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A global scenario with emphasis on the Indian perspective

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Emergence of antibiotic resistance due to the excessive use of antibiotics in medicines and feed additives: A global scenario with emphasis on the Indian perspective

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ABSTRACT

Antibiotics were discovered for medicinal applications, notably in the last century and since then, they have been prevalently employed for prophylactic purposes in various sectors in the last few decades. Due to the non-judicial usage of antibiotics in sectors like agriculture, aquaculture, and animal husbandry, and as therapeutic substances, antibiotics have started to become a nuisance for the environment and human beings. Furthermore, the accumulation of antibiotics in the biosphere has led to the development of antibiotic resistance in microorganisms making it difficult to treat a growing number of infections. Hereafter to understand the holistic picture of the impacts associated with antibiotics on the environment, the evolution of individual antibiotic pathways for therapeutic and non-therapeutic purposes needs to be studied along with their effect on the environment. Most of the recent reviews on antibiotics either concentrate on a particular source, pathway or environmental impact; however, the present state-of-the-art review attempts to summarize and update the possible sources of antibiotics, usage, their impact on humans, and environmental health on a global scale with a special emphasis on India. Also, there is a critical discussion about the various methods employed for the removal of antibiotics from an array of sources, on both water and soil matrix. The review finally emphasize that the implication of stringent regulation and selection of appropriate technology are required to alleviate antibiotics menace from the environment.

1. Introduction

Until the early 20th century, infectious diseases like the plague, cholera, pneumonia, tuberculosis, diarrhoea, gonorrhoea, syphilis, influenza, etc., were the major health concern, which caused millions of deaths around the globe [1,2]. However, with the advent of antibiotics in the second half of the 20th century, chronic degenerative diseases began to dominate. In the early 1920s, the discovery of penicillium paved the way for the golden age of antibiotics and significantly impacted the currently emerging pharmaceutical industry [3]. Furthermore, antibiotics also found application in veterinary uses. The unforeseen growth-promoting effects of antibiotics were found in the 1940s; since then, antibiotics have been utilized as supplements in animal feed [4,5]. However, the first non-prescribed veterinary use was approved in 1951 by the United States Food and Drug Administration, which showed improvement in weight in sub-therapeutic dosages, and later it was approved for practice [6–8]. These antibiotics are

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designed to initiate a biological influence through antimicrobial activity; however, they might have an adverse effect on soil, water, and biosphere, if disposed of unscientifically. As several antibiotics have been discovered and developed since the 1900s, all of these antibiotics have specific reaction mechanisms in different soil or water matrices and as a result it's a tedious task to quantify the risk associated with their release into the environment.

For decades, developing countries like India, with their large population, have been a hub of infectious diseases like cholera, tuberculosis, malaria, hepatitis A, filariasis, visceral leishmaniasis, enteric fever, leprosy, HIV, etc [9]. These diseases resulted in unaccounted deaths, but the discovery of antibiotics changed the face of human civilization. The impact of antibiotic discovery can be seen while studying the economics of five developing countries, often collectively termed as BRICS (Brazil, Russia, India, China and South Africa). In this group of nations, the intake of antibiotics rose significantly between 2000 and 2010 by 76 % and especially in India, the consumption of antibiotics for the year 2013 was 12.9×10^{-9} units (10.6 units per person) [10]. Additionally, animal-related antibiotic consumption in India is projected to see an increase of 82 % by 2030 as compared to 2013 represented in (Fig. S2) [11]. Moreover, for better yield, the practice of using antibiotics in aqua-farming and agro-farming has increased considerably, as farmers spray their crops with antibiotics mixed in fertilizers and pesticides. Due to this extensive application, antibiotics accumulate in the soil and water sources, and as a result, the persistence of these compounds in the environment leads to the emergence of antibiotic resistance in microorganisms [12]. As said by surveys, antibiotic medications in capsule formulation indicate controlled dispersion and decreased functional inactivation, that lowers bacterial antibiotic resistance [13].

The consumption of antibiotics by livestock and poultry has significantly increased compared to human antibiotic consumption for medicinal purposes. Indirect antibiotic consumption via food products like meat, and milk, have increased rather than direct consumption. Therefore, a strategy for curtailing antibiotic misuse should be established and implemented to achieve an acceptable level of antibiotic usage in developing nations [14]. Furthermore, excessive or gratuitous use of antibiotics has become a significant concern leading to problems like antimicrobial resistance, allergic reactions, development of toxicity, and neurological and psychiatric issues in the case of some antibiotics like fluoroquinolones and sulfonamides [15,16]. Additionally, literature also suggests that the unrestricted use of antibiotics as feed has harmful impacts on animal health, which consequently influences human health. If this non-regulated prophylactic use of antibiotics continues to increase, it will eventually lead to a decline in the beneficial medicinal effects of antibiotics. Every antibiotic drug does, in actuality, inevitably end up in the environment, and reports demonstrate that about 95 % of the antibiotics are expelled unmodified [17]. Even while antibiotics are detectable in secondary treatment wastewater in minimal quantities, it can however cause the emergence of infectious agents which can resist certain microbes. Moreover, as the discharged antibiotics are either non or partially degraded naturally, it leads to environmental pollution and hence, antibiotic removal technologies need to be developed and implemented as a solution to counter the threat posed by antibiotic accumulation in the ecosystem [18].

The available literature on antibiotic resistance deals with the occurrences of antibiotics, primarily addressing the prophylactic use of antibiotics and their indirect consumption by humans. Furthermore, very limited literature addresses the gap between the proposed solutions, like behavioural changes and how to implement those solutions through policy changes. In this reverence, the present state-of-the-art review deals with the identification of factors like gratuitous and unprescribed antibiotic usage, which essentially also contribute to the presence of antibiotics in the ecosystem and highlights the fate of antibiotics used in agriculture, aquaculture, and poultry in the last few decades. The article also presents an extensive understanding of the adverse impacts of antibiotics on the environment. It acknowledges the use of antibiotics in various sectors including agriculture, aquaculture, animal husbandry, and medicinal uses and their possible sources along with their remediations and it focuses at the long-term effects of such use on both human health and the environment. Moreover, the study concentrates on the updated antibiotic usage scenario in India, recognizing the unique challenges and factors that contribute to the antibiotic-related issues in the country. This regional focus provides insights that may not be covered in reviews that have a broader scope or focus on other regions. Also, the removal of antibiotics from water and soil matrix inclusion addresses the need to understand and implement effective treatment strategies to mitigate the presence of antibiotics in these important environmental compartments. These aspects may offer new insights and contribute to the existing literature on antibiotics and their environmental implications.

2. Antibiotic for therapeutic use on humans

India has witnessed a 103 % increase in antibiotic usage between 2000 and 2015, which is similar to other low- and middle-income nations because of the common practice of dispensing antibiotics without proper prescription in these countries [19]. In fact, in 2004, the most consumed drugs in Delhi, India, were fluoroquinolone, cefuroxime, and cefixime, a combination of cefixime and clavulanic acid [20]. In this regard, the top five antibiotics consumed in India are cephalosporin, broad-spectrum penicillin, fluoroquinolones, tetracyclines and trimethoprim (Fig. S1). Further, the average dosage of antibiotics consumed by the population size of every 1000 Indian residents has increased by 63 % between the year 2000–2015. Similarly, worldwide antibiotic usage also surged by 65 %, with a 39 % raise in the rate of consumption per 1000 people [19]. Meanwhile, in 2012 World Health Organization (WHO) and the leading medical, pharmaceutical and research societies of India developed the Chennai Declaration to promote practical antibiotic policies and to prevent the overuse of antibiotics [21].

It is generally found that developed nations have higher antibiotic consumption. However, developing countries like India had also shown a rapid increase in antibiotic consumption because of its population explosion in the period of 1975–2010, when the number of inhabitants almost increased to 1.2 billion. As per the recent findings, about 33 % of the Indian population comprises of children between 0 and 14 years and senior citizens (>65 years), who are susceptible to diseases and require the maximum amount of antibiotics [22]. As a result, infants between 0 and 4 years of age were reported to have a significant rate of antibiotic prescriptions of 636 prescriptions per 1000 people [23].

In terms of over usage of antibiotics, it was found that in 2015, the defined daily dose (DDD) of cephalosporin was 1822 per 1000 people, which was around five times more than the DDD in 2005. Also, the DDD of the broad-spectrum penicillin doubled in 2015 in comparison to 2005, whereas in the case of fluoroquinolones, there was a 9 % increase in DDD from 2005 to 2010; however, a 25 % decrease in DDD was noticed in the time frame of 2010–2015 (Fig. S1). One of the main reasons for the decrease in antibiotic use can be attributed to the development of fluoroquinolones resistance genes in human pathogens, due to which the potency of fluoroquinolones decreased and hence was less prescribed.

As elucidated in the study that around one-third (33.6 %) of all outpatient antibiotics prescriptions made in the private medical sector of India was for upper respiratory disorders such as acute upper respiratory disorders (20.4 %), coughing (4.7 %), acute nasopharyngitis (4.6 %), and acute pharyngitis (3.9 %), which arguably doesn't require antibiotic treatment [23]. Due to the higher consumption of antibiotics, the Indian pharmaceutical market is expected to reach the ninth place in the global pharmaceutical market by 2023 with a net worth of 33.18 million USD [24].The excess use of antibiotics has led to the prevalence of them in the natural ecosystem and as a result, they are being indirectly ingested by living beings. This intake of excess amount of antibiotics from soil, air and water can give rise to various unprecedented conditions like biomagnification and bioaccumulation. Therefore, it's imperative to identify the source of antibiotics and establish an effective and efficient removal mechanism for antibiotics from the natural ecosystem as it poses an engraved threat to the biosphere.

3. Antibiotics in feed additives

3.1. Use of antibiotics as growth promoters in fodder

Antibiotics were initially discovered for the remediation of disease but found their utilization as feed additives in animal production. It was first observed in the 1940s that the chickens fed with derivatives of the fermentation of tetracycline grew faster than the others fed with normal feed, thus showing its growth-promoting abilities. Ever since multiple antimicrobials were employed to enhance daily average feed efficiency in livestock, a practice known as “growth promotion” emerged [25]. These advantages led to the acceptance of growth-promoting antibiotics in cattle production, which also offered added benefits like livestock protection, useable tissue clearances, and ecological security. Although the detailed mechanism of growth-promotion was unknown, the net advantage of providing antibiotics to cattle that were used for human consumption continued to be quantifiable [26,27]. Thus, due to the increase in antibiotic consumption rate, the usage of antibiotics for growth promotion also accelerated.

Currently, due to the rising population, antibiotics consumption has been increasing every year due to the utilization of growth promoters in cattle production [28]. This increasing population has risen the demand and also the competition in the market. Nowadays, people desire better quality products like better quality hens, meat, eggs etc., bigger egg sizes and thicker milk from cows to obtain other dairy products in better quantity and quality. In order to maintain this chain of demand and supply, the animals are fed with sub-therapeutic antibiotics growth promoters (AGPs) for better growth and increased yield of dairy and poultry products. The use of AGPs makes them stand out against the other competitors in the market, but with these benefits, the excess AGPs also contaminate the ecosystem. Further, this also leads to the accumulation of antibiotics in dairy and poultry products, which may have an adverse effect on consumers if not addressed thoroughly.

The amount of antibiotics used for animals has an impact on the levels of resistance the bacteria develop against antibiotics, which also transcends to humans, though the exact health impacts of this bacterial consumption are poorly understood [29]. Quinolones, third- and fourth-generation cephalosporins, and macrolides are cited by the Food and Agriculture Organization of the United Nations, World Organisation for Animal Health, and WHO as key priorities for threat assessment in livestock utilization. In a study [11], found that antimicrobial intake per kilogram of animal produced in the world was predicted to be 45 mg/kg, 148 mg/kg and 172 mg/kg for cattle, fowl, and pigs, respectively.

With the emergence of this situation, regulatory bodies are determined to take necessary steps to reduce the use of antibiotics and promote alternatives like phytogenic feed additives into the market, which shows improved results in gut health, weight gain, and improved immunity against pathogens than AGP [30]. The alternatives to the use of antibiotics are like cinnamon, a potential plant derivative that was approved by the US government, tends to possess more anti-inflammatory properties and act as an anti-microbial agent, thereby enhancing gut health [31]. Similarly, when the plants undergo secondary metabolism, it produces phenolic compounds like tannins, polyphenols and some essential oils, which can be utilized in feed additives for poultry and swine production. These secondary metabolites are proven to improve the quality of meat produced by reducing oxidative stress (which causes weight loss) and also boost immunity in combination with anti-microbial activity [32].

The excessive use of antibiotics in animal feed results in the persistence of antibiotics and antibiotic-resistant microbes, which are being spread over different components of the ecosystem (water, air, soil, etc.), and as a result, they directly or indirectly affect animal and human health (Table S1). Consequently, nutritional experts are concerned with the presence of antibiotic resistant bacteria (ARB) in animal-derived food and their impact on the supplied food, which can render them unfit for consumption. Similarly, epidemiologists are also concerned with disease breakouts spawning due to resistant pathogens, whose origin can be backtracked to animal-derived food. Further, biologists are trying to compare different resistant genes and the pervasiveness of specific genes in humans and animals as its difficult to quantify and state how human infections are influenced by animal feed antibiotics. As of now, scientists can only draw some primitive conclusions that how a risk factor might influence the prevalence of a particular disease [33]. In this regard, the direct and indirect effects of antibiotic use in animal feed on human health are illustrated in (Fig. 1) and (Table S2) [34,35].

3.2. Antibiotics use in aquaculture

Aquaculture is one of the key sectors of the food industry that considerably contributes to the presence of antibiotics in the environment, which is majorly used for reducing the risk of diseases associated with fishes [36]. In this veneration, antibiotics like fluoroquinolones, tetracyclines, sulphonamides etc., have been prevalently employed in fish farming as an attempt to eradicate the increasing prevalence of diseases in fishes. This excessive use of antibiotics in aquaculture poses serious public health challenges because of the growth of bacterial resilience as well as the existence of antibiotic residues in culinary cells that can trigger allergic reactions in hypersensitive people [37].

Formation of antibiotic resistance genes (ARGs) in aquaculture can occur through two mechanisms: vertical and horizontal gene transfer (HGT). The HGTs tend to be the most common and potent mechanism, in which bacteria undergo a four-step process of conjugation, transduction, transformation, and mutation [38]. Further, in the transformation process, mobile genetic elements (MGE) shift the ARGs to host bacteria [39]. Additionally, during the transfer stage, integron and plasmid mediation have been identified to occur in aquaculture, in which plasmid mediation is responsible for developing single resistance ARGs [40]. Furthermore, ARB, compared to the host bacteria, demonstrates various antimicrobial resistance (AMR) mechanisms, including detoxification of antibiotics, inhibition of antibiotic accumulation within cells, target protection, and substitution [41].

According to International Market Analysis Research and Consulting Group, the Indian fish marketplace surpassed a capacity of 17.4 million tons in 2021 [42]. As a result, the Food Safety and Standards Authority of India outlawed the use of pharmaceuticals in aquaculture in 2011, enforcing a strict limit on tetracycline,

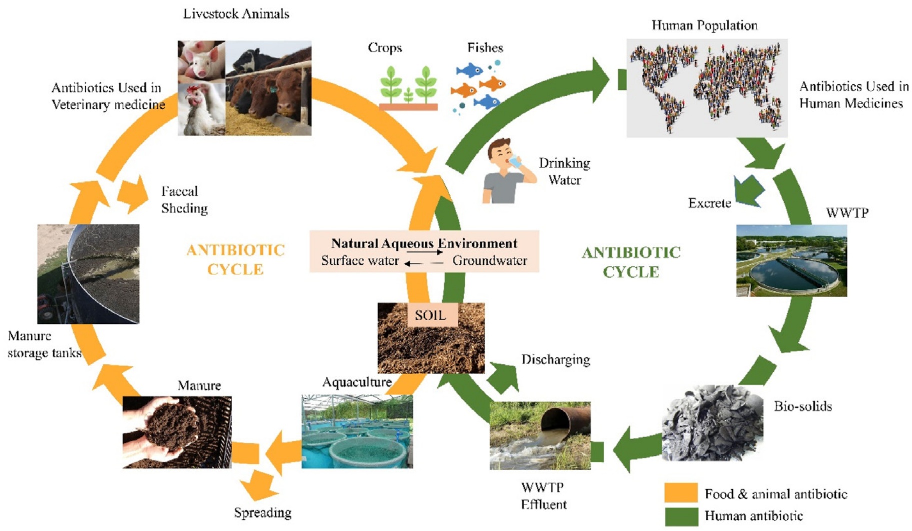

Fig. 1. Pathways of antibiotic transformation and movement in soil, water and wastewater environment inspired from [34].

oxytetracycline, trimethoprim, and oxalinic acid residues of less than 0.1 mg/kg in fishes [43]. The shrimp culture has played an extensive part in Indian culinary history that started emerging in the early 1990s and in the 2000s, India became the fifth biggest producer of shrimps on the global stage. In the shrimp culture, the antibiotics that are preferably used are ciprofloxacin, chloramphenicol, erythromycin, co-trimoxazole, and tetracycline. Usage of antibiotics in aquaculture is categorized as therapeutic, prophylactic, metaphylaxis (a grouped form of antimicrobials to cure infections) and prophylaxis (single and grouped form to prevent diseases). Further antimicrobials developed a potential to build up in the tissues of fishes and shrimps before they are released out from their body [44]. Additionally, the research conducted in India on shrimp culture suggests the development of antimicrobial resistance, which concluded from the results obtained from analysing 192 samples, where bacteria were isolated from pond sediments, pond water, and shrimps. The results indicated that bacteria isolated from pond water and shrimps have high antibiotic resistance and even some among them were also multi-drug resistant [45]. Thereby adopting better quality measures to prevent antibiotic contamination and proper investigation and monitoring would assist the farmer in producing antibiotic-free shrimps [46].

The usage of antibiotics in aquaculture tends to eliminate the microorganisms, which infect the aquatic species and thus, indirectly accelerate their growth (Table 1) and use of chemotherapeutants in aquaculture (Fig. S3). However, these antibiotics are non-nutritive in nature but are still used for promoting growth [47]. For bacterial infections, antibiotics were adopted for treatment either for therapeutic or prophylactic uses and they turned out to be a primary contributor to antibiotic pollution in the environment. Due to antibiotic pollution, humans are affected by severe side effects, which may differ based on the type of antibiotic residuals present in the body of fish. To control this alarming situation, proper standards should be formulated and implemented by the Food and Agriculture Organization in consultation with WHO, which are essential to maintain the low levels of risk associated with antibiotics intake [48].

3.3. Application of antibiotics in agriculture

Antibiotics are extensively used in agriculture to diagnose and reduce numerous ailments in crops and to promote crop yield [59]. Similarly, an adequate amount of water is also necessary for improving crop yield. In this regard, sources like rivers, lakes, and precipitation are majorly responsible for meeting this irrigation water requirement. Furthermore, it is estimated that 2500 km^3 of water is used every year for irrigation globally, with around 1200–1800 km^3 being contributed by rivers, lakes etc. and the rest through precipitation [60]. However, due to emerging concerns like global warming and climate change, rainfall patterns are getting altered with the shrinkage of surface water sources. In addition, the rising population calls for increased food production, which further amplifies the problem of water shortage [61]. Likewise, due to water shortages and inadequate irrigation infrastructure, agriculture consumes 90 % of the water in India [62].Fertilizers used for agriculture also contain a large number of antibiotics, whose residues accumulate in soil (Table 2). Similarly, effluent discharged from wastewater treatment plants also contributes to increased antibiotic concentrations in the river water, which is a common source for irrigation [63]. The ARG present in the treated wastewater (TWW) while being used for agriculture can promote the spreading of ARG to other bacterial community [64].

The use of antibiotics in agriculture can impact human beings through two pathways, first, by manure collected from animals, which has been exposed to antibiotics and second, by using water comprised of antibiotics for irrigation. These antibiotics ingested by plants accumulate with time and affect the consumers, when they are harvested and consumed [69]. In a study [70], three mechanisms were outlined that can pose a hazard to public health as a result of agricultural antibiotic usage namely infection directly through resistant pathogen emanating from agricultural activities without human-to-human spread, second human infection by a resistant pathogen, which breaches species barrier leading to human-to-human spread, and the last, a HGT directly transmit the resistance genes to human pathogens. In another study [68], it was suggested that antibiotics get absorbed via root absorption, namely photosynthesis-class of fluoroquinolones tends to affect the antioxidant properties of corn plants during respiration. Similarly, the presence of antimycin in potato leaves and cipro in other minor plants causes damage to cell proteins and structures of nucleic acid present in plants. Further antibiotics in nitrogen metabolism tend to affect the folic acid synthesis and later take part in oxidative metabolism and the seed germination process of plants.

As good quality vegetables fetch a premium price in the market,

Table 1
Use of various antibiotics on different aquatic species.

Antibiotic	Species	Usage	Dosage	Reference
Oxytetracycline (Controlling bacterial infections in fishes)	Salmonids	To prevent cold-water disease (Flavobacterium psychrophilum) in freshwater-reared salmonids	50 mg/kg for 24 h (oral)	[49] [50]
	Catfish	To treat hemorrhagic septicemia (*Aeromonas liquefaciens*) and *pseudomonas* infection	82.5 mg/kg fish per day for 10 days with feed	[49] [51]
	Lobster	Control of gaffkemia caused by *Aeorccus viridian*	1 g/pound of feed, sole ration for 5 days	[52]
Sulfamerazine	Salmonids and catfish	For the control of furunculosis in salmonids (trout and salmon) caused by *Aeromonas salmonicida and* also for the control of bacterial infections caused by *Edwardsiella ictaluri* in catfish	50 mg/kg fish body weight for 5 days consecutively	[53]
Sulfadimethoxine-ormetoprim combination	Salmonids Catfish	Used as the feed for treating infection in salmonids *Edwardsiella ictaluri* and *Aeromonas salmonicida* in both catfish and salmonids	29–50 mg/kg body weight	[54] [55] [56]
Formalin	Salmon/Trout eggs	Control of protozoa	1000–2000 μL/L	[57]
	Catfish, largemouth bass and bluegill	Control of protozoa	15–250 μL/L (dependent on temperature, species and type of pond)	[57]
	Salmonids, reared	Control of protozoa	15–250 μL/L (dependent on temperature, species and type of pond)	[57]
	Other finned fish	Control of external protozoa	15–250 μL/L (dependent on temperature, species and type of pond)	[58]
	Shrimp	Control of fungi of the family *Saprolegniaceae* on the eggs of all fish species	25–100 μL per litre	[58]

mg/kg – milligram/kilogram; g/pound – gram/pound; μL/L – Microliters/litre.

Table 2
Antibiotics used in agriculture and their purposes.

Antibiotic	Brand name	Class	Use	Reference
Streptomycin	Agrept, Agri-mycin, Agri-strep, Fructocin, Plantomycin	Aminoglycoside	Control of fire blight, wildfire (*Pseudomonas syringae* pv *tabaci*) and blue mold (*Peronospora tabacina*) diseases	[65,66]
Oxytetracycline	Biostat, Glomycin, Mycoshield, Terrafungine, Terramycin	Tetracycline	On pear for control of *Erwinia amylovora* On peach and nectarine for control of *Xanthomonas arboricola* Against bacterial spots Control *Erwinia amylovora* on apple To mitigate symptoms of lethal yellows diseases caused by phytoplasmas	[67]
Gentamicin	Agry-gent, Bactrol Plus	Aminoglycoside	To control fire blight of apple and pear Control various bacterial diseases in vegetables and crops caused by species *Erwinia*, *Pectobacterium*, *Pseudomonas*, *Ralstonia*, and *Xanthomonas*	[67]
Oxolinic Acid	Starner	Quinolone	Control fire blight in apple, pear, and related plants	[68]

farmers often carry out spraying antibiotics or injecting them into the crop at consistent interludes, which safeguards their plants against parasites; as a result, they stay well and green till yield. In this regard, Streptocycline, which is a combination of two antibiotics, streptomycin and tetracycline, is mixed with a host and is one of the antibiotics sprayed on crops. Further, streptocycline is also used on humans for treating multidrug-resistant tuberculosis and some cases of tuberculosis meningitis [71]. Resistance to streptomycin is already high and its large-scale non-human use could further worsen the situation [72,73]. Additionally, the usage of streptocycline on plants was approved by the Central Insecticide Board and Registration Committee after observing the symptoms/infections like leaf blot, fire blight, citrus canker, decaying of fruit and stalks, leaf adverts, and soft decays (yellowing and wilting of leaves). But reports showed usage of streptocycline even with the absence of any disease/symptoms, that too without proper guidance of application and monitoring. Agriculturists on the bank of river Yamuna admitted the use of this antibiotic on different crops like radish, coriander, brinjal, cucumber, bottle gourd, cauliflower, cabbage, mustard, fenugreek, and apple gourd despite the recommendation of CIBRC (Central Insecticide Board and Registration Committee), which limits its use on only selected crops like tomatoes, potatoes and beans [71]. The dosage was also very specific for different crops; for instance, in the case of fire blight in apples, a solution of 25–50 ppm; for halo blight in beans, 100–150 ppm; for bacterial leaf spots in tomatoes, 40–100 ppm.

According to the Centre for Science and Environment (CSE), farmers, and fruit growers of Delhi, Punjab, Haryana, Himachal Pradesh, and Andhra Pradesh were unaware of the fact that streptocycline was being used with other pesticides was a combination of antibiotics [71]. Streptocycline was being used as a mix with fungicides by farmers as, for them, it is difficult to distinguish between bacterial or fungal diseases. This is one of the many examples of unawareness of antibiotic usage on crops in India. Further, the antibiotics derived from streptomycin and their uses in agriculture are shown in Table S3. Similarly, the intrusion of antimicrobials into agriculture fields by the usage of animal wastes as manures tends to simulate the bioaccumulation of these antibiotics in plants. Appropriate usage of antibiotics will simulate the required growth in plants. Once the antibiotics have made their way into the soil, their degradation rate depends on the characteristics of the soil, the amount of antibiotic excreted, pH, and the temperature of the environment [74]. Therefore, it's imperative to consider these different factors before predicting the degradation mechanism of any antibiotic in the soil matrix. As soil is the sink for environment, once the antibiotic enters in the soil is passes through other environmental aspects. The (Table 3) summarizes the recent publications on the prevalence of antibiotic in different environmental matrix along with their concentration range and country of occurrences.

3.4. Antibiotic residues in airborne particles ($PM_{2.5}$)

The presence of particulate matter ($PM_{2.5}$) in the atmosphere can interact with antibiotic residues, leading to significant antibiotic exposure in aquaculture, agriculture, and livestock farms. In 2018, $PM_{2.5}$ contributed to a 2.5 % increase in antibiotic resistance in India, affecting both humans and livestock [94]. In this context, the aerosolization of animal faeces contaminated with antibiotic residue on contact with $PM_{2.5}$ present in the atmosphere can increase the aperture of ARGs and ARB to the environment. This phenomenon tends to be more prevalent in poultry farms, where antibiotics are consumed in higher volumes than in cow farms. Farmers face a significant health threat as they can contract and transmit dangerous bacteria and high-risk ARGs, posing a significant health risk to them and their surrounding environment [95]. Furthermore, the MGE were identified as facilitators of antibiotic resistance and found in air conditioner dust samples along with ARB and ARG [95]. In order to combat the spread of antibiotic resistance, it is vital to regulate and monitor the activity of MGE to abate the dissemination of ARGs [93]. Another investigation conducted on antibiotic-contaminated soil to study the influence of rainfall stages on antibiotic transmission and changes in exposure to $PM_{2.5}$ demonstrated that ARGs are sensitive to rainfall intensity and other meteorological factors. Although, rainfall acts as a medium that transfers the ARGs from air to soil [96].

4. Antibiotic resistance and toxicity

Identification of risk associated with antibiotics entering into the human body can be estimated by measuring the daily intake and it will eventually unveil itself through two reactions in humans, i.e., adverse drug reaction and chronic toxicity. Long-term consumption of antibiotics may cause severe side effects, like allergies, digestive problems, renal diseases, and chronic illnesses such as cardiovascular diseases, which can be toxic to human beings. For instance, frequent prescriptions of fluoroquinolone, which was previously considered to be a safe-to-use antibiotic, led to the development of a syndrome known as fluoroquinolone-associated disability, whose adverse effects have affected thousands of individuals in the United States alone. Additionally, in a study [97], stated that the safety of the environment and public health are seriously threatened by the highly toxic antibiotic enrofloxacin as the ill effects of enrofloxacin and its by-products were assessed in the study.

To apprehend the correlation between the routine of antibiotic usage and increasing antibiotic resistance, there must be a proper understanding of antibiotics interaction with different environments (water, air, soil), socially (farmers, animals, and poultry etc.), processing (farming, transportation, storage etc.) and pattern of human use (food preparation and consumption) [98]. The main function of an antibiotic is to combat bacteria; therefore, when bacteria are exposed to antibiotics for a long time, they evolve and build immunity against certain antibiotics. In 2015, it was reported that pathogens such as *Escherichia coli* (*E. coli*) developed resistance to antibiotics such as aminoglycosides (26 %), aminopenicillins (87 %), amoxicillin (65 %), carbapenems (15 %), cephalosporins (78 %), fluoroquinolones (78 %), and glycylcyclines (1 %) [99]. Further, the isolates of *Salmonella typhi* were reported to be resistant to aminopenicillins (5 %), fluoroquinolones (68 %), macrolides (6 %) and trimethoprim (5 %), whereas only the resistance to fluoroquinolones among *Salmonella typhi* has increased from 8 to 28 % from 2008 to 2014 [100]. On the other hand, the resistance to antimicrobials, which are not commonly used, like trimethoprim sulfamethoxazole and aminopenicillin is decreasing.

The resistance to fluoroquinolones has alarmingly increased from 28 % in 2010 to 68 % in 2015 [99]. This problem is not region specific but has affected people globally. In a developing country like India, with a poor healthcare system, cheap antibiotics and direct relation between profit and antibiotic sales are responsible for the pervasiveness of resistant pathogens, terminal neonatal sepsis and healthcare-associated infection. Also, the un-prescribed over-the-counter dispensing of carbapenems in India is the highest in the world, which has significantly contributed to a growing carbapenem resistance among gram-negative organisms [14].

In Karnataka [101], carried out a study to detect antibiotic susceptibility to find the potential ARB species and antibiotic susceptibility was observed in the study for tetracyclines and fluoroquinolones due to their excessive use as prophylactic medication and growth booster. Furthermore, tetracycline resistance was observed in all 187 isolates of *E. coli*. Moreover, 176 *E. coli* bacteria species in total (94 %) were resistant to both ciprofloxacin and levofloxacin, whereas 6 % of isolates were susceptible to both drugs. Further, only 36 isolates (19 %) were cefotaxime and ceftazidime resistant. Ampicillin resistance was present in 18 (90 %) of the 20 Klebsiella isolates, followed by ciprofloxacin, levofloxacin (each at 80 %), and tetracycline (80 %). All 20 Klebsiella isolates exhibited multidrug resistance. About 40 % of *E. coli* were resistant to amikacin, cefotaxime, ofloxacin, and carbapenems, and all *E. coli* isolates were resistant to meropenem. Some failed to resist the dosage of chloramphenicol, ceftriaxone, cefepime, cefuroxime, gentamycin, levofloxacin, norfloxacin, and nitrofurantoin [102].

The development of antibiotic resistance can be attributed to various mechanisms; for instance, one of the mechanisms is restricting access to antibiotics, where peptidoglycan act as a protective layer outside the plasma membrane around most of the bacterial cells, which protects them from the external environment. Another mechanism is pumping out antibiotics from the cell wall; for example, pathogens like *Pseudomonas aeruginosa* impel their cell walls to purge the antibiotic drugs that enter the cell (Fig. 2) [103]. For instance, some of the antibiotics like chloramphenicol, fluoroquinolones, trimethoprim and beta-lactams get pumped out of the cell wall. The third mechanism is the change or destruction of antibiotics, where bacteria like *Klebsiella pneumoniae* produce enzymes called carbapenemases, which break down carbapenem drugs and most of the beta-lactam drugs. Bacteria can also develop antibiotic resistance by changing the target site, where antibiotics get attached, like *E. coli* with its mcr1 gene are capable of adding an additional substance to the exterior of the cell wall so that the drug colistin cannot act on it. Additionally, some bacteria may develop new cell processes that bypass the effects of the antibiotics, such as *Staphylococcus aureus* can develop a process which inhibits the drug effects of trimethoprim and changes its target [104]. Apart from antibiotic resistance, the antibiotic residue in the environment causes other consequences in the human and animal bodies, as summarized in (Table 4) and (Table S4) [105].

4.1. Antibiotic load and resistance in India

Antibiotics are widely detected in groundwater, stormwater as well as in drinking water. And one of the reasons for the presence of antibiotics in the environment is the inability of conventional

Table 3
Traces of antibiotics measured in different environmental matrix.

Source	Types of antibiotics	Concentration	Region	Reference
Surface water	Sulphonamides (sulfamate, sulfamethoxazole, sulfadiazine, sulfamethazine)	In summer: 1.1–70 ng/L In winter: 1.0–35 ng/L	Hanjiang River, Central China	[75]
	Sulfamethoxazole	Between 11 ng/L and 112 ng/L	Ebro River basin, Northeast Spain	[76]
	Ofloxacin	17.65–902.47 ng/L	Yitong River in Changchun, China	[77]
	Norfloxacin Erythromycin	ND to 260.49 ng/L 194.4 ng/L	Buckingham Canal, Chennai	[78]
Groundwater	Trimethoprim, Sulfadimidine Sulfadiazine, Sulfamethoxazole, Sulfachloropyridazine, Norfloxacin, Ciprofloxacin and Enrofloxacin	0.44 ng/L to 45.40 ng/L	Water conservation area in the northern part of the North China Plain	[79]
	Ciprofloxacin	20.48 ng/L	Buckingham Canal, Chennai	[78]
	Sulfamethazine Tigecycline	5.2 ng/L 21.3 ng/L	Faisalabad, an industrial hub, Pakistan	[80]
	Ciprofloxacin Azithromycin	18.2 ng/L 43.2 ng/g	Leça river, Northern Portugal	[81]
Sediments	Tetracyclines (chlortetracycline, tetracycline, oxytetracycline, doxycycline)	In summer: 0.86–15 ng/g dw In winter: 1.0–15 ng/g dw	Hanjiang River, Central China	[75]
	Tetracycline, Oxytetracycline, Chlortetracycline, Ofloxacin, Enrofloxacin, Norfloxacin, and Ciprofloxacin	4.7 μg/kg	Huaihe River Basin, China	[82]
	Fluoroquinolones and tetracyclines	2085 ng/g	Xiangjiang River, South Central China	[83]
Drinking water	Sulfonamide metformin, Sulfonamide metformin, Erythromycin, Roxithromycin, Tylosin, Lincomycin, Chloramphenicol, Florfenicol	13.9–76.6 ng/L Average: 46.4 ng/L	Five urban drinking water sources, Chongqing area of the Yangtze River, Tibet	[84]
		20.6–188.1 ng/L Average: 88.45 ng/L	Four township drinking water sources, Chongqing area of the Yangtze River, Tibet	
	Oxytetracycline Sulfamonomethoxine Sulfamethoxazole Sulfachlorpyridazine Sulfadiazine Florfenicol	9.5 ng/L 79.7 ng/L 42.5 ng/L 14.1 ng/L 41.5 ng/L 62.3 ng/L	Hainan Province drinking water sources, China	[85]
	58 antibiotics	Average: 182 ng/L Median: 92 ng/L	Filtered tap water, Chinese market	[86]
	45 antibiotics (highly roxithromycin)	Average: 180 ng/L Median: 105 ng/L	Chinese brands of bottled/barrelled water	
	36 antibiotics (highly dicloxacillin)	Average: 666 ng/L Median: 146 ng/L	Foreign brands of bottled water, Chinese market	
Wastewater	Sulfamethoxazole Sulfapyridine	27.2 ng/L to 596 ng/L 3.7 ngL−1 to 227 ng/L	Wastewater Treatment plant along Ebro River basin, Northeast Spain	[76]
	19 antibiotics In Summer: Dominantly Quinolones and macrolides In Winter: Dominantly Sulfonamides and macrolides	Low to 60.8 μg/L	Two wastewater treatment systems (WWTSs) and their irrigation areas located in the arid northwestern region of China	[87]
	21 antibiotics Highly doxycycline, tilmicosin, and amoxicillin	12.9–459.1 μg/L	Pig farm wastewater, Thailand	[88]
Soil	Highly erythromycin, sulfamethoxazole, and doxycycline	21.79 μg/kg	Beijing-Tianjin-Hebei urban agglomeration	[89]
	Flumequine	Below 100 μg/kg	288 soil samples of Belgium	[90]
	Doxycycline, oxytetracycline, lincomycin and sulfadiazine	0.1 μg/kg to 500 μg/kg		
Air ($PM_{2.5}$)	netillin, chloramphenicol, streptomycin, tetracycline, clindamycin, amikacin, erythromycin, cefotaxime, and co-trimoxazole	Winter- 265.56 μg/m^3 Pre-monsoon- 173.1 μg/m^3	Around 31 % and 20 %, out of 36 bacterial species isolated from PM2.5 showed resistance to antibiotics Nagpur landfill, India.	[91]
	ARG's - ermB, tetE, and thE	39.5–142.5 μg/m^3 (2017) 40.6–150.8 μg/m^3 (2018)	During rainfalls, ARG's found with abundance of 18–30 copies/m^3 in Beijing, China.	[92]
	ARG's resistant to Sulfonamides marcolides tetracyclines aminoglycoisdes β-lactams amphenicols	$6.9*10^{-3}$-0.17 $1.8*10^{-3}$ - $3.3*10^{-2}$ $5.1*10^{-5}$ - $9.2*10^{-3}$ $1.4*10^{-4}$ - $5.8\ 10^{-3}$ $5.5*10^{-5}$ - $4.9*10^{-3}$ $7.1*10^{-5}$ - $9.6*10^{-4}$	16 ARG's subtypes were found in Air conditioner dust in Hong Kong kindergartens.	[93]

ng/L – nanograms/litre; ng/g dw – nanograms/gram dry weight; ND – not detected; μg/kg – microgram/kilogram; μg/L – microgram/litre; μg/m^3–microgram/cubic air.

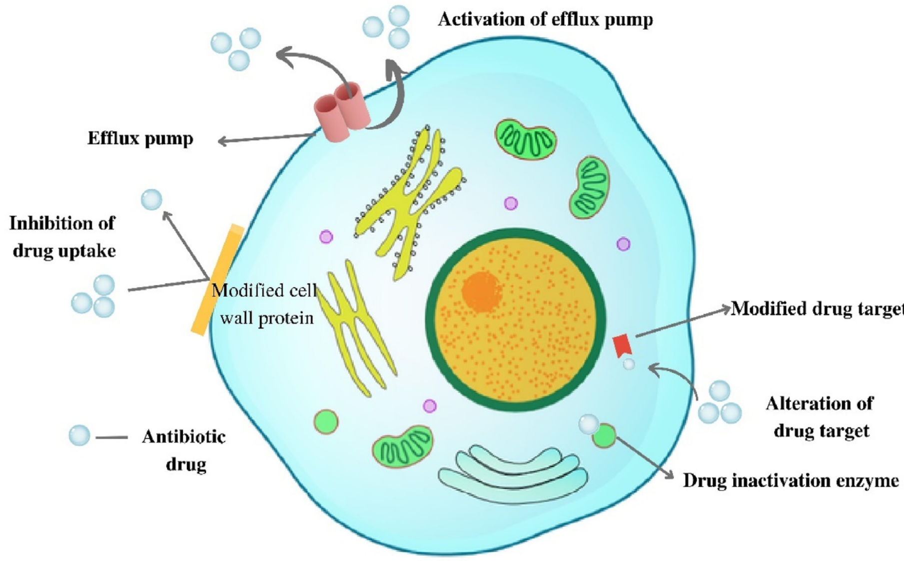

Fig. 2. Schematic diagram showing the general antibiotic resistance mechanism inspired from [103].

sewage treatment plants (STPs) to remove antibiotics from wastewater [117]. Apart from STPs effluents, agricultural and livestock activities are also one of the major sources of antibiotics in water [118,119] In this regard, a study by Ref. [120] observed the contaminants of antibiotic-resistant genes (ARGs) in influent and effluent of three STPs from Delhi and Nagpur, where ARGs were found in the untreated, treated water from STP as well as in irrigation canal water where treated water from one of the STPs was discharged; thus, it necessitates a rigorous post-treatment for their removal before making it fit for reuse. It was also observed that antibiotic contaminants, namely Ampicillin, Fluoroquinolones and Cephalosporins considered for investigation, were found in both effluents and influents of STPs near Yamuna River, where Ampicillin was highest among them [121]. The antibiotic resistance of bacteria was triggered by the use of popular antibiotics like ampicillin, sulfamethoxazole, ciprofloxacin, tetracycline, and chloramphenicol. The intrusion of antibiotics into the water is primarily due to their application in the agricultural and aquaculture sectors or livestock industry and thus, the antibiotic eventually ends up in the wastewater treatment plants. After the treatment of wastewater, antibiotics enter the environment through the treated effluent or through STP sludge that is being employed as manure [122]. Consequently, ARGs are found in the influents and effluents of the STPs and in irrigation canals etc., indicating the requirement for more effective disinfection of TWW.

India is at the centre of a catastrophe as the non-judicial use of antibiotics has fostered a scenario that is essentially ideal for these incredibly resilient microorganisms to endanger our health. Several factors are accountable for the emergence of this antibiotic resistance in India and some of them are listed subsequently.

- Self-medication and access to antibiotics without prescriptions are one of the major reasons for the emergence of antibiotic resistance in India. Further, informal health care and lack of education regarding the dosage of the drugs and infections add to this [123].
- By choosing and administering antibiotics incorrectly, the physician might raise treatment risks and also reduce their effectiveness [124]. These medication errors, particularly in the case of antibiotics, make them more bioavailable for ARB and ARG generation, which ultimately increases antimicrobial resistance.
- The misuse of antibiotics as a result of fierce competition and economic constraints across healthcare infrastructure due to the presence of a large number of pharmacies is a major concern. The large numbers of pharmacies are also difficult to regulate [125].
- Antibiotics are frequently prescribed by Indian medics for illnesses that are easily treatable with just a little extra prudence without antibiotics, which increases the usage of antibiotics. The issue is magnified when the patient disobeys the doctor's advice to finish the antibiotic course which evidently increases the risk of antimicrobial resistance [126,127]. Moreover, the left-over antibiotics from these prescriptions might be used as self-medication or may end up as solid waste in landfill or open dumping, which makes antibiotics more susceptible to developing antimicrobial resistance.
- The unregulated agricultural and aquaculture sector also leads to the irrational routine of antibiotic usage in animals and fish feed [128].
- The lack of knowledge to use proper fertilizers and pesticides to protect and enhance crops also leads to the manifestation of resistant genes [105].
- Improper disposal of wastewater and the lack of proper treatment of polluted water also give rise to the generation of antibiotic-resilient genetic factors in bacteria [129].
- Further, ineffective infection control methods, unsanitary facilities, and improper food management may also contribute to the emergence of antibiotic resistance [130].

The implementation of stringent regulations towards the usage of antibiotics in agriculture, which dictates the health of human beings, needs to be enforced. Further, no particular treatments are available in wastewater treatment plants that focus on the removal of antibiotics and ARGs from wastewater. Constructed wetlands (CWs) are employed as the optimal choice for remediating pollutants small in size and antibiotics, as well as ARGs with a high removal efficiency of around 90 % [131]. Since there are no laws in India to limit the use of antibiotics, the bulk of medications, including antibiotics, can be purchased from local outlets even

Table 4
Levels of resistance to various antibiotics in the environment.

Type of antimicrobial resistance (AMR)	Type of pathogen		Percentage (%) resistance	Antibiotics involved	Reference
AMR in humans	Gram-negative Bacteria	*Escherichia coli*, *Klebsiella pneumoniae* and Acinetobacter baumannii	>70	Fluoroquinolones and third-generation cephalosporins	[106]
		Pseudomonas aeruginosa	≥50		[107]
		E. coli and *P. aeruginosa*	<35	Piperacillin-tazobactum	[106]
		A. baumannii	71	Carbapenem	[108]
	Gram-positive organisms	*Staphylococcus aureus*	43	Methicillin	[109]
		Enterococcus faecium	10.5	Vancomycin	[110]
		Salmonella Typhi	28	Ciprofloxacin	[105]
			0.6	Ceftriaxone	[105]
			2.3	Co-trimoxazole.	[111]
		Shigella	82	Ciprofloxacin	[105]
			12	Ceftriaxone	[111]
			80	Co-trimoxazole.	[111]
		Vibrio cholerae	17–75	Tetracycline	[112]
AMR in food animals	Gram-negative organisms	Bacilli (in cow and buffalo milk)	47.5	Oxytetracycline	[113]
	Gram-positive organisms	*S. aureus* (in cow and buffalo milk)	2.4	Vancomycin	[110]
		S. aureus	21.4	Methicillin	[114]
		Coagulase-negative Staphylococci	5.6		
AMR in fishes	Vibrio cholera and V. parahaemolyticus		100	Ampicillin	[115]
			100	Chloramphenicol	[115]
			67–96	Ceftazidime	[115]
AMR in poultry	Salmonella species (broilers)		100	Ciprofloxacin, gentamicin and tetracycline	[105]
AMR in environment	*E. coli*	Domestic water	25	Third generation cephalosporin	[116]
		Domestic waste and hospital effluents	70		
		Hospital effluents	95		

without a prescription, which makes judicial antibiotic management the need of the hour [132]. The cheap availability of drugs and unregulated antibiotic use has been contributing as a major cause of increased antibiotic consumption and thus resistance [14]. Pharmacies tend to join hands with a particular pharmaceutical brand and dispense only the particular medication for the disease, which leads to the overuse of a certain antibiotic and most antibiotics are dispensed without any proper prescriptions [133]. In India's urban areas, corporate sector pharmacists supply over 67 % of antimicrobial meds without a prescription [134]. Thus, to alleviate the situation, it's imperative to establish and enforce appropriate legislative measures to prevent the over usage of antibiotics, which will eventually avoid the advent of antibiotic resistance in microbes and genes.

5. Antibiotic remediation

For the elimination of emergent contaminants from the water or wastewater, numerous treatment techniques are available such as filtration, coagulation, activated carbon-based adsorption etc. Apart from these conventional methods, the advanced oxidation process has shown a lot of potential for the treatment of emerging contaminants such as endocrine disruptive compounds, personal care items, and also drugs like antibiotics [135]. Further, there are numerous nano-structured photocatalysts capable of degrading antibiotics from wastewater [53]. Furthermore, innovative hybrid biological wastewater treatment processes that integrate multiple redox mechanisms and biomass adaptations which might be able to eradicate various antibiotic agents [136]. In another study [137], investigated the removal rates of seven particular antibiotics such as ampicillin, naproxen, sulfamethoxazole, erythromycin, chloramphenicol, cefoxitin, trimethoprim and bezafibrate in four different “STPs” in South India. They showed that sulfamethoxazole was the most prevalent component in all effluents, with the greatest levels of 3.2 μg/L in a STPs outflow. The removal efficiency of bezafibrate was around 100 %, while it was 60–100 % for sulfamethoxazole, cefoxitin, and ampicillin.

There are presently two distinct approaches for the remediation of antibiotics; one is degradation, which can attain about 90 % removal of antibiotics and the other technique is sorption, but the best way is to prevent antibiotics from entering into the ecosystem [138]. Antibiotics can be removed by both absorption and degradation through membrane separations, activated sludge process, CW and combined biological processes. Further, tertiary treatments like Fenton and ozonation processes can be employed for the removal of resistance genes [139]. In this regard, ARB and genes that were identified in both influent and effluent of a wastewater treatment plant located in Germany were eliminated with the help of an additional ozonation process following physico-chemical and biological process [140]. Recently, many traditional and emerging technologies have been employed for the removal of antibiotic-resistant microbes and genes from various matrices and some of those are elucidated subsequently.

According to Ref. [141], the two principal environmental incursion sources that contribute to antibiotic contamination includes human sources like hospital and sewage discharge, and animal sources like agriculture, aquaculture, and poultry. Once the source has been identified, then optimum remediation technique can be implemented. Adsorption was the most investigated method of antibiotic removal and gives high removal options with modified substances in favourable conditions [79], followed by pyrolysis, photocatalytic degradation and biodegradation. Further, CWs can remove up to 100 % of antibiotics present in contaminated water when operated in optimal conditions [142]. Removal efficiency of the antibiotics and ARG's will be based on the removal method considered for the particular scenario as well as the targeted antibiotics as described briefly in Table S4. New regulations need to be implemented in the wastewater treatment plants for removing them and further research needs to be conducted for converting them into non-toxic products so that the environment can be protected.

5.1. Diverse methods for removal of antibiotics from wastewater

5.1.1. Anaerobic digestion

Anaerobic digestion (AD) is considered one of the cost-effective technologies for eliminating antibiotics from wastewater in wastewater treatment plants. However, it has been found that antibiotics have the potential to lower the methane production of AD [143]. The most commonly found antibiotics in swine wastewater are sulphonamides, tetracyclines and macrolides. Both biosorption and biodegradation in AD are implemented for the management of swine wastewater treatment plants. Additionally, magnetic nanoparticles act as an absorbent material and demonstrated 67 % removal of ciprofloxacin in AD, concomitantly aiding the removal of other pollutants as well [144]. Moreover, carbon-based conductive materials can be used in the process of AD as well to enhance the bacterial interaction and degradation mechanism of the pollutant. Co-substrate, like straws has also shown high removal of antibiotics in AD through the mechanism of co-metabolism and adsorption, when employed for swine wastewater treatment [145]. Also, high removal efficiency for antibiotics such as tetracycline, sulfamethoxazole, azithromycin and tylosin was observed in treatment units like anaerobic sequencing batch reactor [146]. Therefore, all these investigations warrant the use of anaerobic technologies like AD for the removal of antibiotics from wastewater.

5.1.2. Constructed wetlands

The CWs were employed for the elimination of multi-pollutant antibiotics in swine wastewater, which exhibited 85−99 % removal of oxytetracycline and ciprofloxacin in different flow configurations, where vertical flow gave the optimum performance. Immobilization and elimination of antibiotics were observed in CWs, as antibiotics get removed from wastewater and are further absorbed by plants as it undergoes degradation, making CWs more efficient than other conventional processes like activated sludge processes [131]. Conventional methods of treating swine wastewater require more land and energy to recycle that water. A study by Ref. [147] adopted CW to eliminate antibiotics from urban wastewater and obtained 61 ± 38 %, 96 ± 29 % and 60 ± 26 % removal of doxycycline, trimethoprim and sulfamethoxazole, respectively. Although CW requires a large area and high hydraulic retention time for the removal of antibiotics from wastewater, its integration with advanced treatment methods can be envisaged as an effective solution for wastewater remediation.

5.1.3. Algae-based technologies

Contemporary research indicated that algae-based technology as a potential technology for the removal of antibiotics from wastewater through adsorption, accumulation, biodegradation, photodegradation, and hydrolysis [148]. In a study [149], investigated the potential of algae-activated sludge technology for antibiotic removal from wastewater. In this investigation, for 24 h of treatment, a maximum cefradine removal of 75 % was obtained. The analysis showed that the microalgae-based technology for eliminating refractory antibiotics has significant applicability and, when coupled with other techniques, may reliably remove these antibiotics. For instance, an advanced mode of treating the antibiotics will be phytoremediation with microalgae and AD along with microalgae cultivation, which is arguably the most economical and efficient way of removing these pollutants [150].

5.1.4. Application of biochar

Biochar demonstrated the potential for the removal of antibiotics from wastewater with high sorption efficiencies. In this regard, suitable biochar produced from different plant-based materials like rice husk, bamboo and pinewood, coconut shells, and sludge and chicken bones-based biochar have been employed for the removal of antibiotics [151]. In a study [152], the removal of sulphonamide was studied by biochar and biochar assisted with H_2O_2 with a synthetic urine matrix. Biochar was derived from cotton straw which was applied as an adsorbent. In order to degrade the antibiotic and improve removal efficacy, H_2O_2 was mixed with the produced biochar, which demonstrated the antibiotic removal efficiency of 60 %. The study also suggested that the sulphonamide was stable in the presence of H_2O_2; however, when only biochar was present with H_2O_2, degradation of sulphonamide was observed. These investigations suggest that biochar can be employed for the sustainable removal of antibiotics from different matrices.

5.1.5. Bioelectrochemical systems

Investigators accredited that the oxidation and reduction process occurring in bioelectrochemical systems could indeed stimulate the elimination of antibiotics from wastewater. In a microbial fuel cell (MFC), the anode eliminates antibiotics by co-metabolic deterioration or uninterrupted oxidation, whereas in a microbial electrolysis cell (MEC), the electrons arriving in the cathode are employed for the reduction of antibiotics [153,154]. By integrating the solar photovoltaic capacitor with the algal-bacterial photo-bio electrochemical system (ABPBS) [155], improved the degradation rate of the antibiotic florfenicol by 44 %, 89 %, and 582 % at the anode while using 3.3 F, 10 F and 100 F capacitor, respectively. Further, in another investigation, for the elimination of sulfamethoxazole at varied COD input rates [156], employed both open and closed circuit upflow anaerobic bio-electrochemical systems (UBES) of 2.3 L capacity. The highest sulfamethoxazole elimination rate obtained was 73.7 ± 2.0 % in closed circuit UBES, which was higher than the removal rate obtained in open circuit UBES. Moreover, a double chamber MFC of 200 mL volume was operated at plug flow mode to improve the sulfamethoxazole removal from wastewater and revealed that current density had a vital role in the reduction of antibiotics [144]. In another interesting investigation by Ref. [157], the rate of biodegradation of the antibiotic tetracycline in wastewater was observed to be accelerated by 1.44 times due to the stimulation of acetate in bio electrochemical systems. All these investigations suggest that BESs can be efficiently employed for the removal of antibiotics from wastewater; however, too high a concentration of antibiotics can have a detrimental effect on the biofilm, thus affecting the removal efficacy.

5.2. Antibiotic isolation from soil

Antibiotics in soil have indeed been found in concentrations ranging from 0.5 to 900 μg/kg [158]. Antibiotic levels in topsoil and bottom deposits are greater than that in waters due to adsorption and contact with solid particulates [159]. The antibiotic's bioavailability and bioaccumulation are inversely proportional to its longevity in the soil. All this is due to the fact that soil micro and nanopores aren't big enough in size for enzymes and microbes to diffuse through them [160]. A thorough search of the relevant literature yielded no articles discussing the removal of antibiotics from the soil specifically for India. Instead, articles were found that dealt with the isolation and identification of antibiotics present in the soil. A study conducted in Chennai by Ref. [161] explored three major fluoroquinolones: norfloxacin, ciprofloxacin, and ofloxacin in the soil surface of two huge dumping sites, as well as arid and damp sludge from STPs. The results showed that wet sewage contains two times higher concentrations of fluoroquinolones than dry sludge, implying that the moisture content of these compounds may be a factor in the enhanced level of fluoroquinolones in moist sludge. In another study [162], examined the physical and chemical parameters, and bacterial communities' predominance in soil samples taken from various sites in the Cachar district of Assam, India. All these studies suggest that soil particles have also been exposed to antibiotics, which can ultimately end up in the human body through the food chain. Further, antibiotic resistance in soil microbes is expected to rise and expand exponentially as a consequence of disposing hazardous compounds and illegal industrial dumping that includes heavy metal pollutants and other therapeutic by-products [163]. Therefore, it's important to develop innovative technologies for the removal of antibiotics from various natural matrices so that they don't directly or indirectly affect human health. In this veneration, the different methods available to eliminate antibiotics from water or wastewater and the isolation of antibiotics from the soil are tabulated in (Table 5) and removal efficiency of various antibiotics with specific treatment methods (Table S5).

When it comes to the remediation of antibiotics, several techniques can be employed and each technique has its own merits and suitability depending on the specific scenario. The AD is a potential approach for antibiotic degradation that employs microbes in the absence of oxygen. It has been discovered that it is effective at removing antibiotics from wastewater and could possibly be used in wastewater treatment plants or biogas generating units. However, the specific type and concentration of antibiotics contained may impact its efficacy [179,166]. A further approach for antibiotic remediation is CWs. These systems remediate wastewater using biological processes that exist in wetland habitats. Through the consortium of heterogenic microbial community and the prevailing redox potential wetlands may assist in the removal of antibiotics. For decentralised wastewater treatment in rural regions, CWs are especially appropriate [180,181]. Application of microalgae or macroalgae in either open pond and closed photobioreactors are also capable to purge antibiotic from wastewater which can prove to be sustainable and economical method [182]. Attention has recently been directed to the use of biochar, a carbon-rich substance generated by pyrolyzing biomass, as a viable strategy for antibiotic remediation. By virtue of its extensive surface area and pore structure, biochar may productively remove antibiotics from water by adsorbing them. However, the properties of biochar, including the form of feedstock and pyrolysis temperatures, could influence its effectiveness [183]. By using microbes capable of directly transport electrons to or from an electrode, bioelectrochemical systems (BES) provide a cutting-edge method for antibiotic removal. Through microbial electrochemical reactions, BES could competently degrade down antibiotics, and laboratory-scale investigation has yielded promising findings. To scale up BES for use in real-world scenarios and improve its performance, further research is necessary [184]. Thus, the choice of an appropriate strategy for antibiotic remediation relies on the specific circumstances and demands. When choosing the most appropriate method, factors including cost, treatment capacity, and any specific antibiotic toxins which are present should be taken into consideration.

5.3. Economical aspect and performance of removal methods

The large-scale implementation and acceptability of a technology largely depend on its economic feasibility. Presently, there are limited studies available that correlate antibiotic removal efficiencies with the financial viability of the technology. Water treatment technologies such as absorption are suitable for antibiotic removal from water due to their high removal efficiency, availability, and cost-effectiveness. Various absorbents have shown an impressive 95 % efficiency in removing fluoroquinolones and sulphonamides from groundwater and soil (Table S5). Further, the use of absorbents like chitosan hydrogel costs approximately 3.157 USD per kilogram as an absorbent to efficiently eliminate contaminants such as ciprofloxacin and enrofloxacin [185].

Additionally, the CW technology consistently achieved a high antibiotic removal rate ranging between 24 and 100 % from contaminated water supplied from a freshwater lake. Meanwhile, contaminated freshwater from the lake, treated with advanced treatment methods, showed removal rates of 16–100 %, compared to 3–100 % for conventional treatment methods that were effective for removing selective antibiotics [186]. In addition, technologies like bio electrochemical constructed wetlands (BES-CWs) can achieve antibiotic removal efficiency up to 95 %, while removal efficiency of antibiotics through conventional CWs typically ranges between 70 and 76 %. Furthermore, use of graphite-based anodes in BES-CWs reduced environmental impact by 25 % and lowered installation costs to about 1.4–1.6 % compared to conventional WWTPs. Although graphite electrodes have higher initial costs and can be offset by reduced maintenance costs due to their corrosion resistance [187].

The treatment cost for each unit of wastewater varies with the treatment method used; for instance, technologies such as AD, CW, activated sludge, BES, sequential batch reactor, and biological processes are cost effective compared to the advanced oxidation process. Furthermore, the MBR demonstrated improved performance in removing antibiotics, while the BES exhibits high removal efficiency but requires highly skilled labour to operate. In contrast, CW and activated sludge processes are less cost-intensive; however, antibiotic removal efficiency is also low for these treatment techniques [188]. The removal efficiency of any treatment unit primarily depends on its loading rate, antibiotic concentration, type of antibiotics and physiochemical characteristics of wastewater. In this context, reduction levels observed in COD and nutrients in the CW process indicated that these parameters influenced its characteristics; however, variation in hydraulic retention time didn't affect the removal efficiency. Furthermore, sediments in CW serve as a platform for ARG's growth phase and require changes in design to overcome this issue [189].

6. Global future perspective

The global pharmaceutical market passed the one trillion USD mark in 2014 and continues to grow at the rate of 5.8 %. Similarly, the Indian pharmaceutical industry has seen significant growth in the past four decades, and it's expected to reach a 130 billion USD market cap by the end of the decade [190,191]. Globally, 25 countries, including India, have identified the prevalence of antibiotics and ARGs in estuaries, coastal water, and sediments [192]. The antibiotic residue from the land and inland surface water ends up in the coastal region through the rivers and impacts the aquatic ecosystem with irreversible effects.

High-pollution sources of antibiotics, like livestock and hospitals, have to restrict the spread of antibiotics into the ecosystem by specifying usage levels. The global exchange of knowledge between the WWTPs is appreciated to regulate ARB and ARGs tracking and measurement and improve treatment unit performance. Further, the established WWTPs should be upgraded with advanced treatment processes that are considered effective and economically efficient for removing antibiotics [193]. In addition, advanced treatment methods can remove ARBs and ARGs from water and wastewater, which further prevents their release into the

Table 5
Remediation methods of antibiotics from water and wastewater and isolation of antibiotics from soil.

Wastewater/Soil type	Remediation/Isolation method	Materials/Parameters	Type of Antibiotic removed/isolated	Removal efficiency/Inferences	References
Human faecal sewage	Anaerobic digestion	magnetite nanoparticles	• CIP	CIP with removal efficiency of 67 % with 2-bromoethanesulfonate enriched magnate nanoparticles.	[164]
Raw wastewater from Urban areas	Constructed wetlands	Phragmites australis Typha angustifolia	• AMX • DC • ERY • Clarithromycin • Sulfamethoxazole • Trimethoprim	Clarithromycin upto 50 %, ERY upto 64 %, DC upto 75 %, AMX upto 45 %, sulfamethoxazole upto 60 % and trimethoprim upto 96 % by varying flow type, flow direction and gravel size in CW's.	[165]
Synthetic wastewater	Algae removal	Chlorella and micro-pyrenoidosa	• Cefradine • AMX	Complete removal of AMX and 75 % of cefradine by microalgae between 6 and 24 h of treatment.	[166]
Synthetic urine	Adsorption by biochar	Biochar from cotton straw	Sulphonamides antibiotics	Removal efficiency 49–74 % in phosphate solution	[167]
Synthetic wastewater	Electro-catalytic oxidation technique	Ti/RuO_2 electrodes	AMT	AMT removal efficiency of 60 % and total organic carbon removal efficiency of 34 % in 60 min of electrolysis	[168]
Hospital effluents from seven different hospitals and synthetic effluent	Advanced oxidation process coupled with other treatment technologies (MBR, CW)	• Ozonation (O_3), • Peroxone (O_3–H_2O_2)	• CAR • DIA • OFL • SIM • SOR • ERY • IBU • DIC • FUR	• 100 % elimination of ibuprofen, CAR, FUR by MBR • 100 % elimination of ofloxacin by CW • CAR, DIA, DIC and FUR were completely reduced by ozonation and peroxone process	[169]
Synthetic wastewater	AOPs	• UV light exposure • Treatment via H_2O_2 • UV/H_2O_2 • Modified Fenton process (nZVI particles with varying doses of H_2O_2) • Modified photo-Fenton process (in the presence of UV light)	CIP	• 100 % removal by modified Fenton and modified photo-Fenton processes • nZVI: H_2O_2 (5:1) resulted in complete removal of 99.30 % within 25 min	[170]
Synthetic wastewater	Adsorption method	Natural MMT Ti-PILC	• AMX • IMP • DIC-S • PCM	• Highest removal- IMP by 82.68 % • 82.68 (IMP) > 23.05 (DIC-S) > 20.83 (PCM) > 4.26 (AMX) mg/g at a fixed adsorbent dose, i.e., 0.005 g/mL	[171]
Synthetic wastewater	Adsorption method	MMT-CA-NFM	CIP	76 % removal when MMT-CA-NFM dose and solution pH were 10 mg/L, 4 g/L and 6.0 respectively	[116]
Synthetic wastewater	Novel integrated adsorption cum membrane filtration process	Microfiltration technique using ceramic membrane	• NOR • OFL	Maximum removal of 98.7 % for NOR and 94.61 % for OFL	[172]
Synthetic wastewater	Adsorption and photodegradation	Novel photocatalyst ZnO-GO/NC	CIP	Maximum degradation efficiency of 98.0 %	[173]
Kashmir Himalayan (India) soil	Isolation	• 16 S rDNA sequence-based phylogenetic analysis • Morphological and Biochemical analysis	Streptomyces sp SM01 produces picolinamycin	• Isolated SM01 - antibiotic producer • Overall yield of the purified compound SM1 - 4 mg per litre culture • Picolinamycin- novel compound	[174]
Soil from the Cachar district of Assam	Isolation	• Morphological, Biochemical and 16S rDNA sequence analysis	• Methicillin • Penicillin • Cefdinir • Ampicillin • Kanamycin • Rifampicin • Vancomycin	• Identified metal tolerance such as *Bacillus megaterium*, *Pseudomonas aeruginosa*, *Bacillus cereus* and Chromobacterium *pseudoviolaceum* • Metal-tolerant isolates were mostly resistant to Methicillin and Penicillin	[162]
Synthetic wastewater	Adsorptive removal	Met-GO/SA	FQ antibiotics such as OFL and MOX	Maximum adsorption amounts of 4.115 mg/g for MOX and 3.436 mg/g for OFX	[128]
Municipal wastewater treatment plants (WWTP), city of Haridwar	Biological treatment, Chlorine-based disinfection process	Isolation of FQ-resistant bacteria by replica plating	FQ antibiotics such as CIP, NOR and OFL	• Concentrations of three antibiotics −6 to16 μg/L • 60–90 % removal in the biological unit • 96 % removal of FQ-resistant bacteria through disinfection	[175]
Synthetic wastewater	Adsorption method	BNNSS synthesis as adsorbent	TC, OFL and CFX	Maximum adsorption of 346.66 mg/g (TC), 72.50 mg/g (OFL) and 225.0 mg/g (CFX)	[176]
Pharmaceutical industry wastewater	Vacuum membrane distillation	CNT@ZIF8 impregnated PVDF-co-HFP mixed matrix membrane	• FQ such as CIP, NOR • TC • DC	>99.4 % removal efficiency for all antibiotics	[128]
Synthetic wastewater	Adsorptive removal	• Acid-activated carbon from Prosopis juliflora wood	CIP and AMX in a single and binary system	• In the single system, 250 mg/g for CIP and 714.29 mg/g for AMX • In the binary system, 370.37 mg/g for CIP and 482.14 mg/g for AMX	[177]
Water sample from river Yamuna	Molecular docking		AMX via Amoxicillin-	Alcaligenes sp. MMA removed 84 % of amoxicillin in 14 days	[178]

Table 5 (*continued*)

Wastewater/Soil type	Remediation/Isolation method	Materials/Parameters	Type of Antibiotic removed/isolated	Removal efficiency/Inferences	References
		Antibiotic tests, Biochemical and Molecular analysis	resistant bacteria, Alcaligenes sp. MMA		

Ti/RuO_2-Titanium coated with ruthenium dioxide, AMT-Amoxicillin trihydrate, AOPs-Advanced oxidation processes, AMX-Amoxicillin, CIP-Ciprofloxacin, OFL-Ofloxacin, EC-Electrocoagulation, EO-Electro-oxidation, CAR-Carbamazepine, DIA-Diazepam, DIC-Diclofenac, FUR-Furosemide, MMT-Montmorillonite, IMP-Imipramine, DIC-S-Diclofenac Sodium, PCM-Paracetamol, MMT-CA-NFM-Montmorillonite-impregnated cellulose acetate nanofiber membranes, Ti-PILC-clay pillared with titanium oxide, NOR-Norfloxacin, ZnO-GO/NC-nano zinc oxide incorporated graphene oxide/nano-cellulose, Met-GO/SA-Methionine-Functionalized Graphene Oxide/Sodium Alginate Bio-Polymer Nano-composite Hydrogel Beads, FQ-Fluoroquinolone, OFX-Ofloxacin, MOX-Moxifloxacin, TC-Tetracycline, CFX-Cephalexin, DC-Doxycycline, BNNSS-Boron nitride nanosheets, CNT@ZIF8-CNT functionalized ZIF8, PVDF-co-HFP-Poly vinylidene fluoride-co-hexafluoropropylene, SIM-Simvastatin, SOR-Sorafenib, ERY-Erythromycin, IBU-Ibuprofen.

surrounding environment. Also, to manage the resistance induced by conventional antibiotics, it must be balanced by switching them with advanced futuristic medicines. Redefined nano-structured systems, which are part of nanomedicines implemented in oncology and cancer therapies, are suggested to be a futuristic way of tackling the existing resistance problem caused by antibiotics and ARGs [194].

The incorporation of emerging technologies like blockchain can also find its application in monitoring the supply chain to orchestrate the usage of antibiotics. The technology can also assist in tracing the pathways leading the antibiotics to the environment, which could further ease research applications. Further, the integration of blockchain with the drug supply chain in terms of product identification, tracing, and product verification can assist in enforcing regulations such as restricting unsanctioned antibiotics from coming to the market [195,196]. Similarly, integrating the pharmaceutical supply chain with the electronic healthcare records of the patient through a blockchain can further enhance the efficacy of monitoring and regulating the usage of antibiotics in non-exigent cases. It is essential to establish a mass balance for the inflow and outflow of antibiotics, considering their use and end-of-life disposal to control antibiotic pollution. Further, having information regarding the different antibiotics used in an area can narrow the scope of monitoring for which regular monitoring and data collection play a critical role. Therefore, blockchain can assist in tracking and further eliminating or alleviating the adverse effect of antibiotics on the biosphere.

7. Conclusion

Excessive and unregulated use of antibiotics for medicinal and feed additives has spread the antibiotic residue in the ecosystem. Consequently, their persistence leads to antibiotic resistance in microorganisms through ARGs and ARBs, which eventually reduce the effectiveness of antibiotics as a medicine. In developing countries like India, this problem is more intensified due to the lack of awareness and absence of stringent guidelines for the antibiotic usage. Various technologies can remove antibiotic strains from environmental matrices; however, their field applications are rare. Furthermore, there is a dearth of investigations on the social and economic impacts of these technologies. Therefore, the mass awareness program combined with the application of stringent regulations for the safe use of antibiotics, including factors like withdrawal period and recommended dosage for humans, veterinary, and livestock, are required to bring down the residual antibiotic concentration below acceptable limits. Finally, technologies proven on lab-scale need to be tested in field conditions to evaluate their practical applicability and operational challenges in the real environment before their commercialization.

Data availability statement

Supporting data that is linked with our manuscript is available in the supplementary data file. However, other data sets like raw data tables will be provided on request to the corresponding author.

Ethical approval

The authors declare that this study does not involve animals.

CRediT authorship contribution statement

Mithuna R: Writing – review & editing, Visualization, Software, Methodology. **Tharanyalakshmi R:** Writing – review & editing, Visualization, Software, Methodology. **Ishan Jain:** Writing – original draft, Project administration, Methodology. **Shivangi Singhal:** Writing – original draft, Project administration, Methodology. **Divyanshu Sikarwar:** Writing – review & editing, Validation, Software, Formal analysis, Data curation. **Sovik Das:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **J. Ranjitha:** Writing – review & editing, Visualization, Validation. **Devanita Ghosh:** Writing – review & editing, Visualization, Validation. **Mohammad Mahmudur Rahman:** Writing – review & editing, Methodology. **Bhaskar Das:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Dr. Bhaskar Das reports were provided by the Vellore Institute of Technology. Dr Bhaskar Das reports a relationship with Vellore Institute of Technology that includes: employment.

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Appendix A. Supplementary data

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