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Harnessing Plants for Ciprofloxacin Pollution: A Green Approach

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ABSTRACT

Antibiotic pollution is a major environmental risk that is contributing to the emergence of antibiotic resistance and threatening public health. This review addresses the sources of antibiotic contamination, focusing on ciprofloxacin, a commonly used human & veterinary antibiotic. Some of the main sources are pharmaceutical manufacturing, agricultural runoff, hospital discharges, and improper medication disposal, which lead to a significant cause of increase in environmental antibiotic levels. Ciprofloxacin has been found in various environmental matrices, such as soil, water, and sediments, with concentrations varying at both Indian and global levels. The review discusses phytoremediation as an effective, green approach for eliminating antibiotics from the environment. Various plant species have shown the capacity to absorb and degrade ciprofloxacin, decreasing the amount of the antibiotic in the surrounding environment. The goal of this review is to evaluate phytoremediation as a potential mitigation method for ciprofloxacin pollution and to comprehend the extent of this pollution.

Keywords: Antibiotic; Antibiotic resistance; Ciprofloxacin; Phytoremediation

1. INTRODUCTION

Soil is one of the major components of the environment essential for supporting life. The continuous release of harmful chemicals, fertilizers, industrial and pharmaceutical waste has led to the depletion of the soil ecosystem. Lately, the usage of antibiotics for treating infectious and harmful diseases in humans, animals, and livestock has increased globally. According to Van Boeckel[1], *et al.* (2015) by the year 2030, the consumption of antibiotics will increase by 67 % in some of the major countries including India. Depending on the class of antibiotics, around 40-90 % of the administered antibiotics reach the environment. In today's healthcare, antibiotics are frequently used agents for treatment. In just over a century, antibiotics have profoundly changed modern medicine and extended human longevity by 23 years[1]. Antibiotics are compounds intended to target bacteria with the purpose of preventing and treating bacterial illnesses. They hinder bacterial cell division or alter essential cellular functions within the cell, which ultimately leads to the bacterial cell's destruction. According to their in vitro effects on bacteria, antimicrobial drugs are divided into two broad categories: bacteriostatic and bactericidal. Bactericidal antibiotics such as Aminoglycosides, Beta-lactams, Fluoroquinolones, and glycopeptides, etc. "kill" the bacteria whereas bacteriostatic antibiotics such as Tetracyclines, Sulfonamides, Macrolides, and Oxazolidinones, etc. "prevents the growth" of bacteria[2].

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Antibiotic pollution in the environment has become a significant issue as a result of its potential threat to humans, plants, animals, and microorganisms. It is one of the most harmful pollutants to the environment. The constant release of even a small amount of antibiotics into the soil and water could result in the emergence of resistance in the various living organisms[3]. Antibiotics present in the environment at low concentrations also accumulate in human bodies through long-term exposure. The majority of antibiotics are excreted in their unmetabolised form because they are not completely metabolised by the body. They then reach soil and water through manure, sewage wastewater, and biosolids. Antibiotic contamination causes the depletion of microbial communities which includes various bacteria responsible for essential ecological functions[4]. It also results in changes in the water and soil properties such as pH, nutrients, and moisture. Increasing antibiotic pollution leads to various toxic impacts on humans, plants, and animals. The main causes of antibiotic resistance are typically attributed to drug overuse and misuse. Antibiotic pollution can have detrimental effects on human health and contribute to the emerging global health risk of Antimicrobial Resistance (AMR). Antibiotic resistance develops in bacteria, viruses, fungi, and parasites, making antibiotics less effective or useless in treating diseases. Fig. 1, represents that the extensive usage of antibiotics has led to a selection pressure that has aided in the evolution of isolates with resistance[5]. Over time, many infectious organisms have developed resistance to the medications meant to kill them, decreasing the effectiveness of the agents. Antimicrobial drugs that were once utilized to treat pathogens are no longer effective against an increasing number of them[6].

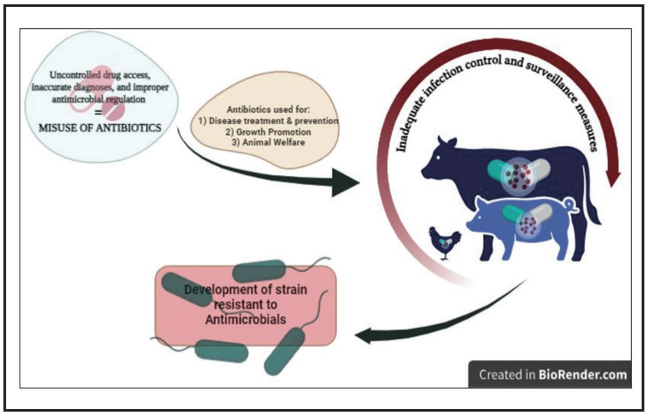

Figure 1. Development of antibiotic resistance strain[5,6].

Keeping in mind the negative impacts of antibiotic contamination, their removal from the environment has become very essential. The most befitting treatments compared to physicochemical and conventional methods are bioremediation and phytoremediation. These are considered economical and sustainable approaches for effectively reducing environmental contaminants by utilizing microbes and plants respectively[7]. Due to the expensive cost of physicochemical methods, alternative biological technologies are becoming more and more popular, especially those that rely on the remediation potential of plants and microorganisms[7].These remediation techniques don't require any expensive equipment, skills, labour, and management therefore, the best approach to eliminate antibiotics from the environment is using antibiotic-remediating plants. This method is eco-friendly, can be applied easily on large contaminated fields, and improves soil properties[8].

This review focuses on the significant issue of antibiotic pollution, with particular attention to the commonly used fluoroquinolone antibiotic i.e. Ciprofloxacin. To prevent the spread of antibiotic resistance and manage environmental antibiotic pollutants, the present review attempts to emphasize the role of phytoremediation strategy. The bioremediation and phytoremediation techniques, highlighting the potential of phytoremediation to mitigate ciprofloxacin pollution were also analysed.

2. ANTIBIOTIC POLLUTION SOURCES IN THE ENVIRONMENT

Since the antibiotics were discovered, there has been an exponential increase in demand for and production of them globally. As a result, of increased production, they are also continuously released into the environment as metabolites and degradation products. Agricultural runoff, anthropogenic effluents, livestock farms, slaughterhouses, landfill runoff, and Wastewater Treatment Plants (WWTPs) are all potential sources of antibiotic pollution, as shown in Fig. 2. The illustration also depicts the closed-loop entry of antibiotics into various ecosystems and their eventual return to the source[9]. The main source of antibiotic pollution in the environment is considered to be WWTPs. Antibiotic residue-containing wastewater is produced by pharmaceutical industries, residential areas, livestock farms, and hospitals which ultimately ends up in WWTPs. However, over-the-counter use and improper disposal of expired antibiotics from residential areas, hospitals, and industries also contribute to WWTP systems[9]. The application of manure containing antibiotic residues in agricultural fields contaminates the soil, which in turn contaminates surface water and groundwater. Antibiotic residues are also present in the sludge produced by WWTPs, which is either dumped in landfills or used as a soil conditioning agent in fields. There are various sources of antibiotic pollution, some of the major sources are discussed below.

2.1 Residential Wastewater

Residential wastewater, also known as domestic or household wastewater, is widely acknowledged as a major contributor to antibiotic contamination[10]. The disposal of unused antibiotics and the excretion of unmetabolised antibiotics by humans are two ways that antibiotics enter the wastewater system. No proper wastewater treatment can lead to the introduction of antibiotics into natural water bodies and further to the soil and food chain. Such kind of environmental contamination can cause a significant risk to public health, as it may reduce the effectiveness of antibiotics in treating infections by promoting the spread of antibiotic-resistant bacteria.

2.2 Hospital Wastewater

Conventional wastewater treatment methods are generally incapable of adequately treating the wastewater discharged by hospitals, which increases the risk of release of antibiotics into the ecosystem. Due to the widespread use of antimicrobial drugs in healthcare institutions, hospital wastewater is a significant source of antibiotic pollution. Together with other medications, disinfectants, and pathogens, this wastewater has significant concentrations of antibiotics[11]. These substances are flushed into the sewage system through cleaning procedures, laboratory operations, and patient care. Hospital wastewater has a higher percentage of antibiotics than normal wastewater[10].

2.3 Slaughterhouse Wastewater Discharge

Antibiotics are commonly utilised in livestock farming to enhance growth and prevent disease, which causes an accumulation of antibiotics in animal tissues. Wastewater produced during animal slaughter may contain residues of antibiotics that are subsequently introduced into the environment. Antibiotics can remain in treated water because traditional wastewater treatment plants are usually not built to efficiently eliminate pharmaceutical compounds[10]. As a result, these contaminants may find their way into water bodies, endangering aquatic life by disturbing ecosystems and encouraging the growth of bacteria resistant to antibiotics.

2.4 Agricultural Effluent

The key cause of antibiotic pollution in agriculture is the extensive usage of antibiotics in livestock farming. Antibiotics are frequently given to livestock animals, such as cattle, pigs, and poultry, to cure infections, promote growth, and prevent diseases[12]. Although animals can metabolize most antibiotics, a significant amount is excreted in the undigested form in their urine and feces. The use of antibiotic-treated animal manure as fertilizer on fields increases the risk of antibiotics entering into the soil or water bodies through irrigation or rainfall.

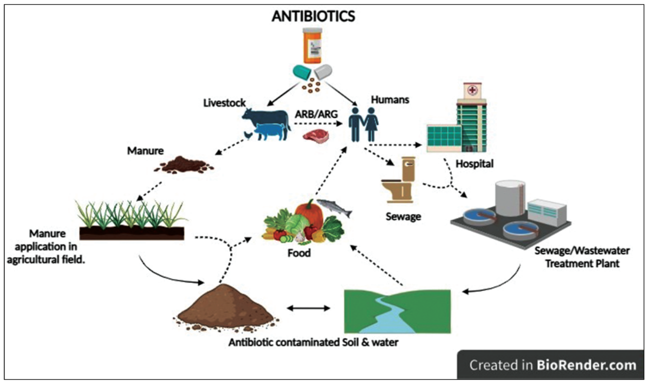

Figure 2. Reoresentation of the various source of antibiotic contamination in environment[10,11].

3. CIPROFLOXACIN & ITS CONCENTRATION IN WATER: GLOBAL & INDIAN SCENARIO

Lately, the concerns regarding the ecological effects of antibiotics have grown immensely as they inhibit major functions like nutrient regeneration and the carbon and nitrogen cycles in the environment[13]. Fluoroquinolone (FQ) antibiotics are currently among the most extensively utilised antibiotics in medical practice. It has been estimated that the antibiotic market is valued at around 2.2 billion USD, which is 16.8 % of the total pharmaceutical sales in India[14]. FQs account for up to 25 % of all antibiotic usage in India, where the greatest proportion of antibiotic intake is 3.75 specified daily dose/1000 population daily[15]. For human administration, the three main FQs—ciprofloxacin, norfloxacin, and ofloxacin—are authorised. The most widely utilised & effective fluoroquinolone is ciprofloxacin. Ciprofloxacin had the largest global value at 1.3 billion dollars, followed by ofloxacin at 900 million dollars[16].

Based on their pharmacokinetic profile and spectrum of activity, fluoroquinolones are categorised into four generations[17]. Table 1 provides an overview of different generations of Fluoroquinolone[17].Ciprofloxacin is a second-generation fluoroquinolone. Its molecular formula is $[C_{17}H_{18}FN_3O_3]$ and has a 331.3 g/mol molecular weight[18]. It is a widely used human & veterinary drug to treat various bacterial infections and is also used as a growth promoter for livestock. Ciprofloxacin shows activity against many gram-positive and negative bacteria. It acts by blocking bacterial DNA synthesis, resulting in bacterial cell death. It functions via two mechanisms; either by inhibiting the activity of major target DNA gyrase or secondary target DNA Topoisomerase IV[19]. It easily enters into the environment through sewage, treated water from wastewater treatment plants, manure applied to agricultural fields, livestock farming, and leachate from landfills. It has been observed that around 50-60 % of CIP gets excreted in unmetabolised form through human urine and 15-25 % through faeces[13]. Antibiotics like ciprofloxacin are known to be very stable and persistent within the environment.

Table 1. Overview of the different fluoroqunolone antibiotic generations

Generation	Examples	Spectrum of activity	Clinical use
Ist	Nalidixic Acid Cinoxacin	Effective against Gram-negative bacteria	Restricted usage because of resistance development & narrow range. Commonly used for urinary tract infections.
IInd	(a) Norfloxacin Ciprofloxacin (b) Ofloxacin Lomefloxacin	Active againstall Gram-negative bacteriaas well as some Gram-positive bacteria	Effective enough to combat a broader spectrum of illnesses, such as skin, gastrointestinal, and respiratory infections.
IIIrd	Levofloxacin Sparfloxacin Gatifloxacin	Increased efficacy against Gram-positive bacteria & improved coverage against Gram-negative bacteria	Used to treat sinusitis, bronchitis, pneumonia, and other respiratory diseases.
IVth	Moxifloxacin Trovafloxacin Gemifloxacin	Effective against certain anaerobic bacteria as well as a broad spectrum of Gram-positive and Gram-negative bacteria.	Effective for severe respiratory & intra-abdominal infections. Moxifloxacin showed increased activity against anaerobes.

Antibiotic contamination of the environment has been reported in several Asian countries, including China, India, and Japan, in recent years. Fig.3 summarises the ciprofloxacin concentrations found in various sources across several nations[20]. Antibiotic concentrations in sewage sludge are greater than those in sediments. Due to their potent adsorption onto sewage sludge.

It has been reported that the concentration of ciprofloxacin in Indian wastewater treatment plants (WTP) is about 40 times higher in comparison to countries such as North America, Australia, Europe, and Asia[21]. The concentration of CIP in the outlet at Okhla WTP, Delhi was 2.5-15 times higher as compared to the outlets in Australia, Italy, U.S.A., Canada, and China wastewater treatment plants[21]. In a cross-sectional study performed in a hospital, seven antibiotics were detected on the outskirts of Ujjain, an Indian city, out of which Ciprofloxacin was one of the antibiotics used most frequently in the hospital. Also, the residue levels of CIP in wastewater were highest[22]. Table 2 summarizes the various reported ciprofloxacin levels in water and wastewater.

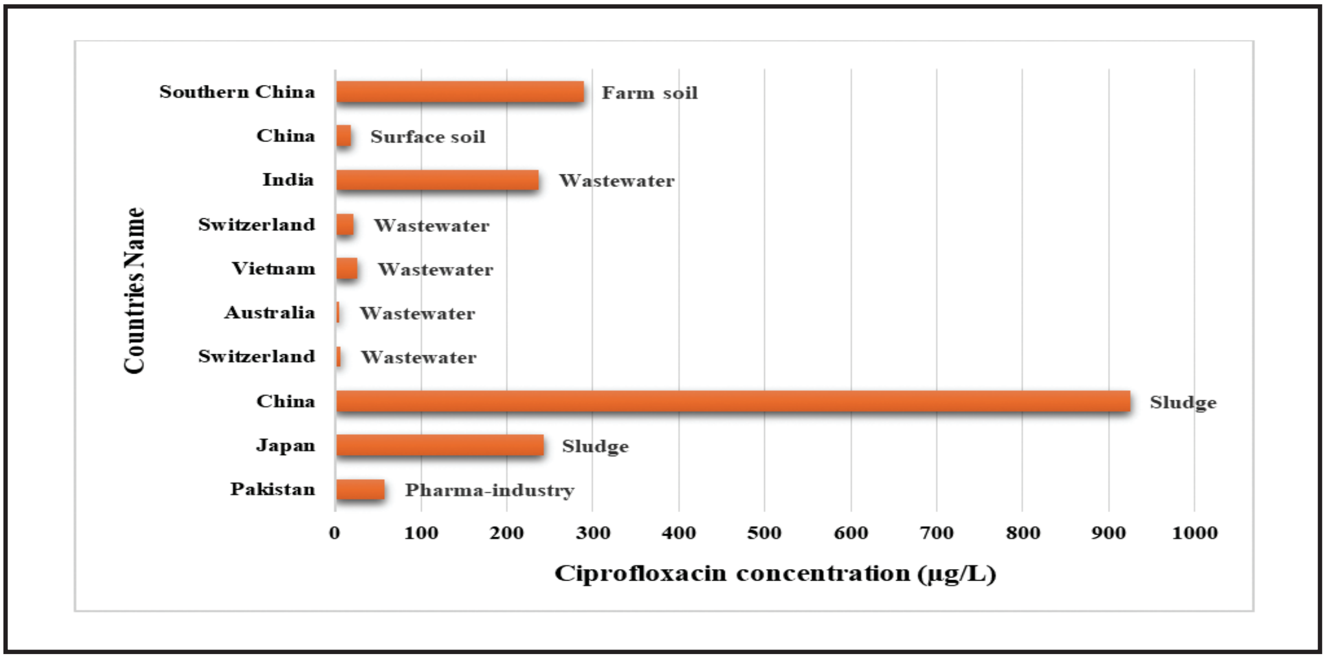

Figure 3. Illustration of the ciprofloxacin concentration detected in different countries from various sources.

Table 2. Reported concentration of ciprofloxacin in river, lakes, wastewater/sewage treatment plants, surface water, and wells of India

Site of sample collection	Year of study	Detected concentration of CIP (ng/L)	Reference
Chennai City & Suburbs; Tamil Nadu: Sewage treatment plants, Groundwater	2022	20.48	23
Nagpur; Maharashtra: Sewage treatment plants, Nag & Pili River	2014	5,080-28,230	24
Hyderabad; Patancheru Enviro. Tech Ltd. Plant:	2009	25,00,000-65,00,000	25
Lakes		>5000-10,000	
Surface & groundwater		14,000	
Wells		12,000-11,00,000	
Isakavagu-Nakkavagu River		1,40,00,000	
Effluent treatment plant		2,80,00,000- 3,10,00,000	
Patancheru Wastewater Treatment Plant	2007		26
Ujjain; Madhya Pradesh: Hospital Effluent-R.D. Gardi Medical College	2010	2,36,600	22
Delhi;	2013		27
Yamuna River (winter):		1440-1190	
Okhla Sewage Treatment Plant:			
Influent		20,100	
Effluent		8000	

4. BIOREMEDIATION

Worldwide attention is focused on the rise of antibiotic-contaminated soil. As it easily enters into the natural ecosystem and has become a matter of concern for animals, plants, microbes, and humans. Therefore, an effective remediation method for antibiotic-polluted soil is the need of an hour. Various conventional physicochemical methods are not practiced due to their damaging effect on soil, high expenditure, and labour cost. Technologies like chemical oxidation, electro-kinetic remediation, extracted washing, and nanomaterial remediation cause vast changes in the pH and moisture content of soil[28]. It has been observed that in comparison to physicochemical technologies, biological technologies such as bioremediation and phytoremediation are more reliable, practiced, promising, low cost, and environment friendly. Bioremediation utilizes naturally occurring microbes, fungi, and plants to break down or detoxify the harmful environmental pollutants into less toxic forms, that pose a threatto human health and the environment[29].

4.1 Types of Bioremediation Techniques

Based on the application site, bioremediation techniques can be classified as either

4.1.1 In-situ Bioremediation

In-situ bioremediation is the process of detoxifying, degrading, or eliminating the toxins by improving the metabolic properties of the microbial community present in the contaminated site[30]. The most efficient bioremediation technique is in situ because it needs less mechanical work to remove toxins that are spreading and stop pollutants from traveling or being carried away to other treatment facilities[31].

4.1.2 Ex-situ Bioremediation

Ex-situ bioremediation, as an alternative, treats pollutants in the samples that have been excavated. Due to the significant work involved in removing contaminated soil from the site and moving it offsite, this categorisation is not widely used. To perform Ex-situ remediation, the proper soil oxygen, moisture, and nutrient conditions must be introduced offsite[29,31].

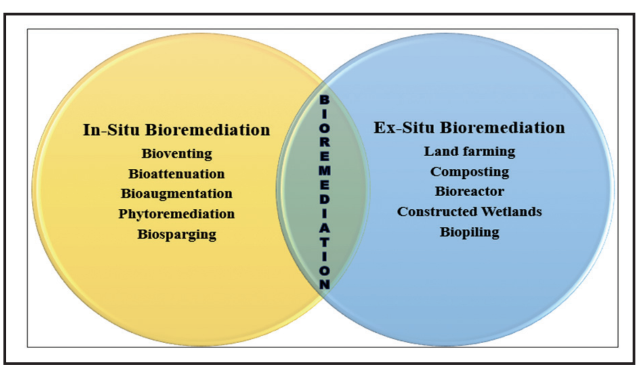

Figure 4. Different types of techniques used for In-situ & Ex-situ bioremediation methods[31,32].

Fig. 4, illustrates the various types of techniques under each category of bioremediation. Each one of these methods has specific applications, advantages, and disadvantages. Out of all the bioremediation techniques, phytoremediation is a widely utilised approach due to its economic and environmental benefits. In the following discussion, we have explored its type, pros and cons.

5. PHYTOREMEDIATION: A GREEN SOLUTION FOR ANTIBIOTIC POLLUTION

Phytoremediation is an eco-friendly technique that includes the usage of associated microbes and plants. It is one of the promising technologies that utilize the plant's capability to remediate harmful contaminants like antibiotics from the soil. It's a much cheaper and more sustainable method. It is a substitute technique that can be utilised instead of mechanical conventional clean-up methods, which frequently have large capital and energy requirements. This technique uses plants to degrade, remove, extract, or sequester the antibiotics[33]. Various plants, such as (*Ocimum basilicum*, *Brassica juncea*, *Lactuca sativa*, and *Zea mays*), are commonly used to remove various contaminants from the environment[34]. The pros and cons of this method, are listed in Table 3.

Table 3. Pros and cons of phytoremediation[35,36]

PROS	CONS
It is an eco-friendly process and not expensive.	Only restricted to shallow soil and water.
It can preserve the soil and water ecosystem	It requires a long period for the complete elimination of pollutants from the environment.
Suitable for contamination levels that are medium to low.	Cannot be applied in developed areas where there is less availability of land.
It is an in-situ remediation process	Not applicable in environment that have high pollutant concentrations.
Helps in improving the soil quality and promotes productivity	Relies on soil characteristics and environmental factors.

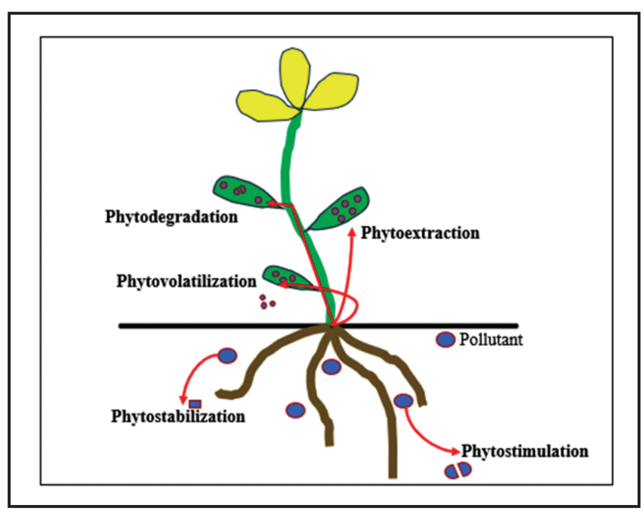

Figure 5. Illustrates the different types of phytoremediation techniques[29].

There are five categories of phytoremediation techniques; phytostabilization, phytovolatilization, phytodegradation, phytostimulation, and phytoextraction as shown in Fig. 5.

5.1 Phytoextraction

It is the method by which plants store toxins in their roots, aboveground shoots, or leaves. This method gathers minimal concentrations of pollutants from a large area.

5.2 Phytodegradation

It explains how organic contaminants are absorbed from sediments, soil, or water and subsequently change into a form that is less mobile, less harmful, or more stable.

5.3 Phytostabilisation

Plants use this approach to lower the movement and migration of pollutants in the soil.

5.4 Phytovolatilisation

Pollutants are absorbed by plants and released as volatile chemicals into the atmosphere via their leaves.

5.5 Phytostimulation

Natural compounds released by plant roots encourage the growth of microbes, which in turn break down pollutants in the soil.

6. PHYTOREMEDIATION OF CIPROFLOXACIN USING VARIOUS REMEDIATOR PLANTS

Phytoremediation of antibiotics can be achieved by using different species of antibiotic- remediating plants like Daucus carota L. (carrot), Brassica juncea (L.) Czern (mustard),Lactuca sativa L. (lettuce), Vigna radiata L. (Mung bean), Cicer arietinum L. (Chickpea), and Cymbopogon citratus (lemon grass) etc. Phytoremediation helps in restoring the natural habitat, removing the contaminants without transporting soil to another place[35]. Various investigations and studies have been performed to analyze the remediation potential of different plant species. The use of phytoremediation has demonstrated the enormous potential for ciprofloxacin removal from the environment. Table 4 summarizes reports where phytoremediation technology is used for treating ciprofloxacin contaminated environment.

The results of these investigations suggest that ciprofloxacin concentrations can be efficiently reduced by plant-based remediation techniques utilizing microbial interactions in the rhizosphere, root uptake, and accumulation in plant tissues. Comparative studies of several plant species reveal the variation in their effectiveness based on variables such as ciprofloxacin concentration, surrounding circumstances, and the plant's natural detoxifying capacity.

7. CONCLUSION & FUTURE PROSPECTS

The production and widespread usage of fluoroquinolones in human and animal medicine has become a matter of great concern. Out of all antibiotics, ciprofloxacin is now becoming the number one antibiotic contaminant, as it is commonly found in the environment. Ciprofloxacin pollution causes toxic impacts on plants, and the emergence of antibiotic resistance among microbes, humans, and animals. According to several studies, a high level of ciprofloxacin is detected in wastewater/sewage treatment plants and rivers of India. There are several ways through which ciprofloxacin enters the environment; the main pathway through which it does so is when the antibiotic is not totally absorbed by the gut of humans or animals and hence gets eliminated into the surrounding environment. Due to the slow rate of fluoroquinolone biodegradation, residues and metabolites are easily detectable in soil and water sources. Antibiotics are susceptible to biological degradation processes by microorganisms and plants present in soil and water. It is recommended that an

Table 4. Summary of research studies using various phyto-remediator plants for the removal of cipfofloxacin

Selected Plant	CIP concentration	Results	References
Eichhornia crassipes-Grown in Hydroponic conditions	10 ,100, and 1000 µg/L	84.38%, 67.95%, and 62.36 % of total CIP accumulated in roots within 7 days of theexperiment. After 14 days in response to CIP stress Superoxide dismutase & catalase activities showed an increase. After 21 days decrease in chlorophyll content was seen. Leaves turned white and shriveled.	37
Cicer arietinum-Grown in Hydroponic conditions	15-25 mg/l	After 7 days, a remediation rate of 60% was observed for CIP. A decrease inthe length ofthe root and shoot of the plant due to toxicity.	38
Acrostichum aureum L. & *Rhizophora apiculate Blume*- Pot Experiment	10 mg/kg	After 14 days, a remediation rate of 65% was observed for CIP. After 21 days, no effect on growth rate; CIP found mainly in root tissue samples	39
Brassica juncea L. Czern- Grown in Hydroponic conditions	5-10 mg/l	After completion of 12 days remediation rate of 50%-63.2% was observed for CIP. Whereas at higher concentrations of 20 to 60 mg/l; decrease in percentage remediation, root & shoot length.	40

environment-friendly approach for making an antibiotic free environment like phytoremediation is used. The plant's root and shoot act as a hyperaccumulator and eliminate the contaminants from the natural environment. A prospect for enhancing the effectiveness of phytoremediation involves the synergistic use of microbes and plants. Integrating the complementary abilities of both biological systems, microbial communities, and plant-based remediation can improve the degradation and uptake of antibiotics. Antibiotics can be broken down by microorganisms into less toxic substances that plants can absorb and further detoxify. This combination strategy may lead to the more thorough and effective removal of antibiotics from contaminated areas. It can be stated that the plant-microbe synergy is the upcoming future in the field of biological remediation methods. Although it has theoretically well-known aspects, research studies for the remediation of antibiotics are needed for a better understanding and implementation of this synergistic technology.

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