increased severity of infections (Al-Waili et al., 2012).

Antibiotics used in food animals can affect the public health because of their secretion in edible animal tissues in trace amounts usually called residues. For example, OTC and chloramphenicol residues have been found above the regulatory standards in honey (Ortelli et al., 2004; Saridaki-Papakonstadinou et al., 2006). Some drugs have the potential to produce toxic reactions in consumers directly while some other is able to produce allergic or hypersensitivity reactions and disorder of the
haemopoietic system (Paige et al., 1997). For example, β-lactam antibiotics can cause cutaneous eruptions, dermatitis, gastro-intestinal symptoms and anaphylaxis at very low doses. Such drugs include the penicillin and cephalosporin groups of antibiotics (Tillotson et al., 2006). Indirect and long term hazards include microbiological effects, carcinogenicity, reproductive effects and teratogenicity. Microbiological effects are one of the major health hazards in human beings. Antibiotic residues consumed along with edible tissues like milk, meat, eggs and honey can produce resistance in bacterial populations in the consumers. These bacteria might then cause difficult-to-treat human infections. Certain drugs like 3-nitrofurans and nitroimidazoles can cause cancer in human population. Similarly, some drugs can produce reproductive and teratogenic effects at very low doses consumed for a prolonged period of time (Tillotson et al., 2006).

5. Regularities for Antibiotics residues in Honey

Honey is an important commodity which is traded internationally. For international trade, all member countries generally accept standards set by the Codex Alimentarius. However, individual countries also have their own separate standards. Following standards of antibiotics in honey were reviewed: Codex Alimentarius, EU, US, Canada, and Australia. The use of antibiotics in beekeeping is illegal in some EU countries. Moreover, there are no Maximum Residue Limits (MRLs) established for antibiotics in honey according to the European Community regulations, which means that honey containing antibiotic residues are not permitted to be sold (Mutinelli, 2003). Codex Alimentarius standard (Codex Stan 12- 1981 Rev 1 1987 Rev2 2001) for residues of pesticides and veterinary drugs, states that the products covered by this standard shall comply with those maximum residue limits for honey established by the Codex Alimentarius Commission. Internationally agreed safety requirements of a number of veterinary medicines in food have been recommended by Joint FAO/WHO Expert Committee on Food Additives (JECFA) and adopted by Codex. However, no Maximum Residue Limits have been set for antibiotics in honey or even proposed (FAO, 2008).

The European Union (EU), on its part, regulates honey under the Council Directive 2001/110/EC. The standard for antibiotics in food is listed in Regulation (EU) No. 37/2010 – it stipulates that each antibiotic must have an MRL before it can be used on a food-producing species. But there are no MRLs for antibiotics in honey, which means the EU does not allow use of antibiotics for treatment of honeybees. EU has also set a provisional MRL of 25 ppb for oxytetracycline in honey, chloramphenicol (0.3 ppb) and nitrofurans (1.0 ppb) (FAO, 2005). Some countries, like Switzerland, UK and Belgium, have established Action Limits for antibiotics in honey, which generally lies between 0.01 to 0.05 mg/kg for each antibiotic group. Action Limits are the level of antibiotics in honey beyond which the sample is deemed non-compliant. In the US, Canada and Argentina,
preventive treatments with antibiotics are considered a routine procedure to prevent outbreaks of AFB. Consequently, various strains of *P. larvae* showing resistance to antibiotics, such as OTC, have been discovered in Argentina (Akbaria *et al.*, 2012) as well as in many areas of United States (Tuzen and Soylak, 2005).

6. Conclusions

The presence of antibiotic residue in food is particularly dangerous for human health, so it is essential to monitor their residues in food. Honey quality and safety are essential concerns of current society. There is an ever-increasing international honey trade, and this global market requires universal standards for the protection of consumers. The future use of veterinary chemicals in apiculture is required to continue productivity and profitability. However, increasingly sensitive analytical methods place the use of therapeutic drugs in jeopardy without compliance standards for exporting countries. The establishment of a worldwide consensus on legitimate best practice veterinary chemical usage in beekeeping and determination of appropriate MRLs for these and natural toxin contaminants in honey should be pursued. Standardized and updateable analytical protocols need to be established to determine contamination of honey from legitimate chemical usage. Thereafter, the Residues of Veterinary Drugs in Food Committee of Codex can be approached for the implementation of suitable standards for honey. It should be noted that significant scientific evidence might be required to support claims for an MRL for some chemicals. A worldwide concerted effort is required to uphold the all-natural, wholesome and “clean and green” image of honey.

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