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Review Article

A Review of Veterinary Antibiotic Pollution in the Agro-Environment of Pakistan: Alarm Bells Are Ringing

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Abstract

Veterinary antibiotics (VAs) are widely used in Pakistan for growth enhancement, production, and in the prevention and treatment of infectious diseases in the livestock and poultry industry. Their emergence into the agro-environment began during the resource utilization of farmyard and poultry manure. However, these bioactive organic pollutants are non-degradable in the natural environment and can be uptaken by plants, eventually ending up in the human food chain. Despite the danger these antibiotics pose, unfortunately, it is an issue that still remains underreported, especially in Pakistan. As such, this review critically summarizes the current consumption, exposure pathways, strategies for controlling dissemination, and serious environmental concerns associated with VAs. Additionally, the fate of antibiotics in the dry arid climate of Pakistan is thoroughly explained along with the lack of monitoring and strict legislation in developing countries. It is reported that antibiotic consumption negatively impacts raw manure, hence suggestions such as limiting the consumption of antibiotics from the source, proper disposal of farmyard manure with effective technologies, and remediation techniques are introduced. Finally, the authors highlight the importance of farmer's education and awareness campaigns in the pollution control of antibiotics, as the problem can only be properly addressed with the cooperation of government agencies, companies, and involved stakeholders.

Keywords: Farmyard manure; Antibiotics; Environmental pollution; Soil matrix; Strategies

Introduction

'Antibiotics' are termed as organic substances that are either extracted as byproducts of secondary metabolism of fungi, actinomycetes and bacteria or are prepared in pharmaceutical industries to counter the pathogenic microorganisms in living biota (Thiele-Brun and Peters 2007; Alduina 2020). Many antibiotics are widely used in feed as additives or injected in the blood (Zhu *et al.* 2017). In relation to that, veterinary antibiotics (VAs) have been utilized for the last seven decades, with their consumption increasing daily (Kuppusamy *et al.* 2018). To fulfil the requirements of meat and milk, the livestock industry is exponentially growing, and with the increase in the number of animals, the risks of animal infection and prevalence of pathogenic microorganisms increase as well (Selaledi *et al.* 2020). It is estimated that, in 2030, the usage rate of VAs will increase a hundredfold (Boeckel *et al.* 2015), with the concentration of these antibiotics consequently growing exponentially in agricultural soils, surface water, as well as in groundwater resources (Hu *et al.* 2010). The livestock industry's irrational consumption causes the release of 30–90% of antibiotics as parent compounds or as secondary products. Such excretions must be monitored carefully, as these are the primary cause of antibiotic pollution (Benarab and Fangninou 2020). Chen *et al.* (2019) reported that nearly 70 kinds of antibiotics were detected in the agricultural environment. Current evidence suggests that a high concentration of antibiotics interferes with genes' functionality and imposes severe concerns on the genetic sequences. There are several entry channels of these antibiotics, with the most crucial route occurring through the food chain, and this is directly linked to manure utilization in agricultural lands (Coyne *et al.* 2020). The intake of these

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antibiotics through the food chain imposes a potential threat to the human body's cell functioning and gut microbiota (Francino 2016). Furthermore, due to the misuse or overuse of antibiotics in Pakistan, a large number of the population develops antibiotic resistance (Saleem *et al.* 2020). In fact, this has become an issue plaguing many nations as, around the world, it has been reported that drug resistance-related diseases caused 700,000 deaths per annum (Alduina 2020).

Most studies only indicate the situation in developed countries, with reports considering developing countries, such as African and some Asian countries' ecological health, unavailable (Selaledi *et al.* 2020). Moreover, research publications collating the regulations and counter-strategies to cope with antibiotic pollution in the food chain of developing countries are very limited or unavailable, and no critical reviews have been conducted to compare and elaborate the impact of antibiotic pollution. Due to this, monitoring and controlling the prevalence of antibiotics, antibiotic-resistant genes, and corresponding microbial communities are necessary to protect the agro-ecosystem and consumers (Du and Liu 2012). Similarly, a thorough understanding of this newly emerging pollutant is required to predict and minimize its spread. Above all, the prime objectives of the current review are to discuss the following key points: (1) the use and abuse of antibiotics in the developing world with prime focus on Pakistan, (2) reservoirs of veterinary antibiotics, (3) the fate of antibiotics in the soil matrix, and (4) strategies to counter the effects of the emerging pollutant.

Use and Abuse of Antibiotics in the World and Pakistan

Globally, it is reported that 63,000–240,000 tons of antibiotics are consumed per annum, and by 2030, it is projected there will be a nearly 67% increase in the consumption of antibiotics (Tasho and Cho 2016). The annual global consumption of veterinary antibiotics in developed and underdeveloped countries is presented in Table 1. According to research, China leads in antibiotic consumption (Hu *et al.* 2010; Cycoń *et al.* 2019), with other developed countries, such as Germany and the USA, consuming tons of veterinary antibiotics as well (Du and Liu 2012).

Pakistan has a vast livestock and poultry market. It is estimated that the country has nearly 67.3 million large ruminants, 89.6 million small ruminants, and 1,230 million poultry (Rahman 2019). Pakistani farmers commonly transplant rice in standing water, and under these circumstances, there are significant chances of antibiotic leaching. Stoob *et al.* (2007) reports that wet conditions increase the leaching ability of VAs up to 15 times more than dry conditions. At the root cause of the issue are the indiscriminate and extensive use of antibiotics for the production of milk and meat along with the widespread availability of over-the-counter (OTC) medications that do not require a prescription. Furthermore, potent drugs against infectious diseases are misused by untrained veterinary doctors, uneducated local farmers, and fraudulent medical practitioners (Ali *et al.* 2020). However, due to the lack of surveillance and resources, there are no exact or estimated public reports about the consumption of VAs in Pakistan (Rahman 2019; Saleem *et al.* 2020).

Reservoirs of Veterinary Antibiotics

Land application of livestock waste is a common practice around the world, and it is the primary entry route of antibiotics in the agro-ecosystem (Fig. 1). In developed countries, the farmyard manure is treated before its application on agricultural soil. In Pakistan, the soils are impoverished in organic matter content (1.29%). Due to farmers' miserable economic conditions and as a means to enhance agricultural soils' fertility status, 49% of farmyard manure is used as organic fertilizer and directly disposed of on land (Rahman 2019). Slaughterhouses are widespread in Pakistan, and nearly 8,000 tons of blood meal is produced annually to serve as a soil conditioner. Furthermore, due to the incomplete assimilation in an animal's gut, several kinds of antibiotics are also generated as liquid waste (Table 2). Therefore, several studies have been conducted worldwide to determine and control antibiotic dissemination in freshwater and wastewater effluents (Wei *et al.* 2011; Du and Liu 2012). Kumar *et al.* (2005) investigated the antibiotic concentration in manure slurry and reported up to 216 mg L^{-1} of antibiotics. In another study, it has also been reported that 50–60% of antibiotics are excreted as the parent compound or as an active metabolite in urine (Feinman and Matheson 1978). Fick *et al.* (2009) thoroughly investigated several antibiotics in wastewater effluents discharged by pharmaceutical companies and found a very high concentration of quinolones (14 mg L^{-1}). Hamscher *et al.* (2002) investigated the influence of liquid waste material and reported tetracycline concentrations of 172 mg kg^{-1} at 20–30 cm depth of soil. This illegal discharge of hazardous compounds pollutes freshwater reservoirs and local communities. Afterwards, livestock wastewater gets mixed with sewage water, where it becomes a sink of antibiotics. Antibiotics in the dissolved or liquid form get transformed back to the parent compound; however, in the process, some antibiotics become inactive and are conjugated as acetylated metabolites (Christian *et al.* 2003; Chen *et al.* 2017). Due to the scarcity and high cost of freshwater, the farmer community generally disposes of or uses wastewater for irrigation purposes. Over time, the continuous dumping of solid livestock waste, unprocessed sewage water, and treated wastewater for irrigation becomes the primary reason for the buildup of heavy metals and VAs in the agricultural lands (Sardar *et al.* 2018). Owing to high mobility and leaching capacity, liquid waste is considered more dangerous than dry manure.

Table 1: The annual global veterinary antibiotic consumption in developed and underdeveloped countries

Country	Consumption per annum (tons)	Reference(s)
Australia	932	(Kim *et al*. 2010a, b)
Brazil	2225	(Kim *et al*. 2010a, b)
China	210,000	(Hu *et al*. 2010)
Denmark	105	(Du and Liu 2012)
France	764	(Du and Liu 2012)
Germany	1900	(Tasho and Cho 2016)
India	1890	(Hu *et al*. 2010)
Iran	1178	(Hu *et al*. 2010)
Italy	662	(Hu *et al*. 2010)
Japan	524	(Hu *et al*. 2010)
Norway	6	(Kim *et al*. 2010a, b)
Russia	915	(Hu *et al*. 2010)
South Korea	1278	(Du and Liu 2012)
Spain	343	(Hu *et al*. 2010)
Sudan	675	(Hu *et al*. 2010)
Sweden	16	(Kim *et al*. 2010a, b)
Turkey	1195	(Hu *et al*. 2010)
UK	308	(Kim *et al*. 2010a, b)
USA	14,600	(Du and Liu 2012)

Table 2: The occurrence of veterinary antibiotics in different sources of livestock wastewater

Source(s)	Compound	Concentration	Reference(s)
Liquid Livestock manure	Chlortetracycline;	0.03–183 mg L^{-1}	(Hu *et al*. 2010)
Pig effluent	Chlortetracycline;	157 mg L^{-1}	(Popova *et al*. 2017)
Animal wastewater	Sulfadiazole	2.3–211 μg L^{-1}	(Wei *et al*. 2011)
Slurry from pig farm	Sulfachloropyridazine	703 μg L^{-1}	(Kay *et al*. 2005)
Swine wastewater	Sulfonamides	685.6 μg L^{-1}	(Cheng *et al*. 2018)
Swine wastewater	Norfloxacin	0.28 μg L^{-1}	(Zhu *et al*. 2020)

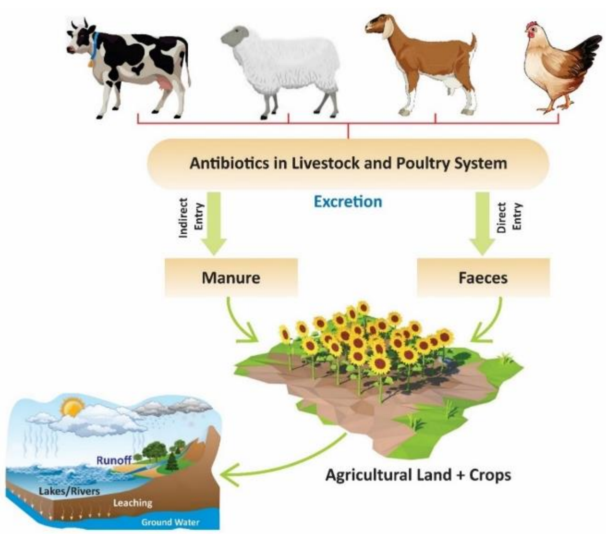

Fig. 1: Modes of entry of VAs into the agro-ecosystem through livestock and poultry

Fate and Consequences of Veterinary Antibiotics in the Soils of Pakistan

Once the antibiotics enter the soil matrix, they are prone to sorption/desorption or sequestration, transportation (leaching and surface runoff), transformation (biotic and abiotic), and uptake by the plants (Grossberger *et al.* 2014; Kuppusamy *et al.* 2018). The fate of antibiotics in an environment mainly depends on polarity, hydrophobicity, and the antibiotics' water-solubility properties (Christou *et al.* 2017) as well as on physicochemical properties of soil such as pH, cation exchange capacity (CEC), mineral ions, soil or dissolved organic matter contents, soil structure, and texture (Vasudevan *et al.* 2009; Wu *et al.* 2013; Park and Huwe 2016).

Mineralogy of Pakistani Soils

Pakistan's climatic conditions are dry arid with long hot summers and short, mild winters. The soils lack organic matter and are alkaline with pH levels ranging between 8.35 and 9.05 (Ahmad *et al.* 2020). Soils of this region mainly possess kaolinite, mica, vermiculite, and smectite type minerals. These minerals determine specific chemical characteristics of soils. For example, kaolinite-dominated soils have low CEC, whereas soil with a high amount of vermiculite retains high CEC. These factors are known to influence the dissemination of organic pollutants, such as antibiotics.

Sorption/Desorption/Sequestration

Antibiotics entering the soil with manure application remain mostly on the soil surface (Aust *et al.* 2009; Ostermann *et al.* 2013). The adsorption and desorption mechanisms are observed with non-polar and neutral antibiotics, whereas the polar and ionizable antibiotics remain in the soil solution (Thiele-Bruhn *et al.* 2004; Wegst-Uhrich *et al.* 2014). For instance, sulfathiazole and sulfamethazine (which are neutral/cationic nature in a soil solution) express their high sorption affinity with ionic soil surfaces at pH levels lower than 7.5 (Kurwadkar *et al.* 2011). Divalent cations in soil form complexes with tetracycline (Hamscher *et al.* 2002), hence, the type of cations in the soil also controls the adsorption of Vas (Fig. 2). The sequestration of VAs into micro or nanopores with aging also decreases their bioavailability and bio-accessibility, albeit a certain amount remaining in the soil system (Forster *et al.* 2009). For the time being, the acute toxicity of VAs is reduced due to this process; however, sequestration is a reversible process that later releases sequester VAs back into its bioavailable form (Zarfl *et al.* 2009). Permanent unavailability of VAs occurred with the physical diffusion of these antibiotics into soil organic matter, oxides, or clay interlayer nanopores and with the formation of enzymatically catalyzed covalent bonds (Gulkowska *et al.* 2013; Jechalke *et al.* 2014).

Runoff/Leaching

Transportation of antibiotics occurs either via surface water bodies or groundwater aquifers when they dissolve in the soil solution (Alder *et al.* 2001; Davis *et al.* 2006). Soil pH plays a prominent role in the runoff and leaching of antibiotics. The charge of dissociating functional groups changes, with the pH of the soil fluctuating and consequently influencing the transport behavior of VAs. Since the pH of Pakistani soil is mostly alkaline or above 7.5, leaching of the negatively charged antibiotics (*e.g*., sulfonamides) can increase (Kurwadkar *et al.* 2011; Strauss *et al.* 2011). In another research, weakly acidic antibiotics (*e.g*., naproxen) were found to be present in the soil solution, and this kind of antibiotic exhibited high movement due to the dissociated carboxylic functional group (Schaffer *et al.* 2012).

Low soil organic matter contents (<1%) might enhance the mobility of antibiotics in Pakistani soil. It is reported that as soil organic matter increases, the sorption of antibiotics increases while the mobility decreases (Borgman and Chefetz 2013). On the other hand, an increase in dissolved organic matter content enhances VAs' mobility (Kulshrestha *et al.* 2004). It is reported that well-plowed soil amended with manure highly prevents the transport of VAs to groundwater, because small macropores play a key role in controlling the movement of VAs in soil (Kay *et al.* 2005). Antibiotics are easily transported from one part of the manure or wastewater applied field to the other or nearby water bodies due to flood irrigation, which is the well-practiced irrigation method in Pakistan. The transport of antibiotics also occurs with shared farm machinery and wind erosion (Dalkmann *et al.* 2012).

Transformations

The primary remediation mechanisms of antibiotics involve adsorption, biodegradation, hydrolysis, and volatilization (Gurmessa *et al.* 2020). Veterinary antibiotics like β-lactams, macrolides, tetracyclines, fluoroquinolones, and trimethoprim mainly follow the adsorption mechanism, whereas sulfonamides type antibiotics are generally removed along with the biodegradation mechanism (Li and Zhang 2010; Jia *et al.* 2018; Sui *et al.* 2018; Zhang and Li 2018).

Impact on Microbial Diversity

The microbial community structure holds great potential to sustain and improve soil productivity and partially cope with food security and soil degradation (National Academies of Sciences, Engineers and Medicine 2018). Singh and Trivedi (2017) stated that microbes are responsible for soil and crop productivity's essential functions. Indeed, bacteria play a crucial role in the supply of macro and micronutrients through host-specific interactions (Lehto and Zwiazek 2010). However, microbial activity and efficiency directly depend on the environmental conditions; soil microflora, bacterial communities and other microorganisms face severe threats due to the accumulation of bioactive hazardous substances (*e.g*., antibiotics) in soil (Cycoń *et al.* 2019). Prolonged exposure to these antibiotics leads to the development of resistance in the soil's microbial community, which eventually affects the resident's health. The toxicity due to these antibiotics can also impart changes in the normal functioning of bacterial and microbial populations. Ultimately, these antibiotics result in the death of essential microbes that provide nutrients, imbalance in the community structure, and increased occurrence of several types of antibiotic-resistant genes (Knapp *et al.* 2011). In addition to soil microbial communities, farmyard manure laden with antibiotics also significantly impacts microbial communities in crop plants (Cycoń *et al.* 2019). Animal manure is a primary source of ARBs in the soil matrix, and most of the species are reported as human pathogens (Yang *et al.* 2013). In relation to that, the application of animal manure disturbs the proportion of endophytic bacterial populations in crops (Zhang *et al.* 2013). Similar results were reported in another study that cattle and poultry manure could enhance the abundance of antibiotic-resistant genes in root endophytes (Zhang *et al.* 2019).

In the context of environmental conditions, soil properties are of utmost importance. Along with other physicochemical factors, soil texture is relatively vital, due to the role it plays in the survival of fecal bacteria in agricultural soils (Franz *et al.* 2014). Antibiotics have a varied correlation with microbial structure across several textural classes, and it is imperative to understand the influence of antibiotic consumption and excretion along with its correlation to the indigenous microbial community.

Entry of Veterinary Antibiotics in the Food Chain

Irrational and repetitive disposal of farmyard manure laden with antibiotics may ultimately build up concentration high enough to enter the terrestrial environment as an active hazardous substance (Bassil *et al.* 2013). Because this is the first entry channel of antibiotics in the animal and human food chain, the possibility of bio-accumulation and bio-magnification of VAs at this stage cannot be ignored (Fig. 3). Previous studies reveal that oxytetracycline, chlortetracycline, penicillin, and sulfamethazine have moderate bio-accumulation potential (Thiele-Brun and Peters 2007), while tylosin, monensin, bacitracin, and virginiamycin have low bio-accumulation potential (Luby *et al.* 2016). Different plant organs and tissues have different responses to the toxic effect of these antibiotics, with their response depending on the concentration of antibiotics and exposure time. Hillis *et al.* (2011) conducted a detailed investigation and reported that lower antibiotic concentration enhances nodes and internodes' growth, while cotyledons and roots showed a negative growth response.

Chitescu *et al.* (2013) reported that root crops are more prone to antibiotic accumulation, as they directly contact soil and farmyard manure. The uncontrolled raw manure

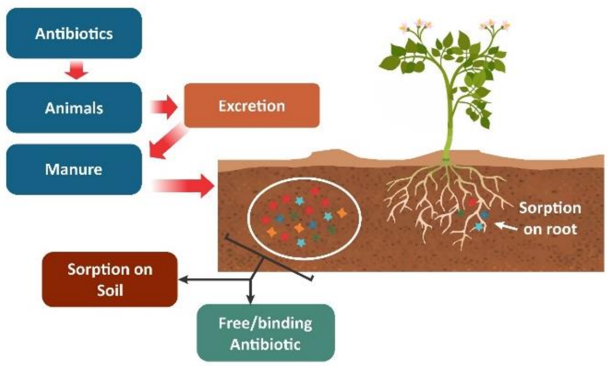

Fig. 2: Sorption behavior of veterinary antibiotics in the soil matrix

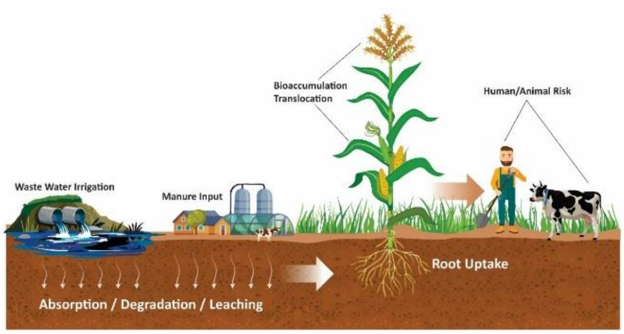

Fig. 3: Possible pathways of veterinary antibiotics in the soil and food chain

application threatens the safe production of staple foods such as potato, millet, wheat, and corn. Recent studies have also revealed the possible molecular level impact of antibiotics on plants' metabolic functioning (Zhang *et al.* 2020). Minden *et al.* (2017) investigated the woody plants' remediation potential and highlighted that such plants could restore the antibiotic polluted soils.

Strategies to Counter Veterinary Antibiotic Pollution

The potential outcomes of antibiotic and corresponding resistant gene pollution cannot be ignored. Regulations and strategies must be adopted to reduce the deterioration of the agro-ecosystem. Targeted awareness companies can reduce this emerging pollutant entry in soil, plants, and the food chain. Nonetheless, it is important to note that these strategies can only be adopted if governments provide financial support to poor and uneducated farmers, as such financial benefits will provide them with the necessary resources and encourage them to adopt farm level strategies and cooperate with the legal authorities.

Proper Disposal of Farmyard Manure

The proper disposal and recycling of farmyard manure is also an important area to be determined, and it should be cost-effective and easy to adopt by farmers and other stakeholders. At the commercial scale, millions of tons of livestock waste are generated annually, and its disposal would require enormous resources, necessitating the implementation of policy plans by governments and local administrations on the utilization and safe disposal of this organic waste. Numerous reports have been published about the aerobic techniques to counter antibiotic pollution, and these techniques are claimed to be highly (> 99%) efficient (Ho *et al.* 2013; Song *et al.* 2020).

Physiochemical Strategies

There are several conventional and advanced techniques to control antibiotic pollution and corresponding resistant determinants in the agro-environment.

To deploy the advanced treatments, we recently conducted a series of experiments using ultraviolet (UV) radiation against antibiotic-resistant bacteria in biologically treated wastewater. The wastewater samples used in our previous study were collected from a cyclic activated sludge system. As a disinfectant of treated wastewater, UV radiation substantially impacted phenotypes and genotypes of antibiotic-resistant bacteria. We found that the proportion of Gram-positive and Gram-negative bacteria varied with UV fluence (Zhang *et al.* 2019).

Strong oxidizing agents are one of the newly adopted strategies, since the ozone can oxidize several classes of organic materials (Nakonechny *et al.* 2007). A recent study by Chu *et al.* (2020) showed favorable results on cephalosporin's remediation (β-lactam class). In this study, ozonation, irradiation, and heat treatment were used for degradation, and ozone showed 79.9% removal efficiency, while 85.5% by radiation; 71.9 and 87.3% by heat treatment at 60 and 90°C for 4 h, respectively. However, a major disadvantage of ozonation is its high cost, need for equipment, and gross energy consumption.

Fenton's reagent is a demanding technique among the various oxidation processes due to its strong oxidizing efficiency (Gan *et al.* 2009). Moreover, Photo-Fenton and Fenton procedures have a higher antibiotic removal percentage than the traditional Fenton procedure. Rozas *et al.* (2010) achieved complete removal of ampicillin at 3 and 10 min for photo-Fenton and Fenton, respectively, by adjusting different variables like Fe^{2+} concentration (87 mol/L), H_2O_2 (400 mol/L) and pH (3.5).

The photolysis involves direct and indirect use of light to decompose organic effluent into intermediates, which in turn can be hydrolyzed into non-toxic end products (Lofrano *et al.* 2017). Despite photolysis being more economical than other methods, it can only be useful for freshwater containing light-sensitive compounds. Apart from that, the process' efficiency is strongly dependent on the nature, pH, and fate of antibiotics (Shi *et al.* 2020).

The Electrochemical (EC) disinfectant technique is comparatively easier to adopt and apply, and it is known to work without the requirements of chemicals and complicated procedures. Therefore, in our previous work, we conducted a laboratory-scale EC experiment to explore the wastewater's antibiotic-resistant status and investigated various antibiotic drugs: tetracycline, sulfadiazine, penicillin, erythromycin, vancomycin, gentamicin and chloramphenicol ofloxacin and ciprofloxacin. It was found that EC disinfection decreases the relative abundance of antibiotic-resistant genes, thus, proving to be a promising technique to control antibiotic dissemination (Li *et al.* 2019, 2020).

Adsorption

Adsorption is an easy method for removing organic compounds, but it has not been widely proven to eliminate antibiotics (Yu *et al.* 2016). Based on the forces involved, adsorption can be categorized as physical and chemical. The most common adsorbents used to remove antibiotics are clay mineral, biochar, carbon nanotubes, bentonite and activated carbon. Méndez-Díaz *et al.* (2010) achieved approximately 90% removal efficiency of sulfonamides and imidazoles by using activated charcoal as an adsorbent. Similarly, by batch and continuous techniques, trimethoprim was maximum (Kim *et al.* 2010a, b). Kim *et al.* (2014) used single and multi-walled nanotubes to absorb sulfamethoxazole and lincomycin and found that single-walled nanotubes were more efficient at adsorbing pollutants. Hence, due to its low cost, high yield, and lack of hazardous byproducts, it is well adapted for the separation and disposal of antibiotics. In contrast to the specific methods described above, adsorption can also be applied to water that contains a high proportion of antibiotics or organic matter, with the disadvantage being that these are only removed and concentrated.

Several membrane processes are commonly used in various applications, with this method permitting separation and concentration by transferring it to the membrane. Reverse osmosis, ion exchange, nanofiltration, ultrafiltration, and combined processes have been used to achieve the goal of separating antibiotics through membrane processes. Combined and hybrid methods are the most efficient for application at the industrial level. Therefore, integrated processes were used. In the case of degradation in which most microorganisms are sensitive to certain chemicals or mechanisms, combined methods must be used. Similarly, advanced oxidation processes must also be used as a pre-treatment process in which organics or contaminants are pre-treated to convert them into less toxic substances that can be easily broken down and disposed of (Homem and Santos 2011). A combination of Fenton and reverse osmosis was used to remove amoxicillin (Elmolla and Chaudhuri 2010). Although this method is an effective and potential technique, it is not used to remove antibiotics due to its complexity.

Biological Pathways of Antibiotic Degradation

The scientific community has adopted biodegradation due to its low cost, ease of operation, and absence of toxic byproducts generated. The biological degradation of antibiotics can be achieved with plants, biocatalysts, and microorganisms, each of which has its own advantages and disadvantages in the effective removal of antibiotics. The outcome of these processes depends on factors such as temperature, pH, and structure.

Composting

Composting includes a series of manure management activities that use microbial processes to aerobically decompose organic matter, stabilize waste, and reduce pathogens and odors. In some cases, organic materials such as dried leaves and sawdust are mixed with manure pile to balance the carbon and nitrogen ratio and improve aeration and nutritional status. The compost can also be turned to increase the utilization rate of oxygen in a pile (USDA 2009). During composting, the temperature of the manure pile is increased by microbial processes. However, manure incubated at a lower temperature shows less treatment efficiency. Hence, antibiotic treatment is attributed to temperature-dependent abiotic processes such as adsorption and degradation. Kim *et al.* (2012) noted that compounds produced during composting by microbial processes formed complexes with antibiotics (sulfamethazine, chlortetracycline, and tylosin). In several studies, the lower removal efficiency was reported for ciprofloxacin (Selvam *et al.* 2012), sulfamethazine, monensin (Dolliver *et al.* 2008) chlortetracycline (Bao *et al.* 2009).

The collective effect of different antibiotics is primarily responsible for the enrichment of antibiotic resistance in conventional composting (Song *et al.* 2020). Our recent research article has thoroughly investigated the role of conventional composting in the degradation of commonly used veterinary antibiotics (*e.g.*, lincomycin, chlorotetracycline, sulfamethoxazole, and ciprofloxacin). To ensure the comparability of results, 50 mg/kg was selected as a uniform concentration of each antibiotic. We found that ciprofloxacin had a more significant influence on the physicochemical and biological characters of compost. The antibiotics were gradually degraded in all the treatments; even so, the degradation rate was lower in a treatment comprising a mixture of antibiotics.

However, conventional composting cannot efficiently control antibiotics, antibiotic-resistant genes, nor antibiotic-resistant bacteria. Several classes of antibiotics (*e.g.*, tetracyclines and sulfonamides) remain high in the final compost. Indeed, the impact of composting is still unclear, requiring further comprehensive investigation. To explore the composting process and its stage-specific effect on antibiotics, we conducted temperature-programmed aerobic composting and found that the controlled thermophilic

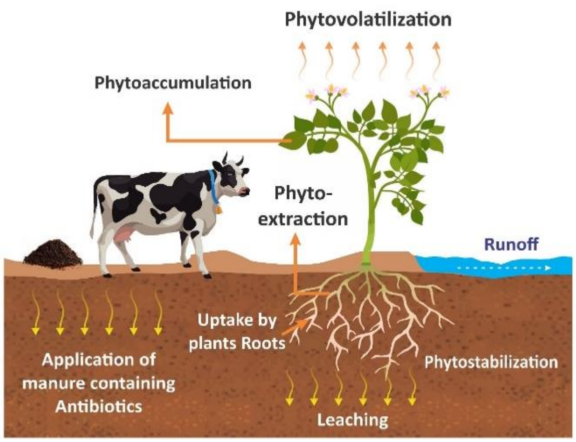

Fig. 4: Various approaches for phytoremediation of VAs

phase increased the degradation of sulfamethoxazole, while the abundance of ARGs was reduced. Temperature reduction enhanced ARGs, which may be due to the rebounding of potential carriers. Furthermore, controlled composting was still insufficient to counter these newly emerging pollutants, and optimization of operational conditions was suggested (Sardar *et al.* 2021).

Anaerobic Digestion

Anaerobic digestion is a two-step process in which part of the organic manure is first hydrolyzed and then changed into volatile fatty acids by acid-forming bacteria (Macias-Corral *et al.* 2008). The methanogenic bacteria then convert volatile fatty acids into methane (Macias-Corral *et al.* 2008). Several studies have been conducted for antibiotic removal by anaerobic digestion from farmyard manure (Arikan *et al.* 2006; Arikan 2008; Mitchell *et al.* 2013) and swine manure (Stone *et al.* 2009). Sara *et al.* (2013) reported that antibiotic biodegradation efficiency increased by thermal pre-treatment before anaerobic digestion.

Phytoremediation of Veterinary Antibiotics

Plants are the natural sink of environmental contaminates and hazardous substances (Tasho and Cho 2016) and so, VAs that are laden in the soil from livestock waste are taken up by plants (Bassil *et al.* 2013). This continuous exposure leads to bioaccumulation and eventually phytotoxicity to the crops. A schematic mechanism behind phytoremediation is presented in Fig. 4. The accumulation of these antibiotics is dependent on the concentration and exposure time (Pan and Chu 2017). Generally, plants grown on humus-deficient soils have a high affinity to accumulate antibiotics (Chen *et al.* 2019), with several plant species tested and shown to bioaccumulate the antibiotics (Bassil *et al.* 2013; Chitescu *et al.* 2013; Minden *et al.* 2017). Bao *et al.* (2016) investigated the ability of green pepper, potato, sweet potato, Chinese cabbage, lettuce, carrot, bitter melon, and white gourd to accumulate different classes of sulfonamide drugs. Phytoremediation techniques should be adopted to make the soil safe and reliable, but to adopt such remedial strategies, a compromise may be needed for the resources and economic constraints of farmers. Additionally, there would be a financial burden on stakeholders. Therefore, such programs should be adopted with the support of the government and other administrative agencies.

Regulated Consumption of Antibiotics

The problem with the consumption of VAs in the livestock industry and the disposal of farmyard manure in agricultural fields is well known, but there is a lack of monitoring and legislation implementation. Large scale consumption of VAs for growth enhancement, milk, and meat production is strictly banned in South Korea and China. However, developed countries such as China, USA, and European countries consume these antibiotics, with the production of such VAs still prevalent (Wu *et al.* 2019).

Many countries have improved legislation and banned unnecessary licensing. This could be an excellent strategy to controlling the dissemination of VAs, but dealing with the removal of licensed antibiotics and its popularity among the farmer communities remains a challenge.

Another possible way is to focus on infectious diseases and specify a particular antibiotic's type and dosage. Administrative and medical authorities should carefully examine the animal and prescribe antibiotics only when absolutely necessary (Tasho and Cho 2016; Xue *et al.* 2019). Farmers and medical workers should record prescribed medicine, and administrative agents should regularly monitor their dosage and record (Ali *et al.* 2020).

Awareness Programs

Developing and underdeveloped countries have a vast number of uneducated and poor farmers. Awareness on the proper disposal of waste, environmental pollution, safe production, and effects on human health is limited (Buelow *et al.* 2020; He *et al.* 2020). To efficiently control environmental pollution issues, especially antibiotic pollution, all solutions must begin with education. Both the government and private sector should be called upon to develop awareness campaigns to educate stakeholders such as influential scientists, young researchers, and educated farmers on the use and abuse of antibiotics and train them to properly treat the livestock waste on their lands.

Concluding Remarks

Although the fertility status of soil is dependent on the application of farmyard manure, it is evident from the current review that antibiotic consumption can negatively impact raw manure. Thus, this source of antibiotic pollution must be addressed. A useful strategy would be the implementation of a ban on the misuse of drugs. As proposed in this review, the scientific community and government agencies should develop policies and legislation to counter and restrict this emerging issue. Awareness campaigns must be launched at a large scale to ensure the human and animal food chain's safety and to control environmental pollution. All these are crucial to solving the underreported issue in developing countries like Pakistan.

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Author Contributions

Conceptualization, MFS and HL. Graphics: BA, SS and AA. Investigation: MFS, AAQ, MZR, ZW and HRA. Writing, original draft preparation: MFS and HL. Review and editing: MFS, CZ and HL. Funding acquisition: CZ, XL and HL. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

There is no conflict of interest among the authors

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Not applicable

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