Review Article

INFLUENCE OF HEAT TREATMENT ON ANTIMICROBIALRESIDUESIN LIVESTOCK FOOD PRODUCTS:*A REVIEW*

Comment [T1]: Please adjust this title to be Antibiotic, not antimicrobial

Abstract

The use of antimicrobial drugs in livestock production cannot be avoided; it has to be used for various reasons like therapeutics, prophylactic and even as growth promoters. However the irrational use of antimicrobialsin livestock has led to the accumulation of itsresidues in animal tissues and their products.The deposition of residues in food originated from livestock animals is a critical problem in many countries and the problem is more serious in developing countries around the world, due to their potential health hazards. Generallythe residues are more procedurally estimated on uncooked meat, but meat food undergoes varying degree of heat treatment during cooking process, therefore information on heat stability of antibiotics is an important area of research to give a more accurate estimate of consumer's exposure to these abiotic compounds and their metabolites.

It has been stated that heat treatment at different time-temperature combinations degrades and reduces antimicrobial drug residues in animal products. However, cooking processes do not guarantee complete degradation of antimicrobial drug residues. So the objective of this review paper is to illustrate various changes of antibiotic drug residues during cooking process, supported by various studies and finding.

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Key words: Antibiotic, drug residues, heat treatment and heat stability

Comment [T3]: The keyword is antibiotic, but the title says Antimicrobial

Introduction

Antimicrobials are substances either produced naturally by living organisms or produced synthetically in the laboratory and can kill or inhibit the growth of other microorganisms.They are among the essential veterinary medicine compounds related to food animal production, defined as substances that can kill or inhibit the growth of bacteria (Bacanli*et al.*, 2019). The application of antimicrobial drugs is almost unavoidable in the treatment of bacterial infections in animals and humans (Arsene*et al.*, 2021). Globally theuse of antimicrobial drugs in animals istwice that of humans (Aarestrup*et al.*, 2012).Worldwide a total of 63.1±1.5 tons of antibiotics are used in livestock, estimating that over 80% of foodanimals are being treated with these compounds annually (Boeckel*et al.,* 2015). Drug residues are "pharmacologically active substances (whether active principles, recipients, or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal products in question have been administered'' (FDA & European Union). The indiscriminate use of antimicrobial drugs in livestock has resulted in the deposition of residues of these compounds in animal tissues that serve as meat and other livestock productssuch as milk and eggs. Various studies have confirmed the occurrences of antimicrobial drug residues in animal-originated food products and their potential health risk to consumers. The primary objective of every country is to guarantee a safe food resource to its consumers. However, more recently increase in the occurrences of antimicrobial drug residues in livestock products has posed a major public health issue around the globe particularly in developing countries. Estimation of antimicrobial drug residues is mostly done on fresh and uncooked livestock products. However, all food originating from livestock undergoes heat treatment (cooking) at least in some part of the processing line before its consumption. Various studies showed that cooking has a positive effect on the reduction of antimicrobial drugs residing in livestock produce at varying degrees. Therefore the objective of this review paper would be to illustrate the influence of different cooking methods on the effect of commonly used antimicrobials drug residues on meat and meat products.

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Use of antimicrobials in livestock

Veterinary drugs are inevitably used for therapeutic or preventive reasons in parallel with growth promotion (Dong, 2009).The major use of antimicrobial drugs in livestock is for the treatment and prevention of diseases. In many a situation combinations of two or more drugs are required to treat certain diseases. Antimicrobial agents greatly aid in promoting the health and general welfare of animals, by giving relief from diseases and prevent from spreading among the animal lot (Boamah*et al.*, 2016).A significant percentage of all feed manufacturers add antibiotics to animal feed for disease prevention rather than cure of diseases (Landers *et al.*, 2012). Approximately 50% of antibiotics produced in the world account for use in livestock (Erofeeva*et al.*, 2021). The US Department of Agriculture noted that approximately 88% of growing swine receive antibiotics in their feed for disease prevention and growth promotion purposes. The most commonly used are tetracyclines or tylosin (Landers *et al.*, 2012).It is estimated that the use of antibiotics will increase by 67% by the year 2030, with almost twice this increase in countries like China, Brazil, India, South Africa, and Russia.The overall use of antimicrobial drugs in livestock animals has been classified as; sulphonamide

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20%, fluoroquinolones 19%, aminoglycosides 15%, phenols 15%, β-lactams 15%, oxazolidones 8% and tetracycline 8% (Mungroo*et al.*, 2014). The use of antibiotics as livestock growth promotersstarted in the 1940s from the feeding of pharmaceutical wastes containing aureomycin, which has resulted in a significant weight gain in poultry. Following the incident, subtherapeutic antibiotic treatment was applied to poultry and swine from 1946 to 1950. Viewing the effects of antibiotics on the weight gain of livestock farm animals, the Food and Drug Administration (FDA) approved its use in 1951 (Castanon, 2007). The proposed mechanism of antibiotics as growth promoters are, reducing the incidence and severity of infections caused by bacteria, retarding the uptake of nutrients by microorganisms, reducing the secretion of growth-depressing metabolites by gram-positive bacteria; and enhancing the nutrient absorption by thinning the intestinal wall (Huyghebaert*et al.*, 2011). Antimicrobial agents enhance the absorption of available nutrients in intestinal epithelium, promote the synthesis of growth factors and vitamins, and destroy pathogens which effectively reduce the release of toxins (Prescott and Baggot, 1993). Antimicrobial agents as growth promoters are mainly used to improve productivity   (Taylor, 1999).

Comment [T7]: Correct the spelling and space

nCauses for occurrence of antimicrobial residues and its impact on human health

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Poor treatment records, failure to identify treated animals, lack of advice on withdrawal periods by veterinarians, off-label use of prohibited drugs and extra-label drug usage, lack of enforcement of restrictive legislation to use antimicrobial drugs, lack of consumer awareness, use of antibiotics as meat preservatives, use of antibiotics as growth promoters, unethical commercial practices to promote the sale of antibiotics in large quantities; and use of antibiotics by other non-medical and informal health care providers (Ranjalkar*et al.*, 2019 and CAC, 2001).

The use of antibiotics in food animalsaffects public health because of their secretion in edible animal tissues in trace amounts usually called residues. The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced by the human population worldwide (Cars *et al.*, 2008).The major public health significances of drug residue are the development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, and disruption of intestinal normal flora (Beyene*et al.*, 2016).Resistant strains can cause failure of antimicrobial therapy in clinical situations (Nisha, 2008).It was found that animals cannot absorb all antibiotics and approximately, 30–90% of veterinary antibiotics can be transferred to the environment through urine, faces, and waste \-water effluent. Eventually, these antibiotic residues can come into contact with the human

Comment [T9]: Correct the spelling and space through the food chain.Residues of tetracycline in food products pose a significant public health risk as microbial resistance, bone and teeth staining, and teratogenic effects (Morshdy*et al.*, 2013).

Table 1 Pathological effect of some commonly used Antimicrobial drugs

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Antimicrobial agents	**Pathological effects**
Sulfamethazine, Oxytetracycline, and Furazolidone	Immuno-pathological effects, Autoimmunity, Carcinogenicity
Gentamicin	Mutagenicity, Nephropathy
Chloramphenicol	Hepatotoxicity, Reproductive disorders, Bone marrow toxicity
Penicillin	Allergy

(Nisha, 2008; Demoly and Romano, 2005)

Heat stability of commonly used antimicrobial drugs

Antimicrobial drug residues show varying degrees of stability during cooking. Cooking reduces the level of risk exposed to consumers (Rose *et al.,* 1999).Factors affecting the degradation of antimicrobial drugs are; Drug formulation, pharmacodynamics, cooking temperature and time, and shape and thickness of cooked muscle/meat tissues (O'Brien *et al.,* 1981). Degradation of common antimicrobial drugs at 100˚C follows asβ-lactams = tetracyclines (most heat-labile) >lincomycin>amphenicols>sulfonamides>oxfendazole>levamisole (most heat-stable). Based on the Minimum Inhibitory Concentration after autoclaving, antimicrobials may be classified as heat labile, partially heat labile and heat stable.

Table 2 Heat stability of Antimicrobial drugs

Heat stable	**Moderately heat labile**	**Heat labile**
Sulfamethazine, Oxacillin, Oflaxacin, Norflaxacin, Gentamicin, Chloramphenicol, Aminoglycosides, Quinolones, Clindamycin, Trimethoprim, Nitrofurazone and Vancomycin	Ampicillin, Penicillin-G, Carbenicillin, Tazobactum, Rifampin and Amoxycillin	Amoxicillin + Clavunic acid, Cefixime, Tetracycline, Oxytetracycline, Doxycycline and Erythromycin

(Traub and Leonhard, 1995 and Rose *et al.*, 1996)

Influence of heat treatment on antimicrobial activity in tissues/meat

Stability of Tetracycline

Tetracyclines are a group of antimicrobial drugs frequently employed in livestock due to their broad spectrum of activity as well as their low cost, compared with other antibiotics. Currently, there are over 20 tetracyclines available; however, tetracycline, chlortetracycline, oxytetracycline, and doxycycline are mostly used in veterinary practices (Fritze*et al.*, 2007). Within the tetracycline group, doxycycline is heat stable and oxytetracycline is heat liable (Abou-Raya *et al.,* 2013). Kuhne*et al.,* (2010) studied the effect of heat treatment on bound tetracycline and chlortetracycline residues in bone meal. Bone meal containing bound tetracycline and chlortetracycline residues was heated in an autoclave at 133°C for 20, 30, and 45 min and at 100°C for 20 and 30 min and subsequently dried at 103°C for 4 hours. The study showed that the destruction of tetracycline could not be demonstrated at 133˚C. However, the compound significantly decreased by about 50%. Chlortetracycline was found to be less resistant, which brought about a reduction of 90–100% at 133˚C. Heat treatments at 100°C did not bring about any reduction, except for chlortetracycline after extraction without sedimentation. The ordinary boil cooking of meat decreased the initial concentration of tetracycline residues by 56 to 82% (Gratacos-Cubarsi*et al.,* 2007). Roasting, grilling, braising, and fryingresultedin a reduction of 35-94% tetracycline residues in beef and cow liver (Rose *et al.,* 1996).Microwave cooking for 23.9 minutes, boiling for 53.2 minutes, and roasting for 101.6 minutes could able to reduce 90% of tetracycline in leg pieces and chicken breast (Abou-Raya *et al.,* 2013). During cooking tetracyclines degrade to anhydrotetracycline and 4-epianhydrotetracycline, and toxic effects of such metabolites on the consumers are not yet studied (Kuhne*et al.,* 2001). Cooking process with sufficienttime-temperature combination significantly reduces tetracycline residues,thereby minimizing the risk to consumers.

Stability of β- lactam group of Antimicrobials

Beta-lactam antimicrobials, named after the active chemical component of the drug (the 4-member beta-lactam ring), include the 6-membered ring-structured penicillins, monobactams, and carbapenems; and the 7-membered ring-structured cephalosporins and cephamycins. This group of drugs impairs the development of bacterial cell walls by interfering with transpeptidase enzymes responsible for the formation of the cross-links between peptidoglycan strands. They are generally bactericidal toward most bacteria. Benzylpenicillin shows stability at 65˚C. The degradation of the compound increases with an increase in cooking temperature. During cooking, residues leach out into fluids, and discarding the juice can reduce exposure to benzylpenicillin residues (Rose *et al.,* 1997).Residues of penicillin-G in chicken meat extract were reduced by about 80-100% on boiling at 100˚C for 30 min and a 100% reduction was observed when increased the boiling time for 60 and 90 min.Retorting at 120-125˚C for 60-65 min caused a 100% reduction of penicillin-G residue in sausages (Moats, 1997).Madalena*et al.,* (2020) studied the impact of culinary practices-oven or microwave combined with herbs and beer on antibacterial (β-lactams, tetracyclines, sulfonamides, fluoroquinolones, macrolides, and coccidiostat) drug stability and bioaccessibility in chicken meat at two fortification levels. The study concluded that compounds were stable during cooking except for amoxicillin, chlortetracycline, and tylosin (reductions > 50%). Molecular rearrangement and dechlorination reactions are the most probable transformations derived from cooking. The addition of herbs and beer did not benefit the reduction of residues.

Stability of Sulfonamide

Sulphonamide is a broad-spectrum antibiotic, primarily bacteriostatic, and mainly used in gastrointestinal infections, leptospirosis, mycoplasmosis, and pasteurellosis.Planche*et al*., (2022) studied the fate of Sulfonamide in meat during pan cooking and observed that cooking induced significant antimicrobial losses of up to 45% for sulfamethoxazole. However, six potential degradation products of ^{14}C-sulfamethoxazole were detected in the cooked meat. This study highlighted the importance of the cooking step in chemical risk assessment procedures and its impact on the level of chemical contaminants in meat and on the formation of potentially toxic breakdown compounds.Residues of sulfadiazine, sulfamethoxazole, sulfamonomethoxine, and sulfaquinoxaline in chicken meatballs were reduced during boiling (45-61%), roasting (38-40%) and microwaving (35-41%). The reduction observed for the above cooking methods might be explained by; the transfer of veterinary drug residue from the muscle into the boiling water; and the loss of juices that came from the muscle as it was roasted (Furusawa and Hanabusa, 2002). Frying significantly reduced sulfachlorpyridazine residue by 93.25% from chicken breast meat and 87.95% from chicken liver. Trimethoprim residue was reduced to about 97.55% from chicken breast meat and 95.38% from chicken liver by the same cooking process (Murat Kanbur*et al.,* 2014).Furusawa*et al*., (2002) present the net change by cooking on the residues of four sulfonamides (SAs) drugs namely sulfadiazine (SDZ), sulfamethoxazole (SMX), sulfamonomethoxine (SMM), and sulfaquinoxzline (SQ) in chicken muscles. For this purpose, these SAs were fed to chickens at a dietary concentration of 100 mg/kg (each drug) for 7 successive days. On the 7th day of feeding, they were culled and thigh muscles were collected for the study. It was found that the net residues in the muscles cooked by boiling were reduced to 45–61% in 12 min. roasting reduced SMX, SMM, and SQ residues, except for SDZ, by 38–40% in 12 min. Microwave cooking reduced the four SAs by 35–41% in 1 min. Three heat treatment processes; boiling, deep-frying, and microwaving were consecutively applied on chicken balls pre-fortified at the raw stage with four types of sulfonamides (SAs) namely sulfadiazine (SDZ), sulfamethazine (SMZ), sulfamethoxazole (SMX) and sulfaquinoxaline (SQX). The boiling process was carried out at temperatures of 80, 90, and 100°C for 3, 6, and 9 min, and deep frying at temperatures of 170, 180, and 190°C for 3, 6, and 9 min. and microwaving at power of 100, 250, and 440 W for 20, 40, and 60 sec. respectively. After the application of the three cooking processes, SDZ was reduced up to 62%. SMZ reduced to 52%, SMX and SQX up to 62% and 55% respectively. The sequence of reduction on SAs residues for all cooking methods was deep-frying > boiling > microwave (Ismail*et al.*, 2011).

Stability of Nitrofurans

Nitrofurans are synthetic broad-spectrum antimicrobial agents. Nitrofurans are bacteriostatic but, at high doses, their action may also be bactericidal.The use of nitrofurans in food-producing animals is prohibited within the European Union (Commission Regulation 1995) because of their potentially carcinogenic and mutagenic effects on human health (Van Koten-Vermeulen*et al*. 1993). However, it is used in many countries for the prevention and treatment of various gastrointestinal infections, mastitis, and metritis, as growth promoters in livestock. Nitrofurans have short half-lives in animals due to which, they do not generally occur as residues in animal produce meant for food. However reactive metabolites are formed that can bind covalently to macromolecules, such as proteins and DNA.Therefore when animal-origin foods are consumed, the side-chains may be released from the metabolites (European Food Safety Authority, 2015).Metabolites of nitrofurans are bound to tissues which may be released by mild acid hydrolysis and used as markers for detection of residues (McCracken *et al.,* 1997). On heat treatment, Furazolidone degrades to 3-amino-2-oxazolidinone and Nitrofurazone degrades to semicarbazide(Hoogenboom*et al.,* 1991). About 67-100% nitrofurazone remains during the frying, grilling, roasting, and microwaving of pork and liver of pig. The metabolites are largely stable to traditional cooking procedures and present human health risks (Cooper and Kennedy, 2007).

Stability of Quinolones

Quinolones are broad-spectrum antibacterial with excellent tissue penetration combined with safety. They are commonly used for urinary tract, enteric, and genital tract infections.

Enrofloxacin remained stable for 3 hours when heated in water at 100˚C.The residue data from raw tissue were valid for the estimation of consumer exposure to this drug, as well as the calculations of Acceptable Daily Intakesince, the cooking process did not affect enrofloxacin residues, which remained stable during heating. However, the concentration of quinolones decreases due to the meat exudation release into the boiling water (Lolo *et al.*,2006). Sterilization of pork offal mixture (liver and kidney) at 134˚C for 20 min reduced 68% of enrofloxacin residues (Van Egmond*et al.*, 2000). Residues of oxolinic acid and flumequine are more heat stable and they did not degrade during cooking in flatfish(Botsoglou and Fletouris, 2001).The maximum losses of concentration ciprofloxacin and norfloxacin were found to be 12.71% and 12.01% when treated at 120˚C for 20 min, because of their high heat stability, their presence in food might threaten human health (Roca *et al.*, 2010).

Influence of heat treatment on antimicrobial activity in milk

Zorraquino*et al.*, (2011) studied the effect of milk processing at 60˚C for 30 min, 120˚C for 20 min, and 140˚C for 10 sec on the antimicrobial activity of macrolides (erythromycin, spiramycin, tylosin, and lincomycin). The results indicate that treatment at 120˚C for 20 min inactivated 93% erythromycin, 64% spiramycin, 51% tylosin, and 5% lincomycinwhile treatment at 140˚C for 10 sec lowered 30% erythromycin, 35% spiramycin, 12% tylosin, and 5% lincomycin respectively.Heat treatment of milk samples at 140˚C for 10 sec produced inactivation of 17% for kanamycin and 40% for neomycin, and the classic sterilization (120˚C for 20 min) showed a high heat inactivation (>95%) for gentamicin, kanamycin, neomycin, and streptomycin (Zorraquino*et al.*, 2009).Roca *et al*., (2010) studied the effect of different time-temperature combinations on the concentration of quinolones in milk by employing liquid chromatography with fluorescence detection. The result of the study showed that quinolones were highly heat resistant with maximum losses of 12.71% for ciprofloxacin and 12.01% for norfloxacin at 120˚C for 20 min. The effect of boiling on the stability of Oxytetracycline and Sulfamethazine residues in milk using the HPLC– Ultra Violet detector method revealed thatupon heat treatment, the reduction in the oxytetracycline content was 30.5% and 54.1% when boiled for 2 and 5 min respectively.On the other hand, sulfamethazine reduction was 1.7% and 9.5% at the same time-temperature combination. This could be attributed to the low heat stability of oxytetracycline and the high stability of sulfamethazine (Fathy*et al.*, 2019).

Influence of heat treatment on antimicrobial activity in egg

Fresh eggs were spiked with different drug concentrations of albendazole (ABZ) and its albendazolesulphoxide (ABZSO) and albendazolesulphone ($ABZSO_2$) metabolites; flubendazole (FLBZ) and its reduced flubendazole (R-FLBZ) and hydrolyzedflubendazole (H-FLBZ) metabolites; amoxicillin (AMX); and enrofloxacin (EFX) and its ciprofloxacin (CFX) metabolite to evaluate the stability of drug residues in cooked eggs (boiling, microwaving, and omelet making). The study revealed that ABZ and ABZSO concentrations in eggs were not affected by boiling and microwaving, while the omelet-making significantly reduced these molecules. No significant reduction of $ABZSO_2$ was observed in contrast FLBZ and its metabolites FLBZ-H and FLBZ-R residues decreased after the cooking process mentioned.The residue concentration quantified for EFX and CFX did not show significant changes after any of the cooking methods. AMX residues were unstable; with extremely significant drug reduction after all cooking processes (Canton *et al.*, 2019).The concentration of Oxytetracycline and 4-Epi-oxytetracycline residues in quail egg significantly reduced after boiling for 5 min; however, there was no effect on the concentration of sulphadimidine, amoxicillin and Diketo (Saad*et al.*, 2022). The stability of Doxycycline residues in eggs was analyzed by liquid chromatography-tandem mass spectrometry method. The result showed that Doxycycline was reduced by 53% and 50.3% after 4 min of microwaving without cover and with cover, frying reduced by 39.8% in 6 min, and boiling decreased by 29.8% after 8 min. Thus the result concluded that ordinary cooking methods do not eliminate doxycycline residues present in eggs (Gajda*et al.*, 2017).

Future Perspectives and Conclusion

Governments and related agencies have to establisha universally applicable standard for the maximum residue levels in animal-originated food. More research should be done to develop simple and economical field tests to identify drug residue in edible animal products.At the same time, there is needed to study the toxicological effects of antimicrobial metabolites in the human being.In this review, the effects of various cooking procedures on different antibacterial drug residues areoutlined. According to the results and findings of previous studies, we could conclude that cooking at different time-temperature combinations significantly lowers antimicrobial residue from livestock products.However, cooking processes did not ensure a full breakdown of antibacterial drug residues, they only reduced their concentration. Thereforemore studies are required to accurately determine consumer exposure to these antimicrobial drugs through food stuff. At the same time drug withdrawal periods should be strictly followed anduse of antibiotic drugs with shorter withdrawal period should be encouragedto reduce the occurrences of antibiotic drug residues in animal-originate foods.

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Comment [T12]: Add some references about antibiotic

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