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Review

Pharmaceutical Compounds: An Emerging Pollutant (A Review on Plant-pharmaceuticals Interaction)

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ABSTRACT

Pharmaceutical compounds enter the environment through multiple pathways: they are flushed down the toilet, passed unmetabolized through human excretion, rinsed off during showers and discharged directly from manufacturers. Recent studies have shown that these pharmaceutical cause serious problems to animals who consumed it through contaminated water. Due to extensive use of pharmaceuticals in our life its presence in our ecosystem is obvious still we do not know much about its impact on plants. Several studies have been performed to report the accumulation of pharmaceuticals in plants, but only a limited amount of work has been performed towards the toxic effect of these compounds on plants. The aim of this review is to overview experimental evidence of plant-pharmaceuticals interaction, their uptake and their removal by plants and to suggest an open area of research in this new field.

1. INTRODUCTION

With the advancement of the research and technology, the human life is changing. These advancements in technology are meant to produce a beneficial product for human life, but few of them come with a side effect. The pharmaceuticals industry is a good example of such case. The evolution of pharmaceutical industries is an impressive success story. The pharmaceutical products are present everywhere in everyday life. Pharmaceuticals are compounds manufactured due to its biological activity, which acts to prevent or cure the diseases [1]. Before the distribution of pharmaceuticals, its direct effects and side effects on target organisms are analyzed carefully but its potential effect on the environment are neglected to large extent. Due to the increasing use of pharmaceuticals, there is a higher risk of the exposure of pharmaceutical compound to the environment. Therefore there is a higher chance that these compounds can be consumed by animals and plants even if it is not required for their betterment. There is a chance that these unwanted pharmaceuticals may interfere with normal

metabolic activities of the organism and therefore may cause an adverse effect.

In recent past research has shown a serious effect of this newly emerging pollutant on animals but only a few studies have been performed on plants [2]. The studies on plants are mainly focused on the accumulation of pharmaceuticals with possibilities to use the plant as a remediation method for it. A very limited study is focused on the toxic effect of pharmaceuticals on plant [3].

This review addresses the current knowledge on plant-pharmaceuticals interaction, with a focus on pharmaceuticals uptake and phytotoxicity.

2. Release of Pharmaceuticals to the Environment

Pharmaceutical compounds may enter the environment by several ways, such as, through human and animal excretion, from manufactural or users through improper disposal, or the surface drugs washed to the sewage through the shower (shown in Figure 1). During drug treatment, the active components of pharmaceutical products are only partially consumed by the patients and largely excreted from the patient's body, either unchanged (as the same compounds that are present in the dosage form) or as derivatives or metabolites of these compounds [2-4]. Excretion/ shower/ industrial waste, thereby introduces pharmaceutical residues into the sewage disposal system and consequently into wastewater [4, 5]. Currently, wastewater treatment systems are not designed to remove pharmaceutical residues and many of these compounds are released in wastewater effluent and consequently into the aquatic environment [3,6]. Therefore, pharmaceuticals and their degradation products can be detected in rivers, lakes, groundwater, and even possible to be present in drinking water of populated cities [7]. Furthermore, use of recycled wastewater or sewage sludge/biosolids on agricultural and forestry land results in pharmaceutical pollution of the terrestrial environment [2, 8, 9].

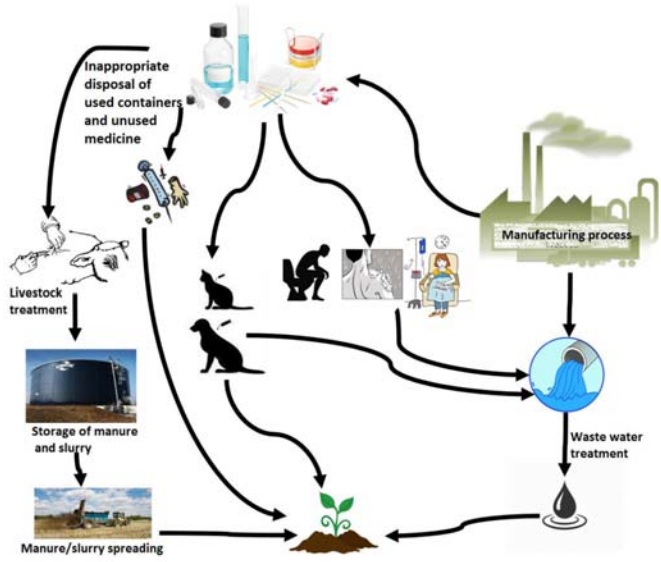

Figure 1. Possible methods of pharmaceutical entry to environment: Figure represent the various methods in which the pharmaceuticals may reach to the soil, and can be available to plants.

The continuous release of pharmaceuticals into the environment is making them pseudo-persistent contaminants, posing a dangerous threat to ecosystems, despite their low concentration in wastewater or agricultural land [10]. The recent studies have reported the presence of low levels of various pharmaceuticals, including antibiotics, analgesic, hormones, steroids, and parasiticides, in treated wastewater, surface water, groundwater, and agricultural soil [5-11]. The low concentration of pharmaceuticals from the environment can be further accumulated in plants and thus may result into bio-magnification. The release of antibiotics in the environment may result in the selection and abundance of antibiotic resistance bacteria in the environment, which can further affect the microenvironment of the plant. Antibiotic-resistant bacteria may reach the environment through the excretions of treated patients, it may also evolve through horizontal gene transfer via conjugation, transduction, and transformation [12].

It is evident from the above paragraphs that the wastewater is a most important source of pharmaceuticals pollutant. The conventional methods for its treatment are not efficient to irradiate the pharmaceuticals [13]. It is assumed that around 50% of the pharmaceuticals are removed and rest end up in the environment. The advanced techniques of wastewater treatment, such as, advanced oxidation processes in combination with ozonation and UV-irradiation help in degradation of pharmaceuticals through hydroxyl radical, and are capable of removing most of the active pharmaceuticals from wastewater [14]. Due to its expensive nature (due to costly chemicals reagent used in this method), this method is only used at few places in Europe and USA. Therefore there is a need to develop a more cost-effective method/improve the existing methods for efficient removal of the pharmaceutical contaminant from the wastewater.

3. Plant-pharmaceuticals Interaction

Pharmaceutical compounds may have an influence on plants in two ways, first by the direct interaction with plant metabolism, or through antimicrobial actions of pharmaceuticals on soil microorganisms (which may be responsible for influencing plant growth by interfering the plant-microorganism symbiosis). The presence of antibiotics in soil may influence the plants through unbalancing the soil fauna, by killing bacteria which may result in the unavailability of food for protozoans and other microorganisms, which may further result in slow degradation of organic substances and therefore lack of nutrient in soil [12].

Several studies have shown the effect of pharmaceuticals on different plants. Most of these studies are performed in laboratory condition with the use of aqueous solutions or nutrient medium doped with different pharmaceuticals. In one report, the absorption pattern of six different pharmaceutical compounds was checked in distinct plants and the authors found out that five of the tested substances were absorbed by plants, such as radish and ryegrass [15]. The pharmaceuticals were found to be amplified in the plant, whereas its level decreased in soil. Several other studies focus on the accumulation of pharmaceuticals in plants, but lack the study of the effect of pharmaceuticals on plant morphology and physiology [15-17]. These studies are important as the plants are directly consumed by human and therefore the pharmaceutical compounds accumulated in the plant may easily get transferred to them.

In 1980 and 1981 two set of experiments were performed by Batchelder

to check the effect of two antibiotics chlortetracycline and oxytetracycline on plants in nutrient and soil system [18-19]. The author observed a very significant decrease in the vitality of pinto beans with an increase in antibiotic concentrations [18]. All plants were observed to be dead at the concentration of 160-ppm in the nutrient medium [18]. In sandy loam (spiked soil), wheat development was slightly affected by both the antibiotics whereas no significant effect was observed in corn plant [19]. Whereas author observed a significant decrease in morphological (such as, bean yields, plant heights, shoot and root dry-weights) and chemical (reduction in Ca, Mg, K, and N contents) characteristic of pinto bean under the influence of antibiotics [19]. The significant deviation in the effect of antibiotics on the pinto bean, in the nutrient and soil system, can be explained by the different availability of antibiotics to the plant. In soil, antibiotics get adsorbed on various minerals and soil organic matters which affects its absorption by plant and may contribute in a deviation of the effect of antibiotics on the plant. Sulphadimethoxine was observed to be toxic to *Panicum miliaceum*, *Pisum sativum*, and *Zea mays* by reducing the growth of roots, hypocotyls, and leaves in plants [20]. The similar effect of sulphadimethoxine was also observed for *Hordeum distichum* in nutrient medium but a decreased effect of sulphadimethoxine was observed in soil system which supports the previous studies by Batchelder [18, 19, 21]. The effect of sulphadimethoxine on *Panicum miliaceum*, *Pisum sativum*, *Zea mays,* and *Hordeum distichum* was attributed to bioaccumulation of antibiotic in plants [20, 21]. Enrofloxacin was observed to be beneficially for plant growth at low concentration whereas at higher concentration it was toxic for the growth of cucumber and lettuce [22]. The effect can be explained as the metabolism of the plant, which can degrade the lower concentration of enrofloxacin in some beneficial compound whereas when presence in higher concentration the plant is unable to process the pharmaceuticals and it exhibits the toxic effect. Different other studies on different plants also have shown the beneficial effect of pharmaceuticals at the low level whereas at the higher level it shows toxic effects [23, 34]. It has been also observed that different parts of the plants show the different response to the pharmaceuticals exposure [24], which can be contributed to the different accumulation of pharmaceuticals, or/and different metabolism of the tissues. Chloroquine, quinacrine, and metronidazole were observed to be toxic to soybean, where metronidazole was observed to highly toxic, whereas chloroquine was least toxic [25]. Chloroquine and quinacrine were either beneficially or with no effect for microbes present in soil whereas metronidazole was observed to be toxic for soil microbes [25]. The author related this difference in effect to the solubility of the compounds, metronidazole is weakly adsorbed to soils, therefore most of the added compound to remain in the soil solution, making it readily available for uptake by the plants. Therefore, the higher observation of metronidazole was assumed to be the reason behind the observed toxicity of the compound for the plant. The study lacks the detection of pharmaceutical compounds in soil and plant, which could be useful to establish the hypothesis. Oxytetracycline when mixed in hydroponic solution for alfalfa growth, it was observed to have significant inhibitory effect at concentrations higher than 0.02 mM [26]. Root growth was observed to be more sensitive to oxytetracycline than shoot, this response is supposed to be due to higher accumulation

of pharmaceuticals in root than shoot. The author proposed that the phytotoxicity might be due to the inhibition of the translational activity of chloroplast and chloroplast (p)ppGpp synthase activity by tetracycline, which is structurally similar to oxytetracycline [26]. The effects of six antibiotics were observed on rice, sweet oat, and cucumber [27]. The authors observed sweet oat and rice to be more sensitive to the antibiotic compounds than the cucumber. Again the differences in response can be attributed to the localization of pharmaceuticals, which has been not tested in the study. A different study was performed to detect the phytotoxic effects of 10 antibiotics on lettuce, alfalfa, and carrot [28]. The authors observed phytotoxic effects of different antibiotics in following order: levofloxacin > chlortetracycline > tetracycline > sulfamethoxazole > tylosin > oxytetracycline > sulfamethazine > lincomycin > amoxicillin > trimethoprim [28]. The authors also observed carrot to be most affected, which gives more strength to the hypothesis that the accumulation of pharmaceuticals in roots are affecting the plants. A study on the effect of non-steroidal-anti-inflammatory drugs was performed on radish and lettuce plant showed morphological and physiological changes in plants [29]. The study showed a significant change in photosynthetic properties and morphological characteristic of plants after exposure to pharmaceuticals. The authors observed the Fv/Fm (maximum quantum yield of photosystem II (PSII)) to be not significant then threshold whereas, Tfm (the time needed to reach maximum chlorophyll fluorescence intensity measured when all PSII reaction centers are closed) and PI (abs) (Performance index of electron flux from PSII based to intersystem acceptors) were observed to be decreased after four weeks of pharmaceuticals exposure. Which is in agreement with previous studies, where it has been shown that Fv/Fm is the least sensitive factor to different stresses than the other factors such as area, Fv/Fo (Efficiency of the water-splitting complex on the donor side of PSII), PI(abs) and ABS/RC (Absorption flux per reaction center) [30]. Table 1 summaries and suggest a definite phytotoxic effect of different pharmaceuticals in the plant.

Table 1. Phytotoxic effect of different pharmaceuticals in the plants.

Pharmaceutical compounds	Group	Plant	Phytotoxic effects	Reference
Acetaminophen	Nonsteroidal anti-inflammatory drug	Barley	87.8 mg/Kg of drug was observed to reduce fresh and dry mass of root and leaves.	[31]
Amoxicillin	Antibiotic	Carrot Lettuce Alfalfa	10000 µg/L was observed to be toxic for root growth 1 µg/L was observed to be toxic for root growth	[28]
Chloroquine	Anti-malaria drug	Soybean	With increase in drug concentration (0-16g/Kg of soil) plant growth decreases	[25]

Table 1. Continued.

Pharmaceutical	Group	Plant	Phytotoxic effects	Reference
Chlortetracycline	Antibiotic	Pinto beans	Plant growth was affected when grown in sandy loam but no effect was observed in clay loam (concentration 10mg/L)	[18,19,25]
		Carrot Lettuce	1000 µg/L was observed to be toxic for root growth.	
		Alfalfa	100 µg/L was observed to be toxic for root growth	
Diclofenac	Nonsteroidal anti-inflammatory drug	Horseradish	Viability was observed to be reduced by 65%.	[32]
		Flax	Viability was observed to be reduced by 48%.	
Enrofloxacin	Antibiotic	*Cucumis sativus* *Lactuca sativa* *Phaseolus vulgaris* *Raphanus sativus*	High concentration (5000 µg l^{-1}) was observed to have toxic effect on Post-germinative development of plant.	[22-24]
Ibuprofen	Nonsteroidal anti-inflammatory drug	*Lemna minor* L.	25% inhibition of growth in plant culture exposed to 1 mg L^{-1} of Ibuprofen.	[32]
Levofloxacin	Antibiotic	Carrot	10000 µg/L was observed to be toxic for root and shoot growth.	[28]
Lincomycin	Antibiotic	Lettuce Alfalfa	10 µg/L was observed to be toxic for root growth	[28]
		Carrot	10000 µg/L was observed to be toxic for root growth	
Metronidazole	Antibiotic	Soybean	With increase in drug concentration (0-4g/Kg of soil) plant growth decreases	[25]
Oxytetracycline	Antibiotic	*Phragmites autralis*	>10 µg/L concentration cause toxic effect to root and photosynthetic activities. Plant observed to be died at 160ppm concentration. 1000 µg/L was observed to be toxic	[18,19, 26-28]
		Pinto beans		
		Carrot		

Table 1. Continued.

Pharmaceutical	Group	Plant	Phytotoxic effects	Reference
		Lettuce	for root whereas, 10000 µg/L was observed to be toxic for shoot growth. 10000 µg/L was observed to be toxic for root growth.	
Quinacrine dihydrochloride	Anti-protozoal	Soybean	10.6mg/g concentration was observed to be very toxic for seed germination	[25]
Sulfamethazine	Antibiotic	*Phragmites autralis* Carrot Lettuce Alfalfa	>10 µg/L concentration cause toxic effect to root and photosynthetic activities. 1000 µg/L was observed to be toxic for root growth. 10000 µg/L was observed to be toxic for root growth.	[27, 28]
Sulfamethoxazole	Antibiotic	Carrot Lettuce	100 µg/L was observed to be toxic for root and shoot growth 10000 µg/L was observed to be toxic for root growth	[28]
Sulphadimethoxine	Antibiotic	*Amaranthus retroflexus* *Pisum Sativum*	300 mg/L was highly toxic during postgerminative development	[20, 21]
Tetracycline	Antibiotic	Carrot	100 µg/L was observed to be toxic for root whereas 1000 µg/L was observed to be toxic for shoot growth.	[28]
Trimethoprim	Antibiotic	Carrot Lettuce Alfalfa	Toxic for root growth high concentration (>10mg/L)	[28]
Tylosin	Antibiotic	Carrot Lettuce Alfalfa	10000 µg/L was observed to be toxic for root growth 10 µg/L was observed to be toxic for root growth	[28]

The mechanism of the action of pharmaceuticals can be linked to the elevated production of reactive oxygen species (ROS). Metabolism of drugs may generate a reactive intermediate which can reduce molecular oxygen to form ROS. These reactive species can then interact with nucleic acids and macromolecules to cause toxicity response. The elevation in ROS level due to pharmaceutical exposure is not well studied topic in plants but it has been intensively studied in the case of animals [33-36]. Recently acetaminophen (in the concentration as low as 87.8 mg/Kg of soil) was observed to produce superoxide anion radical, resulting in lipid peroxidation and cell death in barley plant [31]. The authors also observed the toxic effect of acetaminophen in the form of a decrease in fresh and dry weight of root and shoot of barley plant. The evidence indicates that the ROS and oxidative processes are involved in toxic response of pharmaceuticals even if the mechanisms by which ROS are generated is not fully characterized. Additional research is needed to establish the mechanism of the pharmaceutical interaction with plants.

If pharmaceutical compounds are contaminating the soil, there is also a need to find out the ways to extract these contaminants from the environment. Phytoremediation is a method, which utilizes plants and the associated rhizosphere microorganisms to remove or transform toxic chemicals from the environment [37, 38-40]. Plants for phytoremediation are selected on various factors such as the ability to extract or degrade the contaminants of concern, adaptation to local climates, high biomass, deep root structure, compatibility with soils, growth rate, easy for planting and maintenance, and ability to take up a large amount of water through their roots. Reports have shown plants can be very useful for remediation of pharmaceutical compounds [3, 41]. Myriophyllum aquaticum, Vetiver, and lettuce plants have been observed to remove tetracycline in 100% from the aqueous medium [41-42]. Several other studies have shown the removal of different pharmaceuticals (such as: diclofenac, ibuprofen, acetaminophen, sulfadimethoxine, naproxen, caffeine, and several others) by different plants (such as: horseradish, barley, duckweeds, Lemna, Typha etc.) [3]. But still, there are much to decipher in this area to find an effective way for the remediation of pharmaceutical compounds from the contaminated soil.

4. DISCUSSION

There are several reports on the presence of pharmaceuticals on wastewater and soil, where the level of pharmaceuticals is significant enough to cause an effect on plants. Different studies have confirmed that the pharmaceuticals are having phytotoxic effects on plants [3,18-29]. Some beneficial effect of pharmaceuticals on plants were also observed but at the low concentration, and it converted into phytotoxic effects at higher concentration [10, 22]. The solubility in water and adsorption by the soil of pharmaceuticals were observed to play an important role in exhibiting the phytotoxic effect [18-21]. The localization and accumulation of pharmaceuticals in the plant are also known to affect the phytotoxic effect [20-24]. From the studies, it can be concluded that pharmaceuticals may be toxic to plant and the effects on plants are compound specific and also different plant species may response to the same compound differently. This behavior of pharmaceutical can be also explained as different plant species contains different level of different enzymes and chemicals and therefore the same pharmaceutical compounds may react

differently in the presence of different substances and may cause different effects on different plant species.

The studies indicate that the pharmaceutical waste may influence the plants, but only limited studies are performed to evaluate these effects. The studies performed are mainly focused on morphological variation. There are thousands of pharmaceutical compounds which may contribute to pharmaceutical waste and further these pharmaceutical compounds may differently affect different plant species, therefore a lot of research is needed to evaluate the effects of pharmaceutical waste on plants. The research is also needed to extend to the level of plant physiology and molecular biology, in the process to understand the mechanism of pharmaceuticals interaction with the plant. The ways of production of ROS in plants as the result of pharmaceutical exposure is needed to explored further. It is also need of the time to develop an efficient and cost-effective method of wastewater treatment. The direct effect of plants in pharmaceutical removal from wastewater treated area has been scarcely studied. The crop plant studies are mainly pointed to plant uptake and public health-related issues; nevertheless, phytoremediation may be a cost effective and efficient way to treat contaminated areas. Therefore, the process of phytoremediation is needed to be understood in regards to incontaminate the pharmaceutical-contaminated environment. There is a lot to explore in this comparatively new area of pollutant.

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