International Journal of Secondary Metabolite
2023, Vol. 10, No. 3, 405–413

https://doi.org/10.21448/ijsm.1247832

Published at https://dergipark.org.tr/en/pub/ijsm Review Article

Review on antibiotics residues and their extraction and detection methods in highly consumed foodstuffs

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Abstract: Antibiotics have been widely used in the food industry, and their utilization has increased tremendously. Foodstuffs sometimes comprise excessive amounts of antibiotic residues due to a lack of awareness and misuse of these valuable drugs. The misuse of antibiotics in foods has led to the growth of bacterial resistance. Over the past century, the increasing use and abuse of antibiotics in food animals have directed to the prevalent transmission of bacterial and genetic resistance between animals and humans. Antibiotic residue from foods is considered a significant contaminant that threatens human health worldwide. Awareness and training on the application of antibiotics among farmers and drug sellers can rationalize the use of antibiotics in food animals. The Government of Oman should create and firmly implement application guidelines to regulate the use and prevent the misuse of antibiotics in foodstuffs sectors. This review aims to explore the current status of antibiotic residue in foodstuffs, and their detection, separation, and identification technologies in use. The review also highlights alternative ways to fight bacterial resistance.

ARTICLE HISTORY

Received: Feb. 05, 2023
Revised: May 11, 2023
Accepted: June 24, 2023

KEYWORDS

Foodstuffs,
Antibiotic usage,
Extraction,
Identification and quantification,
Antibiotic resistance,
Oman.

1. INTRODUCTION

Since their discovery during the 1930s, antibiotics have been used to treat and prevent infections and preserve food, reflecting their dramatic impact on the fields of medicine and the food industry. The rapid application of antibiotics in the food process was initially known as progress in the food industry to be discovered later as a serious threat to human health.

Inappropriate antibiotic use in food animals can generate a potential risk for human or consumer health. Recently this risk increased because of the spread of these antibiotics for treatment, prevention, or growth promotion in almost all livestock (Van *et al*, 2019, FDA 2017). This issue was studied and discussed repeatedly and generated a lot of debate, but no action

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e-ISSN: 2148-6905 / © **IJSM 2023**

was taken to mitigate the possibility of potential transfer of resistance from animals to humans as pathogenic organisms (Diarrassouba *et al*, 2007). The extensive use of antibiotics was evident. For example, in American farms, nearly all dairy cows receive prophylactic beta-lactam treatment post-lactation as a preventive measure. The extensive use of antibiotics was evident. For example, in American farms, nearly all dairy cows receive prophylactic beta-lactam treatment post-lactation as a preventive measure. Ten percent of healthy calves are treated with antibiotics to manage anticipated outbreaks of respiratory disease.

Forty-two percent of kinds of beef received macrolide drugs to prevent liver disease that negatively impacts their growth. Similarly, antibiotics are added to >80% of growing swine food to prevent infections and promote swine growth (Department of Agriculture -U.S., 2007 & 1999). A veterinary prescription is required for antibiotic use in livestock; however, lay farm men often make and administer individual treatment decisions (Raymond *et al*, 2006).

Different types of antibiotics, such as natural, synthetic, or semi-synthetic antibiotics, are available in the markets and are used for treating or preventing infections in humans and animals (Kaza *et al.*, 2023; Wu *et al.*, 2018). The development and uses of antibiotics are one of restorative practices in the healthcare sector. Antibiotics are medications that are used to treat infections caused by bacteria. They work by either killing the bacteria or inhibiting their growth. Doctors often prescribe antibiotics to treat bacterial infections such as pneumonia, bronchitis, urinary tract infections, and skin infections (Tripathi & Tripathi, 2017; Wang *et al.*, 2020; Kumar & Pal, 2018; Chen *et al.*,2019; Phillips, 2003; Kneebone *et al.*, 2010; Jammoul & Darra, 2019; Farouk *et al.*, 2015). Antibiotics can be taken orally in the form of pills or liquids, or they can be administered intravenously through a vein. It is essential to take antibiotics exactly as prescribed by a doctor and finish the entire course of treatment, even if the symptoms of the infection have improved. This is because not completing the entire course of treatment can lead to the development of antibiotic-resistant bacteria, which can be more challenging to treat (Larsson, 2014; Majdinasab *et al.*, 2020; Al Salah *et al.*, 2019; Anand *et al.*, 2012).

The misuse or overuse of antibiotics during the production of food has directed to create antibiotic-resistant bacteria and antibiotic-resistance genes that could accumulate in foodstuffs and humans (Bai *et al.*, 2021; Karkman *et al.*, 2018; Jiang *et al.*, 2018; Rizzo *et al.*, 2014; Chowdhury *et al.*, 2021; Zhang *et al.*, 2020). Evidence is available related to antibiotic resistance in humans due to the vast application and misuse of antibiotics during the production of foodstuffs (Nguyen *et al.*, 2019). People widely use antibiotics to treat various infectious diseases and increase the production of foods. However, many users of antibiotics are not familiar with the proper use and dose of antibiotics for producing foodstuffs. Oman is not an agricultural country, but still, they produce some agricultural products. Furthermore, Oman has a huge number of chicken farms, and they produce chicken meat. The local farms cover about 60% of the protein requirement (Al-Bahry *et al.*, 2009). Farmers and chicken farm owners are using excessive amounts of antibiotics to produce huge crops and poultry. However, no study has been conducted in Oman on the status of antibiotic use and misuse in agriculture. This current review will provide a shade on the adverse effects of antibiotics use in food animals for future research and the correct application of antibacterial agents to reduce the harmful effects of antibiotic residue in foodstuffs.

2. TYPES OF ANTIBIOTICS

Different types of antibiotics are available all over the globe; they are classified based on their mechanism of action and activity. Some common types of antibiotics include penicillin, cephalosporins, tetracyclines, and macrolides (Al-Bahry *et al.*, 2912; Al-Bahry *et al.*, 2019; Hamilton-Miller, 1973; Heesemann, 1993; Henry, 1943; Holten & Onusko, 2000; Kahne *et al.*, 2005; Kang & Park, 2005; Livermore *et al.*,2011; Sykes & Bonner, 1985; Sykes *et al.*, 2015).

Each type of antibiotic is effective against certain types of bacteria, so a prescriber needs to determine by the culture test to select the appropriate antibiotic for a particular infection. Here is a brief overview of some of the main types of antibiotics (Al-Bahry *et al.*, 2912; Al-Bahry *et al.*, 2019; Hamilton-Miller, 1973; Heesemann, 1993; Henry, 1943; Holten & Onusko, 2000; Kahne *et al.*, 2005; Kang & Park, 2005; Livermore *et al.*,2011; Sykes & Bonner, 1985; Sykes *et al.*, 2015):

1. Penicillins: including drugs such as penicillin and amoxicillin and work by inhibiting the synthesis bacterial cell wall. They often treat respiratory tract, urinary tract, and skin infections.
2. Cephalosporins: This group of antibiotics, including drugs such as cephalexin and cefuroxime, inhibits the synthesis of the bacterial cell wall and can inhibit the synthesis of other bacterial cell components. They often treat respiratory, urinary tract, and skin infections.
3. Tetracyclines: including drugs such as doxycycline and minocycline, which inhibit the synthesis of proteins in bacterial cells. They often treat acne, respiratory infections, and sexually transmitted infections.
4. Macrolides: This group of antibiotics includes erythromycin and azithromycin. They inhibit the synthesis of proteins in bacterial cells and are often used to treat respiratory and skin infections.
5. Quinolones: Quinolones, including ciprofloxacin and levofloxacin, inhibit the synthesis of DNA in bacterial cells and are used to treat various infections, including respiratory tract infections, urinary tract infections, and sexually transmitted infections.
6. Aminoglycosides: include drugs such as gentamicin and amikacin and work by inhibiting the synthesis of proteins in bacterial cells. They are often used to treat serious infections such as pneumonia and sepsis.
7. Sulfonamides: including drugs such as sulfamethoxazole. They inhibit folic acid synthesis in bacterial cells and are often used to treat urinary tract infections and skin infections.

3. USE OF ANTIBIOTICS

Antibiotics are medications used to treat infections caused by bacteria. They work by either killing the bacteria or inhibiting their growth and are often prescribed by doctors to treat a wide range of bacterial infections. Antibiotics are available in various forms, including oral pills and liquids, intravenous solutions, and creams or ointments for topical use (Gothwal & Shashidhar, 2015; Liu *et al.*,2017; Abdel-Shafy & Mansour, 2018).

Antibiotics are usually prescribed based on the type of infection being treated and the susceptibility of the bacteria causing the infection to different types of antibiotics. In some cases, a doctor may prescribe a broad-spectrum antibiotic, which is effective against a wide range of bacteria, while in other cases, a narrow-spectrum antibiotic, which is effective against a specific type of bacteria, may be more appropriate (Menkem *et al.*, 2019; Gothwal & Shashidhar, 2015; Liu *et al.*,2017; Abdel-Shafy & Mansour, 2018).

It is worth noting that antibiotics are only effective against bacterial infections and cannot be used to treat infections caused by viruses, such as the common cold or influenza (Joshi & Ahmed, 2016). Using antibiotics unnecessarily or inappropriately can contribute to the development of antibiotic resistance, which occurs when bacteria become resistant to the effects of an antibiotic. This can lead to the spread of antibiotic-resistant bacteria, which can be more difficult to treat and require more potent or specialized antibiotics. It is important to use antibiotics only when necessary and to follow proper prescribing guidelines to help reduce the risk of antibiotic resistance (Gothwal & Shashidhar, 2015; Liu *et al.*,2017; Abdel-Shafy & Mansour, 2018).

In addition to being prescribed by doctors to treat specific infections, antibiotics may also be used in other settings to prevent infections. For example, antibiotics may be given to people who are undergoing surgery or other medical procedures to prevent infections. They may also be given to people who have compromised immune systems, such as cancer patients or HIV/AIDS patients, to prevent infections from occurring (Al-Bahry *et al.*, 2012; Livermore *et al*., 2011).

It is important to be aware of the potential side effects of antibiotics, which can vary depending on the specific drug being taken. Common side effects of antibiotics include nausea, diarrhea, and allergic reactions. Some antibiotics can also cause changes in the normal bacterial flora of the body, which can lead to the development of yeast infections or other types of infections. In rare cases, antibiotics can cause more serious side effects such as liver or kidney damage or blood disorders (Jammoul & Darra, 2019; Farouk *et al.*, 2015; Larsson, 2014; Majdinasab *et al.*, 2020; Al Salah *et al.*, 2019; Anand *et al.*, 2012). If a patient experiences any severe side effects while taking an antibiotic, it is important to contact the doctor as soon as possible.

Overall, antibiotics are essential medications that can be used to effectively treat bacterial infections and prevent infections from occurring in certain situations. However, using them responsibly and only when necessary is important to help reduce the risk of antibiotic resistance. It is also important to be aware of the potential side effects of antibiotics and to follow the healthcare provider's instructions to ensure the safe and effective use of these drugs.

4. SOURCES OF ANTIBIOTICS

1. Several different sources have been used for the production of antibiotics. Some antibiotics are produced by bacteria, while others are produced by fungi (Vannuffel & Cocito, 1996; Walsh, 2003; Sanchez *et al.*, 2004; Levy, 2007; Chadwick & Goode, 1997; McEwen & Fedorka-Cray, 2002). Here is a brief overview of some of the primary sources of antibiotics: Bacteria: Many antibiotics are produced by bacteria as a means of protecting themselves against other bacteria. These antibiotics are often extracted from soil bacteria or from bacteria that live on the bodies of animals. Examples of antibiotics produced by bacteria include penicillins, cephalosporins, and tetracyclines (Levy, 2007; Chadwick & Goode, 1997; McEwen & Fedorka-Cray, 2002).

2. Fungi: Some antibiotics are produced by fungi as a means of protecting themselves against other fungi or bacteria. These antibiotics are often extracted from soil fungi or from fungi that live on the bodies of animals. Examples of antibiotics produced by fungi include griseofulvin and amphotericin B (Levy, 2007; Chadwick & Goode, 1997; McEwen & Fedorka-Cray, 2002).

3. Chemical synthesis: Some antibiotics, such as sulfonamides and quinolones, are produced through chemical synthesis rather than being extracted from natural sources such as levofloxacin, gatifloxacin, moxifloxacin, and sparfloxacin.

5. EXTRACTION OF ANTIBIOTICS

There are several methods available for the extraction of antibiotic residue the from foodstuffs The extraction methods depend on the types of antibiotics. Therefore, the extraction methods are varied based on the classification of antibiotics. All the methods are complex, and they have multiple steps to extract the desired antibiotics. The simplest and most popular methods for extraction of antibiotics from foodstuffs are given as follows:

5.1. Method 1

The food samples are pasted by using a kitchen blender machine. The paste sample (2 gm) is taken into a beaker (50 ml) and a buffer-EDTA solution is added (McEwen & Fedorka-Cray, 2002). The mixture is mixed using a homogenizer, transferred into a centrifuge tube (10 ml), and centrifuged at 3000 rpm for 1 minute. The supernatant part is transferred into another tube and evaporated to 1 ml. The concentrated sample is passed through the solid phase extraction column containing activated silica. An eluent organic solvent is used to clean the antibiotics and concentrate it using a rotary evaporator. The concentrated solution is analysed by using HPLC method. Methanol, acetonitrile, and formic acid are commonly used as mobile phases for the isolation and separation of various antibiotics. Most scientists use methanol and acetonitrile worldwide as the mobile phase because the solvent is affordable and available for enhancing the solubility and the analysis of antibiotics (Witte, 1998; Xu *et al.*, 2020; Li *et al.*, 2020).

5.2. Method 2

The foodstuffs samples (2 gm) are pasted and homogenized by the vertex machine for a few minutes. The sample is transferred into a beaker and added nitric acid and aqueous solution and the mixture is shaken vigorously. Then the sample is centrifuged at 4000 rpm for 10 minutes. After centrifugation, the sample is passed through the filter paper, and the filtrate is evaporated by as usual method until the concentration was 1 ml. The concentrated sample is analyzed by chromatographic method (Betina, 1993).

5.3. Method 3

The collected foodstuffs sample **(**2 gm) is prepared as a paste, taken into a beaker, and treated with acetic acid. The mixture is well mixed for a few minutes, and the sample is centrifuged at a specific rpm for 5 minutes. The supernatant liquid is filtered using filter paper and evaporated until 1 ml (Senyuva *etal.*, 2000; Markina *et al.*, 2020).

6. DETECTION OF ANTIBIOTICS

The literature shows that various types of chromatography, such as paper chromatography, thin-layer chromatography, and ion exchange chromatography, are used as basic tools for isolating, separating, and characterizing antibiotics from the foodstuffs. Due to the improvement of technology, recently High-Performance Liquid Chromatography (HPLC), Liquid Chromatography-Mass Spectrometry (LC-MS), and Ultra-High Performance Liquid Chromatography (UHPLC) are used for the separation, characterization, and quantification of various antibiotics in foodstuffs (McEwen & Fedorka-Cray, 2002; Witte, 1998; Xu *et al.*, 2020; Li *et al.*, 2020). Liquid chromatography-mass spectrometry (GC-MS) is a well-established method for detecting and quantifying various antibiotics in biological and animal samples (McEwen & Fedorka-Cray, 2002; Witte, 1998). However, all the mentioned methods are too expensive for routine analysis. Therefore, for the analysis of antibiotics currently, L.C. system is used coupled with different detectors such as U.V., diode array, and fluorescence detector. They are highly recommended as alternatives (Senyuva *etal.*, 2000; Markina *et al.*, 2020; McEwen & Fedorka-Cray, 2002; Witte, 1998; Xu *et al.*, 2020; Li *et al.*, 2020).

7. CONCLUSIONS

The improper use of antibiotics in the Agri-foods sector can result in antibiotic residues in food products, and these antibiotic residues can adversely affect human health. Several analytical methods were developed globally for detecting, isolating, and quantifying antibiotic residues in foodstuffs. LC-MS is a widely accepted technique for detecting and quantifying antibiotic residues in foodstuffs. Although, the LC-MS technique is highly sensitive, it is expensive and not affordable for the small-scale analysis of residues in foods. Therefore, scientists are always searching for comparatively cheap and available alternatives. As an alternative, scientists are currently using L.C. system coupled with sensitive and powerful detectors such as U.V., diode array, and fluorescence detector to analyse foodstuff antibiotics residues.

Several challenges must be considered when using antibiotics, including the increasing problem of antibiotic resistance, the potential for contamination during the production process, and the cost and accessibility of these medications. It is important to use antibiotics responsibly and only when necessary to help reduce the risk of antibiotic resistance and to ensure that these medications are accessible and affordable to those who need them. Overall, antibiotics are essential tools in treating bacterial infections, however we must use them responsibly to help preserve their effectiveness for the future.

Acknowledgments

The authors are grateful to the University of Nizwa for providing support to finish this review work. The datasets used or analysed during the current study are available from the corresponding author on request.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Mohammad Amzad Hossain, Ahmed Abu Sham and Salem Said Jaroof Al-Touby: Conceptualized the Review articles. **Ali Attia Abedlnaeem Attia Salem, Waleed Khalid Hilal Al Rajhi**: Draft preparation. **Mohammad Amzad Hossain, Salem Said Jaroof Al-Touby**: involved in the drafting and edition. Drafts were critically discussed and revised by all authors.

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