Review Article

Antibiotic Residue- Food Producing Animal Origin and Its Impact on Human Health

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Abstract

Antibiotics are mainly employed for chemotherapeutic, prophylactic purposes and also used as feed additives to promote growth and improve feed efficiency. However, antibiotic residues in animal products may occur, when administration of drug in extra label fashion and not following of withholding or withdrawal period after treatment. A withdrawal period is established to safeguard human from exposure of antibiotic added food. The withdrawal time is the time required for the residue of toxicological concern to reach safe concentration as defined by tolerance. Many of the administered drugs are not completely absorbed from gut and excreted through faeces and urine as either parent compound or its toxic metabolites. The application of manure or farm effluents in agricultural land leads to selection of resistant bacteria, development and transmission of antibiotic resistance genes in the microbes. The antibiotic resistance in animal and human leads to poor response to treatment during illness. The antibiotic residues in animal product causes harmful effect on health and also interfere with the processing of milk and milk products. The present review focuses on antibiotic residues in animal products and its impact on environments and human health.

Key words: Antibiotic, Buffalo, Cattle, Milk, Residue, Withdrawal Period

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Introduction

Antibiotics are substances either produced naturally by living organisms or synthetically in the laboratory, and they are able to kill or inhibit the growth of microorganisms. Antibiotics residue in foods of animal origin are one of the sources of concern among the public and medical health professionals (Bren, L. *et al.*, 2002) Antibiotics are also used as feed additives for the purpose of livestock health maintenance. Apart from this, they are also used as feed additives as growth promoters may result in presence of antimicrobial residues in milk and dairy products, and can contribute to the development of microbial drug resistance and

the spread of resistant bacteria (Stolker, A. A. M. *et al.,* 2007). The residues of Veterinary Medicinal Product i.e. antibiotics present a potential risk to the human population, particularly with the appearance of allergic reactions and interferences of intestinal micro-flora (Dewdeny, J. M. *et al.,* 1991). From the technological prospective, residues of antimicrobial agents in milk can cause significant losses in fermented products, by inhibition of bacterial fermentation in the production processes of cheese or yoghourt (Molina, M. P. *et al.,* 2003). Therefore, accurate detection of low levels of antimicrobial drug residues in milk is of great importance for the dairy industry and for farmers, with a purpose to ensure that the contaminated milk from individual cows are not consigned to the bulk tank (Mitchell, J. M. *et al.,* 2002).The fluoroquinolones antibiotics have wide range of antibacterial activity and have seen increasing use in veterinary medicine because of their effectiveness in treating bacterial infection (A. L. Cinquina *et al.,* 2003). Antibiotic residues in feedstuffs are currently a problem of some magnitude in different parts of the world, particularly due to associated public health concerns that include hypersensitivity reactions, antibiotic resistance, toxicity, teratogenicity, and carcinogenicity (Wageh Sobhy Darwish, *et al.,* 2013). Use of Antibiotic that might result in deposition of residues in meat, milk and eggs must not be permitted in food intended for human consumption. If use of antibiotics is necessary as in prevention and treatment of animal diseases, a withholding period must be observed until the residues are negligible or no longer detected. Hence, the present review focuses on antibiotic residues in animal products and its impact on environments and human health.

Application of Antibiotics

The antibiotics nowadays used for improved performance in growth especially in broilers and fatteners. They may produce improved growth rate because of thinning of mucous membrane of the gut, facilitating better absorption, altering gut motility to enhance better assimilation, producing favorable conditions to beneficial microbes in the gut of animal by destroying harmful bacteria and partitioning proteins to muscle accretion by suppressing monokines. Antibiotics also favour growth by decreasing degree of activity of the immune system, reduced waste of nutrients and reduce toxin formation. In most of the cases only young growing animals and poultry are responsive to antibiotic mediated growth promotion. Indiscriminating use of antibiotics in all cases of pyrexia, inflammation, wounds and viral diseases have widespread residual effects on edible tissues. The use of antibiotics only in specific conditions is justified because the roll of microbial agents is mainly to kill the rapidly dividing invading cells. Animals and poultry are receiving sub therapeutic levels of antibiotics to prevent possible infection. But the antibiotics are specific to their spectrum of activity only in the active multiplying stage of bacteria. But it will not provide overall protection. Only in certain cases like dry cow therapy and surgical procedures are wanting of antibiotic prophylaxis. Antimicrobials are used either directly or indirectly during the production processing and

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storage of milk and milk products. Direct contamination of milk may occur from air and water during processing, storage and transportation. Besides feed given to animals is also source of indirect contamination. Man will be the ultimate consumer of these antibiotic residues. There are some causes of miscellaneous use like lack of awareness, lack of extension activities, inadequate literature supplied by manufacturers, lack of safer drugs and exploitation of more production and profit from animals. FDA prohibits the extra label use of chloramphenicol, furazolidone, nitrofurazone, sulphonamide drugs, and flouroquinolones in lactating animals.

Antibiotic Residues

Several antibiotic classes are extensively administered to food-producing animals, including tetracyclines, sulfonamides, fluoroquinolones, macrolides, lincosamides, aminoglycosides, beta-lactams, cephalosporins and others (Woodward, K. 2004; Jank, L. *et al*., 2017).

Table 1: Maximum Residues Limit (MRL) of antibiotic as per *Codex Alimentarius commission*

S. No.	Name of Antibiotics	Substrate	Maximum Residual Limit (µg/kg)
1	Benzyl penicillin	Milk	4
		Muscle/liver	50
2	Ampicillin	Milk	4
3	Amoxycillin	Milk	4
		Muscle/liver	50
4	Oxacillin	Milk	30
5	Cloxacillin	Milk	30
6	Dicloxacillin	Milk	30
7	Tetracycline	Milk	100
		Muscle	200
8	Oxytetracycline	Milk	100
		Muscle	200
9	Chlortetracycline	Milk	100
		Muscle	200
10	Streptomycin	Liver-Poultry	200
11	Dihydrostreptomycine	Milk	200
		Muscle	600
12	Gentamycine	Milk	200
		Muscle	100
13	Sulphonamides	Milk	100
14	Ceftiofur	Milk	100
		Muscle	1000

Almost 90% of all antibiotics used in farm animals and poultry are reported to be administered at sub-therapeutic concentrations. About 70% of this is for the purpose of disease prevention and 30% are for growth promotion (Kebede, G. *et al*., 2014). The risk of residue from the milk is higher in developing countries compared to develop one. This might be related with lack of facilities for detection and regulatory

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bodies that control the drug residues level in foods in the form of maximum residue limits (Kebede, G. *et al*., 2014). The MRL is defined as the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical that is recommended to be legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed.

Screening/Analytical Method

Microbial Inhibition Test

It is a qualitative or semi-quantitative test is used to detect antibiotic residues in milk and meat. Muller Hinton or Nutrient agar is commonly used to perform agar diffusion test. These tests comprise spores of specific bacteria (*Bacillus subtilis, Bacillus stearothermphillus, Micrococcus luteus* etc), sensitive to particular antibiotics on agar gel including nutrients for bacterial growth and a pH indicator (Chafer-Pericas C. *et al*., 2010). After addition of milk, the plate is incubated at appropriate temperature for growth and germination of bacteria. In the absence of antibiotic residues, the growth of bacteria can be detected visually either by the change of opacity of the agar medium or by the colour change of the pH indicator (Hakem, A. *et al*., 2013, Navratilova P. *et al*., 2008, Dang, P.K. *et al*., 2010). This method is cheap and simple, showed 100% sensitivity and specificity for screening of residues (Dang, P. K. *et al*., 2010), 85.51% of poultry meat samples were positive for antibiotic residue, most of them contained β-lactams and tetracyclines (75.81%), macrolides (44.35%), sulphonamides (36.29%), aminoglycosides (13.71%) group (Thompkinson, K., 2012) and macrolides (12.5%) group of antibiotics in commercial eggs of urmia, Iran (Ehsani, A. *et al*., 2015).

Biosensor

Biosensor is a latest technique used for screening of antibiotics residues in milk. The sensitivity and selectivity of biosensors are comparable to immunoassay methods (Rinken, T. *et al*., 2006). These sensors have shown successful detection of β-lactams (β-Ls), tetracycline, streptogramin and macrolide antibiotics at nanogram per millilitre concentrations in milk and serum (Weber, C. C. *et al*., 2005, Toldra, F. *et al.*, 2006). Microbial biosensor is mostly used for detection of quinolones (Qs) and tetracyclines (TCs). However, these were not sensitive toward detection of macrolides, β-Ls, aminoglycosides and sulphonamides (Kivirand, K. *et al.*, 2015).

Enzyme Linked Immunosorbent Assay (ELISA)

ELISA is most useful and specific test for screening of drug residues in meat, milk and egg. The Competitive ELISA is commonly used for quantitative analysis of tetracycline, fluoroquinolones and chloramphenicol in meat (Yibar, A. *et al.*, 2011, Kim, D. P. *et al.*, 2013). Competitive indirect chemiluminescent enzyme-linked immunoassay (CL-ELISA) is used to determine the chloramphenicol

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(CAP) residues in milk and chicken muscle. The sensitivity of CL-ELISA is 2-3 times higher than conventional ELISA (Tao, X. *et al*., 2012) and able to detect trace amount of CAP as low as 3.19 ng/kg in chicken muscle. In India (Punjab), Gaurav *et al*., 2014 reported that tetracycline residues in milk by competitive ELISA. Out of 133 cattle milk sample, 18 samples were found to be contaminated with tetracycline. The concentration of tetracycline residues in cattle milk samples were found to be in the range 16-134.5 µg/l. Three samples exceeded the maximum recommended tetracycline antibiotic residue levels (MRLs). Sultan *et al*., 2014 reported that enrofloxacin residues in liver sample of poultry, sheep and cattle collected from slaughter house of Mousl city, Iraq. Out 30 samples from each species 17 poultry sample, 8 cattle sample and 5 sheep sample exceeded the maximum residue limits (Permitted MRL by European agency 100-300 µg/kg). The concentration of enrofloxacin in liver sample of poultry, cattle and sheep were 10-10690, 30-3610 and 20-1320 µg/kg respectively. This may be heavy use of enrofloxacin in poultry industry to control diseases.

High Performance Liquid Chromatography (HPLC)

Currently, HPLC is one of the most powerful tools in analytical chemistry. HPLC usage is increasing day by day in the field of residue analysis because, these having variety of mobile phases, the extensive library of column packings and the variation in modes of operations (Jank, L. *et al*., 2017**)**. The residue analysis of oxytetracycline and penicillin G in milk collected from Nazareth dairy farms, Ethopia (Senyuva *et al*., 2000). Out of 400 milk samples 48 samples were found oxytetracycline and penicillin G in the range of 45-192 and 0-28 µg/l, respectively. A total of 497 raw milk samples were collected from different region of individual farms at Macedonia and analysed for chloramphenicol, sulfonamides, quinolones and tetracyclines by HPLC-Diode array detection. The concentration of sulphonamides, quinolones and tetracycline in the range of 13.5-147.9, 0.6-22.0 and 17.4-149.1µg/kg, respectively. None of the samples showed chloramphenicol above MRL (Elizabeta *et al*., 2011). A total number of 250 milk samples consisting of 125 from organized and 125 from unorganized sectors were randomly collected out of which 50 sample from each districts of Bihar. It was found that out of all the milk samples analyzed BY HPLC , eight samples (3.2 %) were found to contain antibiotics residue. Three samples (1.2 %) exceeded the maximum residue levels (MRL) for enrofloxacin antibiotics according to the regulation set by the European Union and the Codex Alimentarious Comission.(Nirala, R. K. *et al*., 2017). In Iran cattle tissue (Triceps muscle, gluteal muscle, diaphargam, kideney and liver) from local market were examined for tetracycline group of antibiotics (tetracycline, oxytetracycline and chlortetracycline) by HPLC method. The tetracycline concentration in Triceps muscle, gluteal muscle, diaphargam, kideney and liver were 176.3, 405.3, 96.8, 672.4 and 651.3 ng/g, respectively. The concentrations of tetracyclines were higher in liver and kidney

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sample compared to other sample (Abbasi, M. M. *et al*., 2012) and it was higher in cured meat product (Senyuva *et al*., 2000).

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Nowadays, the most frequently used analytical tool for detection of a large number of multiclass veterinary drug residues in food (Martins, M.T. *et al.*, 2014, Layada, S. *et al*., 2016). The analysis of antibiotics in milk by LC-MS/MS is more specific and more reliable. Simultaneous determination of 14 antibiotics from different classes includes five β-lactams, four sulfonamides, three tetracyclines, one macrolide and one cephalosporin by liquid chromatography with electrospray ionization (LC-ESI) and triple quadrupole mass spectrometry (MS/MS) (Martins-Junior HA *et al*., 2007), enrofloxacin and tetracycline residues in chicken and pork by LC-MS/MS (Kim, D.P. *et al.*, 2013). Aminoglycoside in animal tissue includes bovine kidney, ovine kidney and poultry liver (Plozza, T. *et al.*, 2011). Out of seventy two samples, twelve samples showed aminoglycosides includes neomycin, streptomycin and dihydrostreptomycin exceeded the MRL. The concentration of neomycin, streptomycin and dihydrostreptomycin were 10000, 300 and 300 µg (Plozza, T. *et al.*, 2011).

Table 2: Antibiotic residue in food producing animal origin

S. No.	Name of antibiotics	Instrumentation	Substrate	Residual level(ppb)	References
1	Tetracycline	HPLC-DAD	Milk	17.4 – 149.1	Elizabeta *et al*., 2011
2	Tetracycline	ELISA	Milk	16-135.5	Gaurav *et al*., 2014
3	Gentamicin	ELISA	Milk	42-360	Senyuva *et al*., 2000
4	Streptomycin	ELISA	Milk	90	Zeina *et al*., 2013
5	Penicillin	HPLC	Milk	0-28	Abebew *et al*., 2014
6	Sulfamethoxazole	UPLC-MS/MS	Milk	4.2	Han *et al*., 2015
7	Sulphonamide	HPLC-DAD	Milk	13.5-147.9	Elizabeta *et al*., 2011
8	β-lactams, Macrolides and Cephalosporin	LC-MS/MS	Milk	--	Martin-Junior *et al*., 2007
9	Quinolone	HPLC-DAD	Milk	0.6-22.00	Elizabeta *et al*., 2011
10	Enrofloxacin & Tetracycline	ELISA	Liver-Poultry	10-10690	Sultan *et al*., 2014

Preventive Measures to Minimizing the Antibiotic Residue in Livestock Products

This section includes recommendations and measures to reduce antibiotic residues in foods of animal origin-

1. Reduce antibiotics use in food animal rearing. Many developed countries have banned its use as growth promoters.
2. Rapid screening methods should be developed for detecting and segregating samples contains above MRL levels of antibiotics.

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3. Appropriate MRLs need to be set by regulatory bodies and should enforce it.
4. Appropriate withdrawal periods should be strictly followed and enforced to make the meat rendered safe for human consumption.
5. Improve the individual and organizational aware by enhancing proper knowledge dissemination.
6. Follow best hygiene practices during animal rearing and avoid unwanted use of antibiotics.
7. Alternates to antibiotics like bio control measures and Ethno-veterinary practices should be developed and followed.
8. Organic poultry farming may be encouraged by providing appropriate incentives to the farmers in form of subsidies.
9. Use of proper processing techniques to inactivate the antibiotic residue, e.g. refrigeration causes inactivation of penicillin.
10. Use of activated charcoal, resins and UV irradiation to inactivate residues.

Conclusion

Use of antibiotics as feed additives at sub therapeutic dose should be strictly prohibited. For therapeutic purpose, it must be used in proper dose for proper time. There are two major concerns in the presence of antibiotic residues in milk, meat and egg. One is allergic reaction even at smaller dose, another development of antibiotic resistance and disruption of soil microbial community. Monitoring of antibiotic residues in milk and milk products, meat and meat products, egg, faeces and urine is necessary to safeguard the health of the consumers as well as minimize environmental contamination.

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