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REVIEW ARTICLE

# Antibiotic residues in milk: Past, present, and future

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**ABSTRACT**

Now-a-days, various types of antibiotics are being used worldwide in veterinary sector indiscriminately for promotion of growth and treatment of the livestock. Significant portions of antibiotics are released through milk of dairy animals unaltered and exert serious harmful effects on human health. This review evaluates and compare researches on antibiotic residues in milk in published literatures from Pubmed, CrossRef, CAB direct, DOAJ, JournalTOCs, AGRICOLA, ScientificGate, Electronic Journals Library, CAB abstracts, Global Health Databases, Global Impact Factor, Google Scholar, Park Directory of Open Access Journals, BanglaJOL and ISC E-Journals. Antibiotics residue in milk was first detected in 60s and then with an increasing trend with highest after 2,000 (188). The highest no. of works, 49 (21.87%) were accomplished in China, followed by Spain, 30 (13.39%); Germany, 11 (4.91%); and USA, 10 (4.46%). Continent-wise highest researches are published from Europe, 105 (46.88%), followed by Asia, 77 (34.38%); South America, 18 (8.04%); North America, 16 (7.14%); and Africa, 8 (3.57%). For detection, Bovine milk sample is mostly used, 193 (86.16%), followed by ovine, 19 (8.48%); and caprine, 14 (6.25%). Acetonitrile was used in maximum cases (77) for processing the samples. Chromatographic technique was the highest, 115 (51.34%) for detection. Residue of β-lactam group have been detected mostly 133 (36.54%), followed by tetracyclines, 51 (14.01%); fluoroquinolones, 49 (13.46%); sulfonamides, 46 (12.64%); and aminoglycosides, 38 (10.44%). This review observe that antibiotics residues are more common in milk samples that are being manifested in increasing researches on antibiotic detection and measures should adopt to cease this residue.

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## Introduction

Every year, 63,151 ± 1,560 tons of antibiotics are being used in livestock worldwide [1] In animal husbandries, antibiotics are applied for both therapeutic and prophylactic purposes [2] Due to some positive impacts, multiple veterinary antibiotics (VAs) have been used worldwide recently for promoting growth and treatment of the livestock [3] The global usage of antimicrobials in animals is double compared to humans [4] Many studies have shown that significant portions (30%–70%) of antibiotics are released unaltered, i.e., with potential antimicrobial activity, into the environment [2] Upon release into the environment, most antibiotics are persistent and biologically active [5] Milk is a highly consumed food item in the world which has also a great value for human health [6] Residues of antibiotics are mainly found in milk due to their injudicious usage in treating infectious diseases of animals [7] Moreover, some antibiotics are being used as feed additives indiscriminately which is another source of antibiotic residues in milk, ultimately responsible for potential public health importance [8].

### *Residue*

European Union (EU) defines residues as "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 has been administered [9]." After being administrated to an animal body, most of the drugs are metabolized for the purpose of detoxification and excretion. In general, most of the parent product and its metabolites are excreted in urine and a

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lesser extent via feces. However, after excretion, portion of the drugs may persist in milk, eggs, and meat for a certain period of time as residues.

### *Antibiotic residue (AR)*

The administered parent antibiotics or their metabolites become deposited in animal tissues and matrix intended to be used for human consumption, where the concentration is beyond the permitted level for a certain period of time, known as antibiotics residues [10].

Among the vital causes of presence of antibiotic residues in milk, dry cow therapy and usage in mastitis treatment are of great importance [11] The developing countries are in greater risk due to residues in milk than the developed ones. Poor detection facilities as well as lack of proper monitoring system of residues in foods considering the maximum residue limits (MRLs) might be taken as vital causes for higher risk of milk derived antibiotic residues [12]

### *Maximum residue limit (MRL)*

Maximum level or concentration of a drug or chemical thought to be non-hazardous and permitted by the regulatory bodies in or on food or feed intended to be used for animal or human consumption at a specified point of time, known as MRL. The unit used for this maximum allowable concentration is milligrams per kilogram of solid products and milligrams per liter for liquids [12].

Milk and other dairy products, which contain drug residues beyond the MRL, causes serious health problems of the consumers [13] Though good quality milk and other related products are a prime need for maintaining proper public health [14], presence of antibiotic residues in those food items and subsequent consumption can cause potential health impacts, such as cancer and hypersensitivity reaction along with development of antibiotic resistance [15] The consequences of such resistance are even more threatening where antibiotics become ineffective clinically. Maintaining proper withdrawal time, established for milk, and other food products can act as a safeguard to resist from hazardous impacts of antibiotic residues.

### *Withdrawal time*

This term is often used more broadly to describe the time needed after drug administration to any food animal where below a determined MRL may be found in marketed meats, eggs, organs, or other edible products. The withdrawal time may vary largely depending on chemical and physical properties of drugs and route of administration [16].

ARs in milk have been one of the major concerns in the recent years. As control policy demands proper detection and quantification approach of ARs in milk, a good number of research works, have been published worldwide in this context to meet up the feasibilities. Previously, some microbiological tests like Delvotest® SP-NT and Copan® milk tests were used officially [17] Though these tests are cheap, rapid, and easy to perform but lack of proper selectivity and accuracy level [17] Chromatographic techniques, in the other hand, are more precise with higher specificity and accuracy, but requires proper sample preparation, sophisticated instrumentations, well trained personnel [11] As possibilities of residues in milk from multiclass type of antibiotics is increasing day by day, accurate analysis of ARs using a well-developed single technique with minimum cost is always a challenge [11] Therefore, the present study evaluate and compare the research studies to demonstrate the trends and to assess the works from past to recent decades for analysis of ARs in milk. Various techniques applied for determination of ARs in milk so far, is also a matter to be evaluated, which could ultimately develop a perception on comparative innovation of techniques over the time.

## Materials and Methods

### *Article selection*

Published literatures related with antibiotic residue detection in milk were collected from Pubmed, CrossRef, CAB direct, DOAJ, JournalTOCs, AGRICOLA, ScientificGate, Google Scholar, BanglaJOL, and E-Journals of ISI (Institute for scientific information). Original articles, published throughout the period of January 1965 to December 2017, were searched using a bibliographic database called "ISI Web of Science" [18] The published literatures were searched using the following keywords: (detection and quantification) or only "detection" or only "quantification" (antibiotic/antimicrobial) and (cow/cattle/bovine, sheep/ovine, goat/caprine, mare, and animal). To find out the maximum articles of similar concept, avoiding the risk of missing due to plural word or multiple words, a sign "*" was used in accordance with the published guidelines [19] The searched items or publications were thoroughly checked and downloaded for detail and critical reviewing later. Only the original research data containing publications, written in English language, were included for our reviewing. The abstracts of the research articles, which contained data regarding antibiotic residues in milk, were selected for reviewing of the whole content. The research works were thoroughly revised and sorted out to meet up the field of interest. A total of 224 literatures have been finally selected for analysis. The full articles were managed in PDF format using Mendeley—a reference management software.

### *Data extraction and analysis*

Various data were collected from the literatures and organized in Microsoft excel worksheet-2013 on the basis of splitting those into six decades (i.e., 1960–1969, 1970–1979, 1980–1989, 1990–1999, 2000–2009, and 2010–2017) under various parameters. The parameters were: (1) country-wise or continent-wise distribution of accomplished researches, (2) detected antibiotics of specific type which were further furnished into the following classes: Beta-lactams (penicillins and cephalosporins), tetracyclines, sulfonamides, fluoroquinolones, aminoglycosides, and miscellaneous, (3) types of animals for samples (bovine, ovine, caprine, and mare), (4) type of sample (i.e., solely milk or milk along with other body matrices and tissues), (5) detection categories (i.e., simultaneous detection of several antibiotics within single class, simultaneous detection of several antibiotics within a specific class and multiclass at a time, simultaneous detection but antibiotics from multiple classes and single in each class, and single detection), (6) detection technique (chromatographic, immunological, microbiological, and miscellaneous), (7) chemicals used in chromatographic technique, and (8) chemicals used for sample extraction and mobile phase and. Data from the Excel sheet were furnished in tabular format. The data were statistically analyzed and presented in both Tabular and Bar diagram format.

## Results and discussion

### *Publications*

In the preliminary step of selection, we found a total of 1,371 articles which could meet up the area of interest. A total of 519 articles were found to contain original research data and English language was used to write up for 497. Out of 497, we did not consider 273 articles for our study due to lack of detailed information (both quantitative and qualitative) on antibiotic residues detection in milk. Therefore, the remaining 224 were taken as our study materials of interest to be reviewed. The results are shown in Figure 1.

### *Antibiotic residue in milk: timeline analysis*

Antibiotic residue in milk was first detected in 60s [20] followed by a swelling trend with a stiff increase in detection after 2000 (188) [21–208] The related published literatures from 2000 to 2009 is 81 (36.16%) in number [128–208], which is more than double in comparison with previous four decades collectively, where number was 36 (16.07%) in total [19,20,209–242] The ongoing decade merely comprises 47.77% research studies (107 in number) among the last 57 years [21–127], which clearly indicates the increasing trends with concern about antibiotic residue in milk and detection accordingly. The results are shown in Figure 2.

### *Country-wise analysis*

Among the countries of the world, the highest no. of works, 49 (21.88%) were accomplished in China, followed by Spain, 30 (13.39%); Germany, 11 (4.91%); USA, 10 (4.46%); and Italy, 09 (4.01%) (Table 1). It is observed that more research studies on detection of antibiotic residue were performed at the developed countries rather than developing countries.

### *Continent-wise analysis*

Most of the research studies in related field have been performed in Europe, 105 (46.88%), followed by Asia, 77 (34.38%); South America, 18 (8.04%); North America, 16 (7.14%); and Africa, 8 (3.57%) so far (Table 1). Among the Asian countries, China is at the top in ranking, 63.64%; so

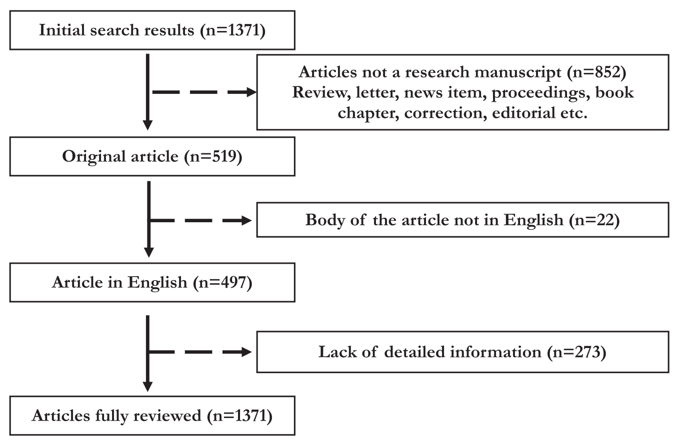


**Figure 1.** Selection and exclusion criteria for scientific publications on antibiotic residues in milk.

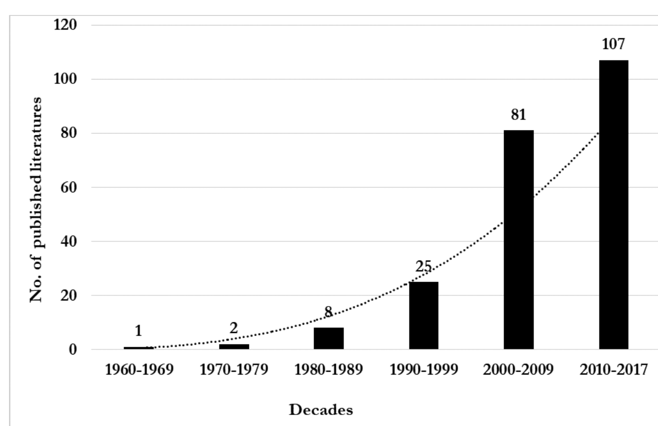


**Figure 2.** Timeline analysis of published literatures on antibiotic residue detection in milk.

**Table 1.** Continent and country-wise distribution of researches on detection of antibiotic residue in milk.

| | Continents | | | | |
|---|---|---|---|---|---|
| | Asia | Europe | Africa | South America | North America |
| No. of researches (%) | 77 (34.38%) | 105 (46.88%) | 8 (3.57%) | 18 (8.04%) | 16 (7.14%) |
| References | [21–24,28,30–32, 36, 37,39,42, 43, 45,49,53,55–62, 64,65,67,68,76, 78–81,83,86,89, 90,95,97–99,104, 106,108,109,111, 115,116, 124,127, 140,141, 147–149, 160, 162,164,172, 174, 176–178,182, 199, 212, 225–235] | [25–27,35,40,42,47, 48,50,51,54, 63, 66,69,72,73,75, 82,85,87,88,92, 96,100–103,105,107, 110,1113,114,118,119, 121–123,125,128–132,134–136, 138,139,142–145,146,150, 151,153–159,161,163,165–167, 169,173,175,180,183, 184,186–189,192,195–198, 200–211,213,214,216,217–224] | [19,29,44,70,181, 236,238,242] | [38,46,62,71,74, 77,93,94,112,120, 137,152,170,171,193, 215,237,240] | [20,34,52,84,91, 117,126,132,179,181, 185,190,191,194, 239,241] |
| Top ranked countries, No. of researches (%) | China, 49 (63.64%) | Spain, 30 (28.57%) | Nigeria, Tanzania, Bosnia, 3 (37.5%) | Brazil, 8 (44.44%) | USA, 10 (62.5%) |
| References | [23,24,28,31–33, 36,37,39,42,42, 45,49,53,55–60, 64,65,67,68,76, 78,80,81,83,89, 97,104,106,108,109, 111,116,127,140,141, 147,148,162,164,172, 178,182,218,235] | [41,54,73,82,85, 88,92,100,101,105, 121,128,131,142,143, 146,150,153,154,156–159, 161,169,173,175,186–188] | [29,44,70] | [38,62,71,77,93, 137,152,171] | [34,52,84,91,117,133, 179,185,190] |

are Spain, 28.57%; Nigeria, Tanzania, and Bosnia, 37.5%; Brazil, 44.44%; and USA, 62.5% for Europe, Africa, South America, and North America continents, respectively (Table 1).

### *Types of samples used for detection*

The highest no. of research studies have been conducted using bovine milk, 193 (86.16%), followed by ovine, 19 (8.48%); caprine, 14 (6.25%); and mare, 1 (0.45%). The production rate, availability of animal and milk, demand, and amount of antibiotic usage might have been considered as important phenomena for selecting bovine milk in most of the cases over others. The majority of the articles, 184 (82.14%) denotes the works on detection of antibiotic residues using milk solely, though a considerable portion of works, 40 (17.86 %) have been accomplished for screening the residues in body tissues and other body matrices along with milk. Results and references are shown in Table 2.

Milk has been found to be categorized as raw or fresh and spiked, raw and non-spiked, pasteurized, unpasteurized, whole milk, skimmed mild, or semi-skimmed milk and various products of milk for detecting the antibiotic residues and innovating the detecting techniques.

### *Types of antibiotics detected*

A total of 364 no. of works with different groups of antibiotics has been performed among the studied literatures. A variable no. of published works is found for different groups of antibiotics, so far. The highest number of works, 133 (36.54%) is found for β-lactam group, which comprise only penicillins, 75 (56.39%) and cephalosporins, 58 (43.61%) and the minimum, 38 (10.44%) in case of aminoglycosides (Table 3). The results are shown in Table 3. The data indicates that the usage of β-lactam antibiotics in milking animal is increasing day by day and thereby raising the concern in this regard. A variable number of works were found differentiating the classes of antibiotics during their detection by applying various methods, especially in chromatographic technique to evaluate and establish their respective detection accuracy.

In descending order, 72 (32.14%) research studies showed the simultaneous detection of a number of antibiotics within a specific class; 71 (31.69%) revealed the technique on detection of a single type of antibiotic at a time, 64 (28.57%) were found to have detected multiclass and simultaneous detection of a number in each class, and the rest of the papers, 16 (7.14%) were on detection of multiclass but single in each class (Table 4).

**Table 2.** Types of samples and animals used for detection of antibiotic residues in milk.

| | Animals for samples | | | |
|---|---|---|---|---|
| | **Bovine (*n* = 193)** | **Ovine (*n* = 19)** | **Caprine (*n* = 14)** | **Mare (*n* = 1)** |
| References | [19–23,25,26,28–30, 32–42,44–47,49–61, 64–73,75–81,83–87, 89–113,115–122, 124–127,130,132–137, 139–145,147,148, 152–160,162–173,175–186, 190–192,194–217, 219–227,229–242] | [48,63,82,88,114,123,132,138,146, 149–151,161,174,187,188,193,228] | [24,27,31,43,62, 74,88,114,123,128, 131,146,189,218] | [123] |

| | Type of sample | |
|---|---|---|
| | Solely milk (*n* = 184) | Milk with other body matrices and tissues (*n* = 40) |
| References | [20–29,31–37,39,41–46,49–54,56,57,60–63,65–70,73–77, 81–97,100–103,105,107–115,117,119–124,126,128–148, 150–162,164,166–171,173–175,177, 178, 182,184–189,191, 193–197,199–204,206–220,224–226,228–235,237,239,240–242] | [19,30,38,40,47,48,55,58,59,64,71,72, 78–80,98,99,104,106,116,118,125,127,149,163,165,172,176, 179–181,183,190,192,198,205,221,227,236,238] |

### *Techniques for detection of residues*

Diversified techniques have been applied for detection of ARs in milk, which are classified broadly as chromatographic, immunological, microbiological, and miscellaneous. The highest no. 115, (51.34%) is based on chromatography, followed by immunological, 58 (25.89%), Microbiological, 38 (16.96%), and miscellaneous, 18 (8.04%) (Table 5). The results are shown in Figure 3. The chromatographic technique is increasingly being used over others, especially the rate is much higher in recent times, due to higher sensitivity and specificity, higher quantification capability. On the other hand, various immunological and microbiological techniques can be applied at a cheaper rate, rapidly with lesser efficiency, though the quantification and detection is not satisfactory.

### *Chemicals used in chromatography*

Acetonitrile has been used in most of the cases, 77 (66.95%) for processing of milk during extraction, followed by methanol, 36 (31.30%); trichloroacetic acid, 31 (26.96%); n-hexane, 22 (19.13%); disodiumethylenediaminetetraacetate, 21 (18.26%); formic acid, 18 (15.65%); oxalic acid, 14 (12.17%); ethanol, 9 (7.83%); and sodium hydroxide, 7 (6.09%) (Table 6). The results are shown in Figure 4. In most of the cases two or more than two chemicals have been used for extraction. Variable concentrations of the chemicals were used in different research studies. The chemicals have been selected based on their chemical nature for easy extraction, price, availability, specificity, type of column used, and nature of antibiotics being extracted out.

Waters BEH C18 (50 × 2.1 mm, 2.1 μm), Waters BEH C18 (100 × 2.1 mm, 2.1 μm), Phenomenex AQUA C18 (150 × 2.1mm, 3 μm), Waters HSS T3 C18 (100 × 2.1 mm, 1.8 μm), Waters Symmetry C18 (75 × 4.6mm; 3.5μm), Waters Atlantis T3 C18 (100 × 2.1 mm, 3 μm), Thermo Hypersil Gold (100 × 2.1 mm, 2.6 μm), Agilent Zorbax SB-C18 (100 × 2.1 mm, 3.5 μm), Waters YMC-AQ (100 × 2 mm, 3 μm, 120Å), Agilent Zorbax Eclipse XDB-C8 (150 × 4.6 mm, 5 μm) columns have been found to be used frequently in chromatographic separation, especially in the recent years.

In mobile phase, Acetonitrile and formic acid combination for chromatographic separation has been used in most of the cases. Acetonitrile still belongs to the top in ranking, 76 (66.09%), followed by formic acid, 54 (46.96%); methanol, 37 (32.17%); oxalic acid, 24 (20.87%); ammonium acetate, 21 (18.26%); acetic acid, 14 (12.17%); heptafluorobutyric acid, 11 (9.56%); and ammonium formate, 8 (6.95%) (Table 7). The results are shown in Figure 5.

### *Main causes of presence of antibiotic residues in milk*

1. Therapeutical uses of antibiotics: Vital cause of presence of ARs in milk is the indiscriminate usage of antibiotics in therapy of infectious diseases, such as clinical mastitis and viral diseases [10].
2. Antibiotics as prophylactics: Sometimes, antibiotics are used in therapy of dry cow [10,243] and management of post-surgical risk, which are also responsible for AR in milk [10].
3. Antibiotics in miscellaneous purposes: There may have direct or indirect pathways of contaminating milk by ARs, when used during processing and preservation of milk and related dairy products [10].
4. If the supplied instructions in the label are not followed accordingly, residues of antibiotics may be found in milk. When an antibiotic is approved only

**Table 3.** Number (%) of antibiotics under various groups or classes detected in milk over the decades.

| | | | Name of Groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | β-lactams | | Tetracyclines | Fluoroquinolones | Sulfonamides | Aminoglycosides | Miscellaneous | Total |
| | | | Penicillins | Cephalosporins | | | | | | |
| No. of works | | | 75 | 58 | 51 | 49 | 46 | 38 | 47 | 364 |
| Percentage (%) | | | 20.60 | 15.93 | 14.01 | 13.46 | 12.64 | 10.44 | 12.91 | 100 |
| Recent two decades | 2000 to 2009 | Nos. | 27 | 24 | 14 | 18 | 27 | 18 | 19 | 147 |
| | | % | 18.37 | 16.33 | 9.52 | 12.24 | 18.37 | 12.24 | 12.93 | 100 |
| | 2010 to 2017 | Nos. | 36 | 28 | 31 | 29 | 16 | 15 | 16 | 171 |
| | | % | 21.05 | 16.37 | 18.13 | 16.96 | 9.36 | 8.77 | 9.36 | 100 |
| Total in two decades | 2000 to 2017 | Nos. | 63 | 52 | 45 | 47 | 43 | 33 | 35 | 318 |
| | | % | 19.81 | 16.35 | 14.15 | 14.78 | 13.52 | 10.38 | 11.01 | 100 |
| References | | | [21,23,26–30, 35,36,39,41, 42,45, 51,52, 60,65,70,73, 74,80, 82,86, 88, 89,98,99, 99,104,105,107, 110,111, 115,117, 120,123–125,129, 131,135, 138,132, 143,150,152,156, 167,180, 184,187, 188,191,193–196, 199–201, 202,203, 214,220,221,223, 224,226,227,229, 230,233,234,239,242] | [32,34,36,39,50, 60,65,66,68,73,74,76,80,82,83,84,86,88,89,93,96, 98,104,105,113, 115,117,118,123,129,131,133,134,138,140,148,150,152,156,167, 171,174,180,184,185,188,190,193,194,196,201,202,207,218,226, 229,230,234] | [25,26,28,30,32, 36,46,49,51, 57,62,63,66, 71,73–75,77, 86,101,104, 108–110,112,115, 117,120,128,129, 132,139,144, 150–152,160,161, 166,188,201, 206,208,215–217, 222,223,225, 227,232] | [25,28, 30–32, 36,43,49, 51,53–56,67, 71,78,87 91–95, 100,104,105,120, 121,128–130,132, 135,139,141,146,147, 150,153,154,156, 157,162,182,186, 189,200,201, 212,219] | [21,24,26,27,32, 36,49,51,53, 56, 66,71,72,85,90, 93,97,103,106,110, 115,120,121,126, 128–130,132,135, 136,139,145,150, 153,156,158,159, 161,163,164,169, 201,203,210, 232,237] | [27,40,48,51, 61,72,102, 108–110,114, 115,127,128, 130,135,137,144, 150,152,161,165, 166,173,177,179, 183,192,197,201, 203,204,209,213, 223,231,241] | [19,24,37,38, 47,49,58,59, 64,69,72,79, 81,94,104, 107,108,109, 115,116,118, 120–122, 128–130,132, 135,144,153, 161,170,172, 175,176,181, 191,198,201, 203,205,211, 223,228,235, 238] | |

**Table 4.** References for detection categories of antibiotic residues in milk.

| | Detection categories | | | |
|---|---|---|---|---|
| | Simultaneous within single class (*n* = 72) | Simultaneous and multiclass (*n* = 64) | Multiclass and single (*n* = 16) | Single (*n* = 71) |
| References | [31,37,38,40,41, 46,48,60,62,67, 70,75,76,77,78, 83,85,92,96,97, 98,100,103,111,112, 118,119,123,125,131, 138,143,145,146,148, 154,163,167,169,173, 175,176,180,182,183, 184,186,187,189, 192–196,198,202,204,206, 209,213,215–217,219, 224–227,229,231,232,234,242] | [21,22,24–27,36,39, 42,44,49,51,53, 56,63,65,66,69, 72–74,79,80,82,86, 87–90,93,94,101,104, 105,107–109,115,118,126, 128,129,130,132, 134–136,139,141,147,149, 150,152,153,155–156,157, 159,161,191,201,203,223] | [28,30,32,47,110, 117,120,121,144, 188,201,230,235,237, 238,20] | [19,23,29,33,34, 35,43,45,50,52, 54,55,57–59,61,64, 68,81,84,91,95, 99,102,106,113,114, 116,122,124,130,133, 137,140,142,151,158, 160 162,165,170–172,174, 177–179,181,185,190,197, 199,200,205,207,208, 210–212,214,218,220–222,228, 233,234,235,238,240,241] |

**Table 5.** References for detection techniques of antibiotic residues in milk.

| Detection techniques | References |
|---|---|
| Chromatographic (*n* = 115) | [19,21,24,25,29,30,33,34,36–41,45,47–50,50,53,55,56,58–60,62,68,69,71–73,75–77,79, 82–87,90,91,93,94,98,100,103–107,111,116,119,122,124–123,129,133,137,141,143,145–147,149, 151–154,157,160,164–166,171,172,175,176,179,181–184,186,189–191,195,196,207,199,205,208,211–215, 218–222,225,227–229,232,235,238,240] |
| Immunological (*n* = 58) | [26,27,29,31,32,34,35,37,39,43–45,58,59,64,65,74,77,78,80,81,88,89, 96,102,106, 113–115,107,118,121,127,130,135,136,139,140,144,148,152,156,159,162,163, 177,180,192,197,200,202,204,207, 209, 210,213, 219,239] |
| Microbiological (*n* = 38) | [22,30,42,46,51,63,70,101,110,112,128,131,138,142,150,161,167,170,174,187,188,193–195,201,202,206,208, 216–218,223,224,226,230,233,234, 241] |
| Miscellaneous (*n* = 18) | [23,61,66,67,92,95,97,99,109,120,123,158,178,193,178,231,242, 20] |

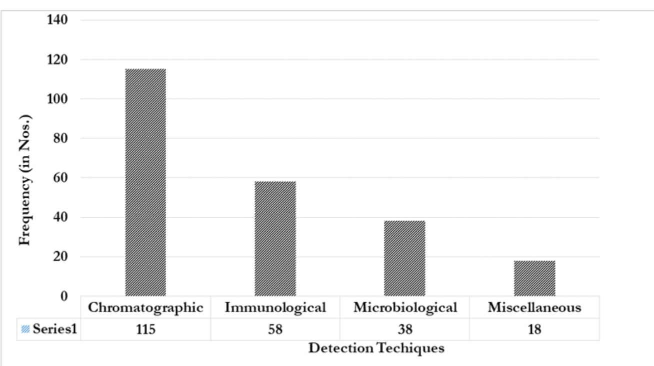


**Figure 3.** Frequency of using various detection techniques for screening of antibiotic residues in milk.

for humans become used injudiciously in animals, or usage in different species where it is not approved, or during a condition where it is not approved, or usage beyond the appropriate concentration, may be referred as extra-label use [244].

5. Lack of maintenance of proper withdrawal time: Without proper maintenance of withdrawal time of antibiotics in milking animal, AR appears in milk at higher concentration [12].
6. Limited detection facilities of ARs and improper monitoring system of residues due to the crisis of strong regulatory organization, may be considered as important phenomena in this issue for developing countries [12].
7. Normal metabolic process of antibiotics is hampered in diseased animals, which can cause antibiotics to remain stored for a longer period of time and higher amount in tissues, ultimately impose a higher risk of residues [16].
8. Lack of awareness of farmers about residual effects of AR from milk in human health [16]
9. Improper education of farmers [16].
10. Inadequate literatures supplied by manufacturers [10].
11. Improper cleaning of antibiotics contaminated equipment after using in mixing or administering process.
12. Improper disposal of empty containers of antibiotics in the farm premises which can contaminate feeds of animals. Animals may lick those or even get exposed through contaminated feeds accidentally [245].

**Table 6.** References for various chemicals used in processing of samples during chromatography.

| Chemicals used in extraction process | References |
|---|---|
| Acetonitrile (*n* = 77) | [19,29,30,33,34,36–41,49,52,53,58–60,62,67,68,71–73,77, 82–87,91,95,98,107,116,122,126,132,145,151–153,164–166,175,181–184,186, 189–191,195,196,198,199,205,208,211–215,218–222,225,227–229,232,235,238,240] |
| Methanol (*n* = 36) | [53,58–60,62,67,68,71–73,75,82–87,97,100,107,116,145,148,166,181–184,190,191,208,211–215,238] |
| Trichloroacetic acid (*n* = 31) | [25,29,33,34,40,48,50,52,53,55,56,58,77,86, 87,93,98,100,112,129,132,146,147, 151–153,157,165,166,178,209] |
| n-hexane (*n* = 22) | [24,33,36–41,49,52,53,67,90,94,98,100,105,143,145,181,189,191] |
| Disodium ethylenediaminetetraacetate (*n* = 21) | [49,52,53,67,90,94,81,100,103,111,175,179,182,195,196,199,205,212,214,232,238] |
| Formic acid (*n* = 18) | [30,33,36,39–41,50,55,68,71,83,100,122,124,149,153,166,176] |
| Oxalic acid (*n* = 14) | [37,53,58,62,67,75,82,87,93,100,104,105,172,199] |
| Ethanol (*n* = 9) | [111,175,179,182,199,205,203,213,214] |
| sodium hydroxide (*n* = 7) | [73,165,175,195,199,232,238] |

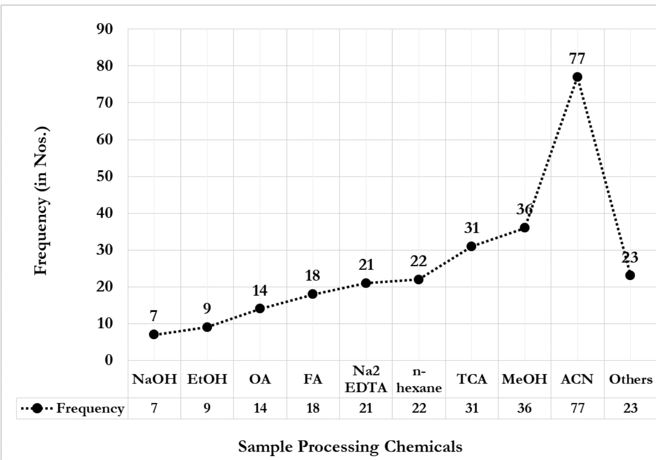


**Figure 4.** Frequency of using various chemicals during processing of milk sample prior to chromatography. *Sodium hydroxide (NaOH), Ethanol (EtOH), Oxalic acid (OA), Formic acid (FA), Disodium ethylenediaminetetraacetate (Na2EDTA), Trichloroacetic acid (TCA), Methanol (MeOH), Acetonitrile (ACN).

13. Insufficient identification of treated cows [245].
14. Miscellaneous factors those influence the presence of AR in milk [246]:
    a) Type and concentration of antibiotics
    b) Excipients used during preparation of medicine
    c) Frequency of milking and quantity of milk collection
    d) Absorbance of udder tissues
    e) Milk yield (AR in milk is inversely related with milk yield) [243]
    f) Individuals factors

### *Potential effects of ARs on public health and in dairy industry*

1. **Antibiotic resistance:** Presence of low level of antibiotic residues in milk and other dairy products causes microorganisms to be resistant against antibiotics. The resistant microbs may be transmitted among the individuals via direct contact or indirectly by exchange of resistant genes in the environment [16].
2. **Allergic reactions:** Residues of various antibiotics are associated with multiple types of allergic reactions, including serum sickness and anaphylaxis, especially in case of penicillins [16]
3. **Carcinogenicity:** Residues of antibiotics possess potential carcinogenic impacts by interacting with cellular elements, such as DNA and RNA [16]
4. **Mutagenicity:** Mutagenic effect is another dangerous impact of ARs, which can cause mutation of DNA molecule or damage of chromosomes [66] Infertility of human being may results from this mutation [16]
5. **Teratogenicity:** Various congenital anomalies may be seen in new born child due to long term exposure of ARs during gestation period [16].
6. **Disturbances in the normal intestinal environment:** Normal habitant of the intestine coexists with others and colonizes to prevent the pathogenic microbs from producing diseases. ARs in milk resulting from usage of broad-spectrum antibiotics may kill a wide range of microflora in the intestine including the non-pathogenic organisms, which can make the disease causing microorganisms more prominent and disrupt the normal intestinal environment [16]
7. **Effects in dairy industry:** Existence of ARs in milk, even in very low concentration is of great concern in dairy industries. The residues of antibiotics can

**Table 7.** References for chemicals used in mobile phase during chromatography.

| Chemicals used in mobile phase | References |
|---|---|
| Acetonitrile ($n$ = 76) | [29,30,33,34,36,40,41,48,49,52,54,59,60,62–68,71,72,75,76,79, 82–87,93,95,98,100,107,116,119,122,126,129,133,137,145–147,151–153,154,165,166,175,179, 181–183,198,199,205,208,211–215,218–222,221,227–229,240] |
| Formic acid ($n$ = 54) | [30,33,34,40,41,36,38,48,50,53,60,68,71,76,79, 82–87,100,103,105,107,111,116,119,122,125,126,129,132,133,143,147,149,152,153,154,157,166,176,198,199,205, 218–222,228,229,240] |
| Methanol ($n$ = 37) | [47,53,58–60,62,67,68,72,73,75,83,97,100,103,107,111,116,124,141,143,145,147,149,152,166,172, 181–184,190,191,208,211,213] |
| Oxalic acid ($n$ = 24) | [37,47,53,58–60,72,73,75,82,87,93,97,100,104,105,111,116,145,149,152,172,181,199] |
| Ammonium acetate ($n$ = 21) | [47,59,111,119,122,126,129,141,146,157,181,198,205,208,212,214,219,222,227–229] |
| Acetic acid ($n$ = 14) | [38,93,84,95,98,100,103,107,116,122,145,164,172,179] |
| Heptafluorobutyric acid ($n$ = 11) | [96,98,133,179,196,205,214,219,220,228,235] |
| Ammonium formate ($n$ = 8) | [50,133,172,179,184,196,199, 208] |

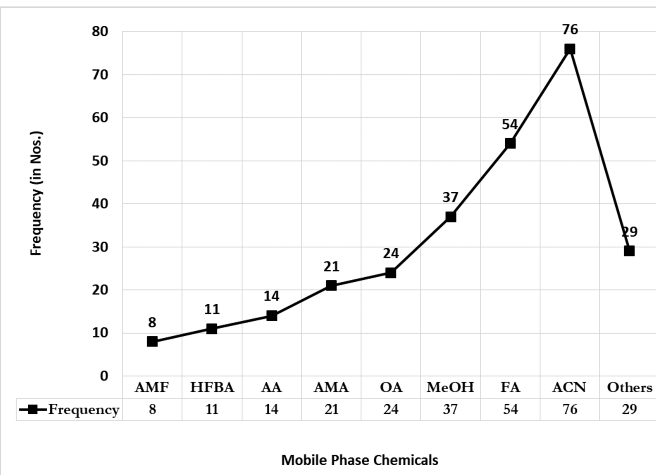


**Figure 5.** Frequency of using various chemicals in mobile phase during chromatography. *Ammonium formate (AMF), Heptafluorobutyric acid (HFBA), Acetic acid (AA), Ammonium acetate (AMA), Oxalic acid (OA), Methanol (MeOH), Formic acid (FA), Acetonitrile (ACN).

interfere with the fermentation process during production of cheese and yogurt by inhibiting the starter cultures [16].

### *Control and preventive measures to avoid ARs in milk*

1) There are two basic approaches to control ARs in milk: (a) Development of highly sensitive detection tools to avoid the false negative results; (b) Usage of appropriate methods for confirmation and quantification of ARs, where possibility of false positive outcome will be minimum [247]Simple, rapid, sensitive, specific, and economic procedures should be developed to analyze ARs in milk, followed by discarding if exceeds the MRL [16]
The MRLs in milk for some antibiotics, established by European Commission (mentioned in council regulation 2377/90/EC) is given below [248]:

| Antibiotics | MRLs in milk (µg/kg) | Antibiotics | MRLs in milk (µg/kg) |
|---|---|---|---|
| Benzyl penicillin | 4 | Gentamicin | 200 |
| Ampicillin | 4 | Neomycin | 1500 |
| Amoxicillin | 4 | Spiramycin | 200 |
| Tetracycline | 100 | Tylocin | 100 |
| Oxytetracycline | 100 | Erythromycin | 40 |
| Chlortetracycline | 100 | Colistin | 50 |
| Streptomycin | 200 | Ceftiofur | 100 |
| Dihydrostreptomycin | 200 | | |

2) The level or concentration of ARs in milk should be under regular basis monitoring and surveillance policies nationwide [10].
3) Following measures can be taken to inactivate some of the antibiotics: (a) Penicillin becomes inactivates following refrigeration. (b) Pasteurization can be used as an important measure to make most of the antibiotics inactive. (c) Some of the antibiotics loss their activity if treated with UV radiation, activated charcoal or resin etc. [10].
4) Development of public awareness through arrangement of some effective activities in this field, facilitated by the expert personnel or organizations [10]
5) Indiscriminate uses of VAs should be strictly prohibited [10].

6) Herbal sources of medicines may be taken in consideration as an alternative option for treating diseases [10]
7) Following guidelines for an effective drug use program:

    a) Paying attention to proper withdrawal times of antibiotics for milking cows [10]
    b) Label instructions should be read prior to purchasing of antibiotics to understand the consequences of usage [16]
    c) Drugs used for lactating and non-lactating animals should not be intermixed, rather storing those in separate places [16].
    d) Maintaining the good hygienic management practices during antibiotic administration [16].
    e) Proper biosecurity should be maintained in dairy farms to avoid infections. Highest priority should be given in maintaining better health quality of dairy animals, where usage of antibiotics can be avoided in large extent [16].
    f) Marking of antibiotics treated cows for easy identification, which will help the milkers to recognize them and withheld milk from marketing up to appropriate withdrawal time [16]
    g) Data regarding treatment of milking cows should be preserved cautiously in written form, where date and cause of treatment, name and dosage of drugs used, withdrawal time must be included [16]
    h) Antibiotics treated cows should be separated from the rest ones and milking lastly to minimize the risk of ARs contamination [16]
    i) Milk should be withdrawn and discarded from all of the quarters following intra-mammary infusion of antibiotics, as infused drug can be disseminated through circulation easily [16].
    j) The dairy producers should be made competent about maintaining proper quality of milk as well as its assurance [16]

## Conclusion

Presently, existence of ARs in milk is one of the burning issues, having great public health interest in many perspectives. According to the research studies, the causal factors of ARs in milk are not very few. A number of causes are also responsible for presence of antibiotic residues in milk. Detection and quantification of residues precisely in cost effective way within the shortest possible time is always a challenge. Few techniques haven been developed recently to detect residues and research studies are ongoing in this field for reaching the feasibilities. From the analysis of literatures in this review, chromatographic technique has been found to be the most sensitive, specific, reliable, and feasible for this modern era. Hence, various modifications in chromatographic methods are still being applied and need to perform comprehensive research works in future to maximize the feasibilities. The rising trends of work in this regard surely denote the alarmingly increasing usage of antibiotic in livestock and threat of residues as well and increasing concern accordingly. Therefore, the appropriate measures should be implemented to cease the ARs in milk.

## Conflict of interests

There is no conflict of interest as declared by the authors.

## Authors' contribution

SS was involved in designing the study, interpretation of data, and drafting the write up of article. JF contributed in manuscript preparation. MHS took part in preparing and critical checking of this manuscript.

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