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ECOTOXICOLOGICAL EVALUATION OF DICLOFENAC, FLUCONAZOLE AND CARBAMAZEPINE ON EARLY GROWTH INDICES OF COTTON.

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Abstract

Background: Drugs are essential for safeguarding human and animal health but have become emerging environmental pollutants. Even trace levels can interfere with biological functions in non-targeted organisms, such as plants and biota that form the foundation of terrestrial ecosystems. Hence, this study seeks to evaluate the impact of selected pharmaceuticals on early plant growth and development. ***MATERIALS AND METHODS:*** The toxic effects of diclofenac, fluconazole, and carbamazepine on early cotton seedling growth were evaluated. Stock solutions of each drug were freshly prepared at concentrations of 25, 50, 100, 200, and 600 ppb and germinated seedlings were exposed to the respective concentrations in six pots per treatment group for 14 days. On day 15, shoot length, root length, and total germination length were measured and subjected to statistical analysis to assess drug induced phytotoxicity. ***RESULTS:*** Cotton growth decreased in a concentration-dependent manner (25–600 ppb). Fluconazole showed the greatest inhibition, while carbamazepine significantly reduced root elongation ($p < 0.00001$). Diclofenac significantly decreased root length ($p = 0.0001$) and germination length ($p = 0.00001$) at ≥ 200 ppb. Root length was the most sensitive indicator of phytotoxicity. ***CONCLUSION:*** Drug residues at trace levels can impair early plant growth, suggesting their potential role as emerging environmental toxic compound and strict monitoring of drug disposal and its impact on environment needed to mitigate the eco hazard.

Keywords: Cotton, Diclofenac, Fluconazole, Carbamazepine, ppb, phytotoxicity.

INTRODUCTION

Medicinal products have improved global health by reducing mortality, increasing life expectancy, and enhancing the acute and chronic disease management. But unsafe healthcare remains a major public health concern, experiencing preventable harm during healthcare delivery.(1)

The release of these medicinal products into the environment through wastewater effluents, agricultural runoff, and improper disposal has emerged as a significant public health concern that frequently escapes removal in conventional wastewater treatment systems.(2) Even at lower concentrations, these compounds can disrupt ecosystem causing unintended effect on plant and non target organisms.(3,4)

The continuous release of antibiotic residues into ecosystems may compromise the effectiveness of existing antimicrobial therapies and increase the worldwide emergence of resistant infections substantially contributing to global morbidity and mortality.(5,6)

Although human exposure through contaminated water and food chains is generally low, their long term impact on human remains an area of active investigation.(2,3) Hence a balanced approach is needed to maximize therapeutic benefits while minimizing health and environmental risks.

In response to these emerging challenges, ecopharmacovigilance has evolved as an extension of conventional pharmacovigilance that shifts the focus from human health alone to encompass the environmental impact of medicinal products. Unlike drug safety monitoring, which focuses only adverse reactions in humans, ecopharmacovigilance assesses how the active pharmaceutical ingredients enter and persist in our ecosystem affecting non target organisms because of overlapping drug target mechanisms across different species. As consumers continue to grow globally, concerns have expanded beyond human health to include the unintended ecological consequences of drug residues released into the environment.(7)

Cotton is a high value commercial crop with considerable economic importance in India.(8) It has reliable seed germination and rapid seedling growth.(9) Seed germination and early seedling growth are recommended endpoints for assessing phytotoxic effects in terrestrial plants.(10)

Diclofenac, Fluconazole and Carbamazepine are widely prescribed medicines with distinct mechanisms of action. These drugs were detected frequently in aquatic environments and recognized as an environmental trace contaminant.(11-13) Since these drugs differ in their physicochemical properties and distinct mechanism, evaluating their effects on cotton seed early seedling growth provides valuable insight into the phytotoxic potential of environmentally relevant medicinal products contaminants and their possible ecological risks to terrestrial plants.

MATERIALS AND METHODS

STUDY DESIGN

The study was carried out for 14 days to assess the phytotoxic effect of the drugs on plant growth. Drugs included in this study were Diclofenac, Fluconazole and Carbamazepine. These drugs were tested on growth parameters of cotton . At the end of the study period Root length, shoot length and total gemination length were assessed.

STUDY SETTING

The study was carried out in experimental laboratory, Dhanalakshmi Srinivasan medical college and Hospital, Siruvachur, Perambalur for 14 days and growth indices were assessed on day 15. Before initiating the study, cotton seed were authenticated by the botanist from Thiru Vi Ka government arts college, Thiruvarur, Tamil Nadu.

GROUPS

Three groups consisting of Group I – Diclofenac, Group II – Fluconazole and Group III – Carbamazepine which include six treatment solutions (0, 25, 50, 100, 200 and 600 ppb) per group tested on cotton.

SEED GERMINATION METHOD

On Day 0, cotton seeds were rinsed thoroughly and soaked in fresh water for 6 hours. To induce germination the soaked seeds were kept in the dark. Subsequently, the germinated seeds were sown in sterilized plastic pots filled with soil and maintained under ambient conditions (29 ± 2°C) with a 12-hour light and dark photoperiod throughout the experiment.

DRUG DOSE AND ADMINISTRATION

Fresh aqueous stock solutions of Diclofenac, Fluconazole, and Carbamazepine prepared on Day 0. The test drugs were diluted with water to prepare concentrations of 25, 50, 100, 200, and 600 parts per billion (ppb). The test solutions were applied directly to soil surface for uniform exposure.

STUDY PROCEDURE

Six identical sterilized pots filled with equal quantity of soil were labelled separately as 0 , 25, 50, 100, 200 and 600 parts per billion (ppb) to which corresponding stock solutions were administered during the study. Three seeds were sown per pot in uniform spacing. They were allowed to germinate under ambient conditions and each pot received corresponding drug solution daily from Day 1 onward to maintain consistent exposure. On the 15th day root length, shoot length and total germination length were measured and taken for statistical analysis.

STATISTICAL ANALYSIS

The shoot length, root length and total germination length of cotton exposed to Diclofenac (Group-I), Fluconazole (Group – II) and Carbamazepine (Group-III) for different concentrations (0–600 ppb) were expressed as mean ± SD (n = 3). Data was analyzed using ANOVA to compare the mean of the study variables using SPSS software version 24.0. The p-value < 0.05 was considered as statistically significant.

RESULTS

A concentration dependent reduction in cotton growth parameters was observed following exposure to diclofenac, fluconazole, and carbamazepine. Fluconazole produced a significant decrease in shoot length (p = 0.0001), whereas diclofenac (p = 0.13) and carbamazepine (p = 0.07) did not show statistically significant effects on shoot growth (Table 01) . Root length was significantly reduced by all three drugs, with diclofenac (p = 0.0001), fluconazole (p = 0.00001), and carbamazepine (p = 0.00001) producing marked inhibition (Table 02) . Total germination length also showed a significant reduction in all treatment groups (p = 0.00001) as mentioned in (Table 03). Fluconazole exhibited the greatest inhibitory effect on shoot growth, while carbamazepine produced marked suppression of root elongation. Root length emerged as the most sensitive indicator of pharmaceutical-induced phytotoxicity in cotton seedlings.

Table 01 : Shoot Length of cotton expressed in centimeter

Growth Parameter	Dose (PPB)	Group I – Diclofenac	Group II – Fluconazole	Group III – Carbamazepine
Total Germination Length	0 PPB	17 ± 1.93	17.5 ± 1.97	16.5 ± 1.86
	25 PPB	17 ± 1.92	17 ± 1.95	16 ± 1.89
	50 PPB	16 ± 1.83	15.5 ± 1.79	16 ± 1.87
	100 PPB	15 ± 1.75	13.5 ± 1.58	16 ± 1.80
	200 PPB	15 ± 1.79	10.8 ± 1.28	15.5 ± 1.76
	600 PPB	13 ± 1.53	11 ± 1.35	12 ± 1.42
P value	—	**0.00001***	**0.00001***	**0.00001***

* p value of < 0.05 considered to be statistically significant

Table 02 : Root Length of cotton expressed in centimeter

Growth Parameter	Dose (PPB)	Group I – Diclofenac	Group II – Fluconazole	Group III – Carbamazepine
Root Length	0 PPB	16 ± 1.86	15.5 ± 1.73	15 ± 1.71
	25 PPB	8 ± 1.03	7.5 ± 0.98	6 ± 0.83
	50 PPB	7 ± 0.98	6.2 ± 0.88	5 ± 0.76
	100 PPB	7 ± 0.91	6 ± 0.87	4 ± 0.65
	200 PPB	5 ± 0.72	4.5 ± 0.62	3.5 ± 0.56
	600 PPB	3 ± 0.56	3.5 ± 0.51	2.5 ± 0.41
P value	—	**0.0001***	**0.00001***	**0.00001***

* p value of < 0.05 considered to be statistically significant

Table 03 : Total germination length of cotton expressed in centimeter

Growth Parameter	Dose (PPB)	Group I (Diclofenac)	Group II (Fluconazole)	Group III (Carbamazepine)
Total Germination Length	0PPB	32 ± 3.46	33 ± 3.56	31 ± 3.34
	0 PPB	32 ± 3.46	33 ± 3.56	31 ± 3.34
	25 PPB	25 ± 2.75	23 ± 2.57	21.5 ± 2.35
	50 PPB	24 ± 2.64	23 ± 2.53	21.5 ± 2.39
	100 PPB	22 ± 2.45	18 ± 2.07	20 ± 2.25
	200 PPB	20 ± 2.23	17 ± 1.91	19.5 ± 2.13
P value	—	**0.00001***	**0.00001***	**0.00001***

* p value of < 0.05 considered to be statistically significant

Image 01 : Group I – Diclofenac

Image 02 : Group II – Fluconazole

Image 03 : Group III - Carbamazepine

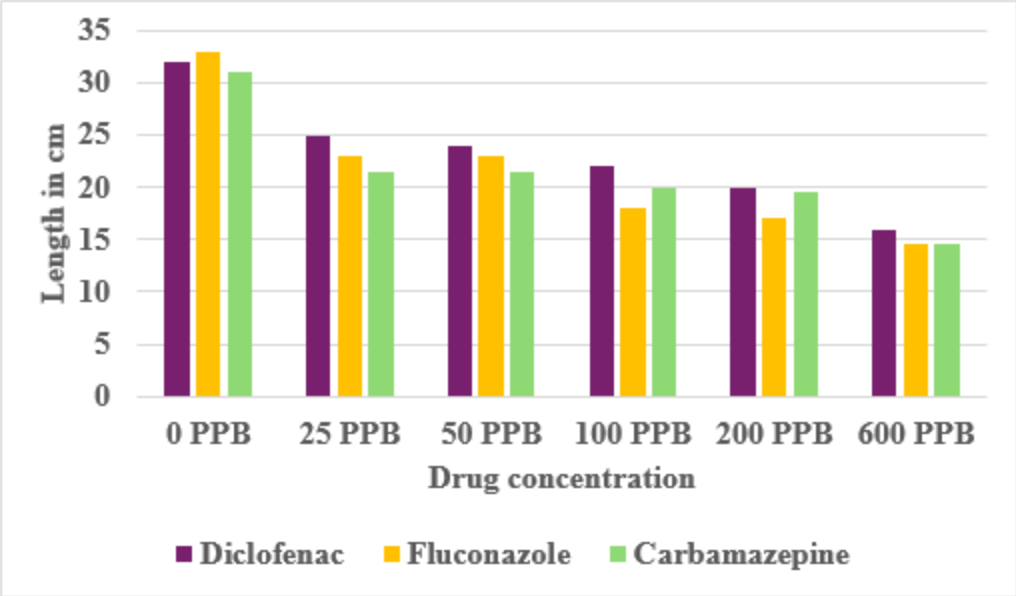

Figure 01 : Total Germination length of cotton (in centimeter) compared between Group I (Diclofenac) , Group II (Fluconazole) and Group III (Carbamazepine)

DISCUSSION

The present study demonstrates an observable dose dependent inhibitory effect of Diclofenac, Fluconazole, and Carbamazepine on the early growth parameters such as shoot length, root length and total germination length of the cotton plant. Negative correlation was observed between drug concentration and plant growth suggesting phytotoxic impact on physiological and biochemical processes that are essential for seed germination and development. Among the compounds tested, Fluconazole demonstrated the most significant reduction in both root and shoot length. Root elongation was more sensitive, showing greater decline at 600 ppb compared to the control. This strong inhibition effect may linked to azole mediated interference of sterol synthesis of cell and disrupting the integrity of membrane, that impairs cellular division and elongation in root tissues. Carbamazepine showed marked growth suppression, with root length declining significantly than shoot elongation.

The observed toxic effect could be related to its interference with ion channel regulation, cell wall development or oxidative imbalance in plants. Even at lower concentrations there were significant reduction in root length thus emphasizing its potential environmental accumulation effects in the soil. Even though Diclofenac has less negative impact compared to Fluconazole and Carbamazepine, still demonstrated a significant decline in root length and total germination length, particularly at higher concentration of ≥200 ppb. Phytotoxic effect of Diclofenac is likely due to oxidative stress induction and enzymatic inhibition, showing its negative influence on plant growth and seed development.

The systematic review by Carballo M, et al. emphasized that exposure to pharmaceutical contaminants specifically antibiotics, can adversely affects normal plant growth.(14) These observations support the present findings, in which exposure to pharmaceutical compounds resulted in concentration dependent inhibition of cotton seedling growth.

De Mastro F et al. investigated the effects of twelve pharmaceutical compounds on germination and early growth of Ocimum basilicum. The authors observed that higher concentrations produced significant reductions in shoot growth, root growth, and photosynthetic pigment content. Low concentrations exhibited minimal phytotoxicity, whereas higher doses caused marked inhibition of seedling development. The study further demonstrated that early growth parameters were more sensitive indicators of pharmaceutical toxicity than germination percentage.(15) Similarly, the present study showed concentration dependent reductions in growth parameters.

Eggen et al.(2011) reported that pharmaceutical residues accumulated predominantly in root tissues and adversely affected plant growth.(16)This supports the present finding that root length is a sensitive biomarker of pharmaceutical induced phytotoxicity.

In our study, even at low concentrations of 25–50 ppb there was a significant reduction in root length, shoot length and total germination length indicating that these residues in the environment pose a potential impact on ecosystem. The

pronounced effect noted in root growth suggests that it is a reliable and sensitive indicator for early detection of drugs induced harm to the plants. These findings illustrate the necessity for continuous monitoring and regulation of drug contaminants in both soil and water ecosystems to prevent negative effect on plant development and health.

CONCLUSION

Further investigations on whether the phytotoxicological effect of these drug compounds in plant and their recognized mechanism of action seen in humans i.e.; cyclooxygenase inhibition by Diclofenac, sterol synthesis inhibition by Fluconazole, modulation of ion channel by Carbamazepine parallel the biochemical alterations in physiological mechanism in plants. Such insights can reveal cross-kingdom pharmacodynamics and identify molecular pathways shared between plant and mammalian systems.

Moreover, long-term studies are needed to assess the chronic phytotoxic effect and the combined exposure of numerous drug residues which will enlighten us with a more realistic and practical visualization of drug induced environmental imbalance. Integrated approach such as designing biodegradable ecofriendly drugs and phytoremediation methods into environmental risk management framework will be crucial for creating a sustainable environmental management strategy and minimizing the ecosystem impact of drug contamination. Drug induced environmental toxicity testing should be included as a routine aspect during drug discovery and post-marketing surveillance process which will ensure that future therapeutics are efficacious to consumers and safer to environment.

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