Anita Singh · Sheo Mohan Prasad
Rajeev Pratap Singh *Editors*

Plant Responses to Xenobiotics

Springer

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ISBN 978-981-10-2859-5 ISBN 978-981-10-2860-1 (eBook)
DOI 10.1007/978-981-10-2860-1

Library of Congress Control Number: 2016962721

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #22-06/08 Gateway East, Singapore 189721, Singapore

Dedicated to Our Parents

Foreword

I am pleased to write the foreword for this book, edited by Dr. Anita Singh, Dr. Sheo Mohan Prasad, and Dr. Rajeev Pratap Singh. They have focused this book on an extremely important area of active research – the effects of environmental xenobiotics on plant function. Plants play an important role in the functioning of all terrestrial and aquatic ecosystems, as well as providing a critical food source for human populations. Unfortunately, human activity can result in soil, air, and water contamination by compounds including metals, radionuclides, pesticides, and other trace organic compounds, as well as newly identified contaminants such as engineered nanoparticles. These contaminants are introduced to the environment through industrial and municipal waste discharges, agricultural activities, and mining practices. The influence of these environmental contaminants on plants can include uptake of the contaminants into the plant, including the edible portion of food crops, as well as effects on plant physiological and biochemical processes. This book highlights important emerging research focusing on the responses of plants to these xenobiotic inputs, including chapters focusing on mechanisms for plant uptake and accumulation of xenobiotics, regulation and degradation of xenobiotics in planta, and plant toxicity to xenobiotics. Additionally, this book addresses the influence of critical emerging practices such as the use of municipal or agricultural wastewater as an irrigation water source. The use of this practice will only increase as we continue to face water shortages; however, the effect of using wastewater as an irrigation source water requires that we fully understand the environmental and human health impacts of this practice. Finally, the book presents information on alternative biodegradable thermoplastics, which could reduce the use of traditional plastics such as polystyrene and polyethylene terephthalate. I believe this book makes an important contribution to our understanding of the impacts of environmental contaminants on plants, and its focus on mechanistic studies and risk assessment will be of interest to researchers as well as policy makers.

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Shannon L. Bartelt-Hunt

Preface

Environmental pollution is one of the major problems due to fast pace of industrialization and uncontrolled exploitation of natural resources. It leads to the enhanced exposure of ecosystems to the substances called xenobiotics. The term xenobiotic is derived from the Greek words ξένος (xenos) = foreigner, stranger and βίος (bios, vios) = life. So, xenobiotics are any chemical or other substance that is not normally found in the ecosystems or that is present at the concentrations harmful to all biological organisms. They include organic contaminants such as pesticides, solvents, and petroleum products and inorganic contaminants such as heavy metals, nonmetals, metalloids, and simple soluble salts. They affect each and every component of ecosystem, and the plants which are the keystone of this system also get affected by the presence of xenobiotics in the environment. In this volume different kinds of xenobiotics are discussed in detail, and their effect and how the plants cope with such situation are explained by different contributions through the following chapters.

Chapter 1. *Environmental Xenobiotics and Its Effects on Natural Ecosystem*: Environmental xenobiotic is a global issue due to several activities, and one of them is the release of pharmaceutical residues in surface water. Recently, the demand for pharmaceuticals versus population growth has placed the public at risk. In addition, the making of unlawful drugs has led to the discharge of harmful carcinogens into the water system. The release of these harmful pollutants results in numerous short- and long-term effects to the natural ecosystem. This chapter takes a critical look at the various forms of environmental xenobiotics present in our ecosystem. In subsequent subheadings, their classification, sources, and routes of exposure to man, animals, and plants have been discussed. Lastly environment-friendly approaches to prevention had been discussed in a broader view and recommendations proffered.

Chapter 2. *Heavy Metal and Their Regulation in Plant System: An Overview*: Environmental pollution due to heavy metals is a threatening issue in the present scenario. In the past few decades, rapid and unplanned industrialization has caused the contamination of land and water. Plants exposed to such disturbed environment experience several physiological and biochemical alterations. However, some plants have acclimatized to the changed situation and developed defense mechanism like immobilization, compartmentalization, etc., to withstand the stressed conditions. This chapter gives an insight to the various physiological and biochemical alterations and mechanisms evolved by these plants growing in contaminated environment.

Chapter 3. *Regulation of Xenobiotics in Higher Plants: Signalling and Detoxification*: Xenobiotics are the chemical compounds that are not internally produced in plants, and their exposure is continuously increasing in plants, due to enhanced industrial pollutants. It can affect the growth, physiology, and other metabolic changes in every organism alone and/or in combination, which varies from species to species. Plants already have a versatile detoxification system to combat these changes (phytotoxicity) arising from a wide variety of natural and synthetic chemicals-xenobiotics present in the environment. One of the important detoxification mechanisms is chemical modification of xenobiotics by the covalent linkage to endogenous glutathione. The reactions involved in chemical modification have two phases: phase I (activation) reactions, which usually involve hydrolysis or oxidation, and phase II (conjugation) reactions, which are involved in synthesis. The resulting glutathione conjugates are exported from cytosol to vacuole via ATP-dependent tonoplast transporter. In addition to this, agrochemicals like safeners are also known to protect the crop plants from herbicide damage without reducing the activity in target weed species by elevating the expression of xenobiotic detoxifying enzymes, such as glutathione-S-transferases (GSTs). So, the present chapter gives valuable information on the different fates of xenobiotics as well as provides better understanding in the field of xenobiotic action in plants.

Chapter 4. *Metabolic Responses of Pesticides in Plants and Their Ameliorative Processes*: This chapter is of great relevance to students, researchers, scientists, and even the general public (lacking any scientific background) at large. Large anthropogenic inputs of pesticides for enhancing agricultural productivity and also for amelioration of vector-borne diseases have led to serious health implications to man and his environment. This is a comprehensive chapter which provides collective information of different types of pesticides, their sources, disadvantages, and toxicity symptoms in target as well as non-target organisms. It also deals with uptake, transport, and metabolism of pesticides in plants. Simultaneously it highlights the detoxification mechanisms adopted by plants to protect themselves from the adverse effects of pesticides. Another important aspect of this chapter is its holistic approach in hinting towards practices which can aid us in designing efficient and cheap vegetative treatment systems for remediation of contaminated soil and water.

Chapter 5. *Assessment of Antioxidant Potential of Plants in Response to Heavy Metals*: This chapter encompasses the complete comprehensive coverage on heavy metal occurrence, translocation, and their toxicities in plants and also the different mechanisms of antioxidants acting on the plant during oxidative stress. Here the chapter incorporates the detailed discussion on the scavenging mechanism of various antioxidants. The chapter further includes the information on traditional antioxidant like enzymatic, non-enzymatic, and secondary metabolites, and it also focuses on the method of assessment of antioxidant potential in *in vivo* and *in vitro* condition. Further, a brief attempt has also been made to provide contemporary and relevant collections of different studies ongoing on the antioxidant potential of plant.

Chapter 6. *Impact of Heavy Metals on Physiological Processes of Plants: With Special Reference to Photosynthetic System*: The present chapter highlights the effect of heavy metals on photosynthetic pigments, photosynthetic apparatus, and light and dark reactions. It helps us to understand in detail how exposure of plants to heavy metals led to generation of ROS and ROS-induced lipid peroxidation which destroy their cell membrane and their associated organelles. This chapter also highlights detail mechanism of the (i) impact of heavy metals on chlorophyll biosynthesis and also on various enzymes involved in chlorophyll biosynthesis and (ii) their effect on electron transport in light reactions and how they affect various enzymes in dark reactions.

Chapter 7. *Impact, Metabolism, and Toxicity of Heavy Metals in Plants*: Heavy metal contamination is a serious problem worldwide. These metals are the major inorganic contaminants of soil, and a considerable large area of land is contaminated with them due to anthropogenic activities. Contamination of agricultural soil by heavy metals has become a critical environmental concern due to their long-term persistent nature and potential harmful ecological effects. Therefore, it is important to study about the entry of these toxic metals in food chain. In this chapter we describe how far heavy metals enter and transport in plants, what are the different strategies of plants at different levels (from binding at cell wall to synthesis of some proteins to bind) to overcome toxic condition, and what are the heavy metal specific toxic effects on plants when exposed to metal-enriched environment.

Chapter 8. *Heavy Metal Accumulation Potential and Tolerance in Tree and Grass Species*: Identification of the role of higher plants in monitoring and in remediation of xenobiotics is important for polluted environments. Heavy metals are most widespread and one of the most toxic constituents of our environment. For selection of trees and grasses for monitoring and remediation purposes, it is necessary to identify plants from diverse environment and classify them based on their tolerance. Thus plants with higher accumulation potential have special tolerance mechanisms that enable them to survive and accumulate metals in higher concentrations compared to other plants. Considering these points, we have tried to identify tree and grass species based on their metal accumulation potential and tolerance so that academicians, researchers, plant breeders, urban planners, and environmental managers can utilize these findings to improve the understanding of the topic and may use the information for sustainable environmental management practices.

Chapter 9. *Microbial-Mediated Management of Organic Xenobiotic Pollutants in Agricultural Lands*: Exposure of plants to organic xenobiotic pollutants leads to several biochemical and molecular alterations producing serious variations in plant physiology resulting in deformed growth and development, ultimately hampering the productivity. As the concentration of these xenobiotics increases, their detrimental effects on plants are also pronounced. Soil microorganisms play crucial role in the management of the detrimental effects of such organic xenobiotic pollutants. They act as a barrier between the plant and the xenobiotic, and with their effective abilities to degrade the xenobiotic, they restrict the entry of these compounds in the plants and hence maintain plant growth and productivity. In this context the present chapter proves significant as it discusses the possible mechanisms for mitigation of the organic xenobiotic pollution load in the agricultural fields and opens up newer areas of research.

Chapter 10. *Metals from Mining and Metallurgical Industries and Their Toxicological Impacts on Plants*: Mining and metallurgical industries have been of great importance in the economic development of a country. However, solid wastes generated from such industries are characterized by elevated levels of essential and non-essential metals which may pose toxic effects on plants growing in and around the dumping sites. Minimum to maximum concentrations of twenty predominantly occurring metals in solid wastes from mining and metallurgical industries have been illustrated in this chapter. Adverse effects of metals exceeding their phytotoxic thresholds on growth performance and physiological and biochemical parameters of crop and medicinal plants have been discussed. The study also emphasizes the impacts of metals on plant community structure in the vicinity of industrial areas. The chapter suggests some future prospects in plausible and better management options of industrial wastes including site restoration by rehabilitation and phytoremediation using native and medicinal plant species.

Chapter 11. *The Risk Associated with the Xenobiotics Released Through Wastewater Reuse*: This chapter addresses the problems arising due to repeated use of wastewater on living system. The application of wastewater releases xenobiotic compounds that include heavy metal, pharmaceutical, pesticides, personal care products, etc. Here in this chapter, the authors have provided an overview of risk assessment arising from entrance of xenobiotic in the environment and also given a brief description of regulatory bodies involved in managing the risk.

Chapter 12. *Silver Nanoparticle in Agroecosystem: Applicability on Plant and Risk-Benefit Assessment*: In the current era, food security, life sustainability, and climate change are the most emerging challenges for researchers. Applicability of nanotechnology represents a novel step in the development and improvements in agricultural sectors to cope with scarcity of increasing food demand. The agricultural sectors can be seen to be clearly benefiting from nanotechnology. In particular, silver nanoparticles are reported to show a prime role in crop protection, antimicrobial applications, supplementation of required nutrients, and pesticide delivery in an optimized and controlled way. However, the negative effects due to the excessive use of these nanoparticles on biological life may also not be overlooked. This chapter focuses on applicability of silver nanoparticles in agricultural sector and points out their risk value to clearly instruct the use of these nanoparticles in a regulated and managed way.

Chapter 13. *The Significance of Plant-Associated Microbial Rhizosphere for the Degradation of Xenobiotic Compounds*: Presently human populations are increasing day by day causing pollution of various xenobiotic compounds in the environment to degrade the soil fertility and health. These xenobiotic compounds (heavy metals and hydrocarbons, pesticides, persistent organic pollutants, POPs), present in soils and waters, create many human and animal diseases (like immunosuppression, hormone disruption, reproductive abnormalities, and cancer). Degradation of xenobiotic pollutants by conventional approaches based on physicochemical methods is economically and technically challenging. Rhizo-remediation and microbial remediation techniques based on plant roots and their associated microbes are the most promising, efficient, cost-effective, environment-friendly, and sustainable technology. A variety of chemicals like organic acids, amino acids, and phenolic compounds are secreted by such plants as root exudates. These compounds play a significant role in communication between plant root and microbes and also are helpful to stimulate the remediation and the efficiency of microbes against xenobiotic pollutants. This book chapter heightens the degradation of xenobiotic compounds with the help of rhizosphere microbes that can be associated with plants to enhance the plant growth and yields as well as degrade the xenobiotic compound into elemental form that can be taken by the plant and microbes as nutrient or carbon source. The application of rhizospheric microorganisms (like bacteria, fungi, and actinomycetes) that interact with plant roots helps in the degradation of xenobiotic compounds without causing any environmental problems and also provides efficient, economic, and sustainable green remediation technology.

Chapter 14. *Biodegradable Polyhydroxyalkanoate Thermoplastics Substituting Xenobiotic Plastics: A Way Forward for Sustainable Environment*: Plastic, a miracle material of modern world, is indispensible and ubiquitous. The stability, durability, and low cost of plastics have attributed for their wide adaptability. Durability and resistance to degradation are desirable features when plastics are in use. Nevertheless, they cause serious problems to the environment when disposed due to their xenobiotic nature. All these issues of xenobiotic plastics translated into the need and concern for the production of biodegradable plastics/bioplastics. Amongst bioplastics, the completely biodegradable polyhydroxyalkanoates (PHAs) have received increasing research and commercial interest owing to their eco-friendly, optically active, elastomeric, and piezoelectric properties, renewable compounds, high degree of polymerization, non-toxicity, biocompatibility, hydrophobicity, and material properties comparable to conventional plastics. The foremost obstacle facing triumphant commercialization of PHA bioplastics is the high price of bacterial fermentation. Photoautotrophic hosts such as plants and cyanobacteria are being explored across the globe for low-cost PHA production. However, large-scale production is still a constraint. Presently, major attempt has been devoted to making PHA production process cost-effectively more feasible by changing the substrate from expensive to cost-effective, engineering efficient microorganisms, improving fermentation and separation processes, or applying mutational approaches/genetic engineering techniques.

So, overall this book contains all the valuable information related to the different kinds of xenobiotics and their impact upon plant physiology and metabolism. It will definitely be useful for the scientists, academicians, researchers, as well as students of different streams.

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Acknowledgment

The editors acknowledge the Head of the Department of Botany, University of Allahabad, for providing necessary facilities. The editor Dr. Anita Singh is thankful to the Science and Engineering Research Board (SERB) for providing fellowship under Start-Up Research Grant as a DST Young Scientist (Grant No. SB/YS/LS/-228/2013). The editor Dr. Rajeev Pratap Singh is thankful to DST (P-45/18) and ICMR for providing the fund and the Director and Head of Institute of Environment and Sustainable Development, Banaras Hindu University, for providing necessary facilities.

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About the Editors

Currently **Dr. Anita Singh** is working as DST-Young Scientist in the Department of Botany, University of Allahabad, Allahabad, India. Her expertise falls under the domain of sustainable agriculture as well as metal remediation. She has done Ph.D. on the topic entitled "Effect of irrigation water on heavy metal contamination of vegetable Crops" under the supervision of Prof. Madhoolika Agrawal from Banaras Hindu University, Varanasi, India. She has worked on Metal remediation, impact of abiotic stress on plant physiology and biochemistry, assessment of Florescence Transients and other plants metabolic activities. Her research capability can be judged from some very good publications in reputed journals. Till date, She has 40 publications including research article, review and chapters to her credit in the reputed international journal/books. During her research period she got International Green Talent Award organized by BASF, Germany. She also got an International Alice J. Murphy Outstanding Achievement Award for excellence in Research and Education leading to better Understanding of the Ecology of the Tropics.

Dr. Sheo Mohan Prasad is Professor in the Department of Botany, University of Allahabad. He obtained his M.Sc. and Ph.D. degrees from the Banaras Hindu University, Varanasi, India. Prof. Prasad has authored more than 138 scientific publications. He has guided 20 Ph.D. students and is supervising 7 research students and 3 P.D.F. on varied aspects of physiology and biochemistry of plants and cyanobacteria exposed to abiotic stresses: heavy metal, pesticide, salinity, high light with special reference to the role of ROS as signalling as well as oxidants. Prof. Prasad is also working as editor and reviewers of several reputed international journals and he is also the life member and Fellow of the Indian Botanical Society and member of The National Academy of Sciences. India.

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List of Abbreviations

AAS	Absorption spectroscopy
ABC	ATP-binding cassette
AChE	Acetylcholinesterase
AgNPs	Nanosilver particles
AMPA	Aminomethyl-phosphonic acid
ANCA	Anti-neutrophil cytoplasmic antibody
APX	Ascorbate peroxidase
BOD	Biological oxygen demand
BRs	Brassinosteroids
CAT	Catalase
CDF	Cation diffusion facilitator
CGWB	Central Ground Water Board
CM-H2DCFDA	Chloromethyl-2',7'-dichlorohydrofluorescein diacetate
COD	Chemical oxygen demand
COX	Cyclooxygenase enzyme
CP	Carboxypeptidase
CPF	Chlorpyrifos
CYPs	Cytochrome P450 mixed function oxidases
Cysteine	(Cys)
DAB	Diaminobenzidine
DDE	Dichlorodiphenyldichloroethylene
DHAP	Dihydroxyacetone phosphate
DHAR	Dehydroascorbate reductase
DHE	Dihydroethidium
DP	Dipeptidase
EDCs	Endocrine disrupting compounds
EDTA	Ethylenediaminetetraacetate
EDX	Energy-dispersive X-ray analysis
EPPP	Environmental Pharmaceutical Persistent Pollutants
EPS	Extracellular polymeric substances
ET	Electron transfer
EU	European Union
FAO	Food and Agriculture Organization
GABA	Gated chloride channel blockers

GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GDP	Gross domestic product
GR	Glutathione reductase
GSR	Glutathione-disulfide reductase
GSSG	Oxidized glutathione
GSTs	Glutathione-*S*-transferases
GT	Glycosyltransferases
HAT	Hydrogen atom transfer
HDL	High-density lipoproteins
HM	Heavy metals
HPPD	4-Hydroxyphenylpyruvate dioxygenase
IA	Image analyzer
IARC	International Agency for Research on Cancer
IMDH	Isopropylmalate dehydrogenase
IRA	Infrared analysis
IRT	Iron-regulated transporter
LIMS	Laser ionization mass spectrometer
LPIC	Lipid peroxidation inhibition capacity
MDA	Malondialdehyde
MATE	Multidrug and toxin efflux
MDHA	Monodehydroascorbate
MTs	Metallothioneins
MPL	Maximum permissible limit
MRP	Multidrug resistance-associated protein
NACHR-	Nicotinic acetylcholine receptor
NBT	Nitro blue tetrazolium
NHPs	Natural health products
NA	Nicotianamine
NPP	Net primary productivity
NRAMP	Natural resistance-associated macrophage protein
NSAID	Non-steroidal anti-inflammatory drugs
OP	Organophosphate
ORAC	Oxygen radical absorbance capacity
PAHs	Polycyclic aromatic hydrocarbons
PCBs	Polychlorinated biphenyls
PCE	Perchloroethylene
PCS	Phytochelatin synthetase
PDR	Pleiotropic drug resistance
PGA	Phosphoglyceric acid
PhACs	Pharmaceutical active compounds
PHE	Phenanthrene
PIXE	Proton-induced X-ray emission
PHA	Polyhydroxyalkanoate
POPs	Persistent organic pollutants
POX	Peroxidases

PPCPs	Pharmaceuticals and personal care products
RA	Rheumatoid arthritis
ROS	Reactive oxygen species
RuBisCO	Ribulose bisphosphate carboxylase
SA	Salicylic acid
SEM	Scanning electron microscopy
SIMS	Secondary ion mass spectrometer
SLE	Systematic lupus erythematosus
SOD	Superoxide dismutase
SSc	Systemic sclerosis
TBT	Tributyltin
TCE	Trichloroethene
THMs	triethylene, trihalomethanes
TLR	Toll-like receptors
TRAP	Total radical trapping antioxidant parameter
UTUC	Urinary tract urothelial cell carcinoma
VLDL	Very low-density lipoprotein
WHO	World Health Organization
XRD	X-ray diffraction
YSL	Yellow-stripe-like
ZRT	Zinc-regulated transporter

Environmental Xenobiotics and Its Effects on Natural Ecosystem

1

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Parveen Fatemeh Rupani,
and Mahammad Hakimi Ibrahim

Abstract

Environmental contamination by xenobiotics is a worldwide phenomenon as a result of human activities resulting from rise in urbanization and population growth. There are numerous sources of xenobiotics ranging from pharmaceuticals to agriculture. Recently, the demand for pharmaceuticals versus population growth has placed the public at risk. In addition, the making of unlawful drugs has led to the discharge of harmful carcinogens into the water system. The release of these harmful pollutants results in numerous short- and long-term effects to the natural ecosystem. This review takes a look at the sources of xenobiotics, their fate in the ecosystem and means of action with possible prevention methods.

Keywords

Xenobiotics • Carcinogens • Degradation

1.1 Introduction

Since the time of the Industrial Revolution, scientific and technological developments permitted humans in the over utilization of resources creating disturbance to the natural ecosystem (Sikandar et al. 2013). The generation of huge amount of toxic substances released from industrial processes caused widespread contamination of the ecosystem. The major contaminants are halogenated and nitrated hydrocarbons (Jain et al. 2005). Several herbicides, insecticides and fertilizers used in

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A. Singh et al. (eds.), *Plant Responses to Xenobiotics*,
DOI 10.1007/978-981-10-2860-1_1

agricultural activities as well as synthetic compounds are produced from industrial activities, namely, pharmaceuticals, agrochemicals, dyes, solvents, halogenated compounds, hydraulics, fire retardants, pigments, etc. (Reineke and Knackmuss 1988). Pharmaceutical wastes have become well known sources of prolonged environmental contamination due to the continous use in anthropoid and veterinary medications. These chemicals are believed to have specific mode of action in the body. The chemical composition of pharmaceuticals lead to possible effects on aquatic flora and fauna as compared to other chemical compounds. However, pharmaceuticals are proposed to pose only a low risk for acute toxicity in the environment. For chronic effects, the situation may be different; nevertheless, there is a considerable lack of information for the chronic effects and its risk of toxicity. In addition, there is little or no informationregarding multi generational life cycle effects, knowing that exposure to toxicity in many aquatic organisms happen during their entire life (Fent et al. 2006). Accordingly, various environmental analyses reported that the drug residues in surface water and treated wastewater are widespread. These chemical compounds that arise from industries are xenobiotics. Xenobiotic compound is persistent in the environment with toxicity effect making them potential health hazards leading to significant impacts on the ecosystem. Therefore, researchers need to focus more on effects of pollution and its prevention techniques.

1.2 Xenobiotics: Sources and Types

Originally, the term xenobiotic comes from the Greek word xenos, which means foreign or strange, and ‘bios’, which means life. Xenobiotics are chemical compounds exhibiting abnormal structural characteristics (Fetzner 2002). The unusual presence of any substance in high concentrations can also be regarded as xenobiotics, for instance, the presence of antibiotic drugs in the human body which may not be produced by the body itself nor is a normal part of diet. At times, a natural substance can be defined as a xenobiotic if it found its way into humans or other animals. Bonjoko (2014) proposed the word ‘xenobiotic’ based on the physiological and biological effects of exogenous substances whether natural or synthetic (drugs, chemicals) on the cells, tissues or organs of the organisms.

Many xenobiotics are potientially hazardous to the organisms which are exposed to them in the environment. However, bioavailabilities of such substances are dependent upon the characteristics of the organism, the chemical, and the environment. Maenpaa (2007) reported that the toxicity of any xenobiotic is related to the bioaccumulated chemical residue in the organism. Xenobiotics may persevere for long term (months to years) in the environment. For example, the polymer structure of lignin, or the constituents of the cell wall of the spores of a few fungi (melanin polymers), may not degrade rapidly in the natural environment (Fetzner 2002). Similarly, in aquatic environments, hydrophobic pollutants which are eventually stored in sediments become hazardous on exposure to benthic organisms. Any exposure to the sediments contaminated by xenobiotics possibly affects the lower trophic levels. It may also result in biomagnification or more serious toxic effects at higher trophic levels (Landrum and Robbins 1990; Lee II 1992; Streit 1992; Newman 1998).

New technologies to determine trace polar compounds have helped to give new insights on the removal of xenobiotics. In the beginning, pharmaceutical products were reported in treated wastewater in the USA, with the range of about 0.8–2 μg/L (Garrison et al. 1976). Thereafter, the UK reported 1 μg/L of clofibric acid in the rivers (Richardson and Bowron 1985). In 1986, Rogers (from Canada) identified the concentration of naproxen and ibuprofen in wastewaters. Accumulation of diclofenac, a pain killer which was used by veterinarian to treat cattle, significantly reduced the population of Asian white-backed and Indian vultures (9 from 150 in 1997 to 25 in 2010) nesting in Keoladeo Natural Park in North Western India. The Geological Survey Department (United States) reported traces of many different drugs and toiletries as well as steroids, insect repellants and phthalates in the water supply. Even though the concentrations were in traces, the effect of chronic exposure can be unpredictable. For example, production of bulk drugs has been recently identified as an important source of environmental pollution which consists of active pharmaceutical elements in certain locations (Gunnarsson et al. 2009; Fick et al. 2010). Also, there are raising concerns worldwide on the pharmaceutical residues found in surface water which can have effects on aquatic organisms. Therefore, there is a major challenge in developing lucid strategy for prioritizing drugs on which to focus the most extensive environmental research efforts for (Fick et al. 2010).

1.3 Sources of Pharmaceutical-Based Xenobiotics

There are different synthesized chemicals present in the environment which may have different interactions with the exposure to humans and the ecosystem. However, the details of these impacts are not adequately studied or understood. Among the different pharmaceutical substances, pharmaceutical active compounds (PhACs) are xenobiotic-based elements that entered the environment as the parent compound or as pharmacologically active metabolites (Bonjoko 2014). PhACs are considered as potentially toxic compounds that are largely used in agriculture and industry. However, for many years the researches were based on the pharmaceutical regulations which were of interest by drug organizations, and less attention was paid on the toxicity and its environmental issues (Jones et al. 2001).

Environmental pharmaceutical persistent pollutants (EPPPs) are the components which are available in waterbodies all over the world. Not much literature is available about the possible negative effects and impacts of EPPP in humans and the environment. Bonjoko (2014) reported that EPP's exposure may cause extinction of species and imbalance of sensible ecosystems (EPPS affect the reproductive systems of, e.g. frogs, fish and mussels). For example, in sewage plants of pharmaceutical industries, large amount of antibiotics and other pharmaceutical compounds have been found. According to the European Union (EU), about 3000 different substances were found in downstream that were used in human medicine such as antibiotics, beta-blockers, analgesics and anti-inflammatory drugs and many others. Likewise, a large number of pharmaceuticals are used in veterinary medicine such as antibiotics and anti-inflammatory (Fent et al. 2006). Bonjoko (2014) explained the potential routes of entry of pharmaceutical and household care products in the environment. It includes:

1. Through patient excretion
2. Direct release into the wastewater system from manufacturing, hospitals or disposed through toilets and sinks
3. Terrestrial depositions, i.e. irrigation with treated and untreated wastewater, sludge application to land, leaching from solid waste landfills
4. Non-pharmaceutical industrial sources, i.e. plastic products
5. Agricultural wastes such as herbicides, pesticides and fertilizers
6. Through ageing infrastructures, i.e. synthetic compounds such as analgesics and antihistamines which were exposed in streams and rivers
7. Drugs associated with plant health
8. Herbal preparations and their interaction with the environment

1.4 Fate/Biodegradation of Xenobiotic Compounds

Xenobiotics with the presence of microbes can undergo biodegradation process depending on the microbe's species and the xenobiotic compounds.

Xenobiotic metabolism undergoes a biochemical modification of pharmaceutical substances (xenobiotics) by living organisms, which usually occurs through specialized enzymatic systems. Enzyme like cytochrome P_{450} secreted in the liver helps in the degradation process and thus excreted by urination, exhalation, sweating and defecation. Biodegradation and oxidation of a parent compound happen to form carbon dioxide and water. Each stages in the degradation pathway is catalysed by a specific enzyme produced by the degrading cell. However, degradation of some xenobiotics depends on its specific compound structure, which includes the required enzymes, for example, oxygenases. These enzymes are metabolized to provide energy as well as reducing equivalent for the degradation process (Bonjoko 2014). Figure 1.1 illustrates the possible environmental fate of a xenobiotic compound.

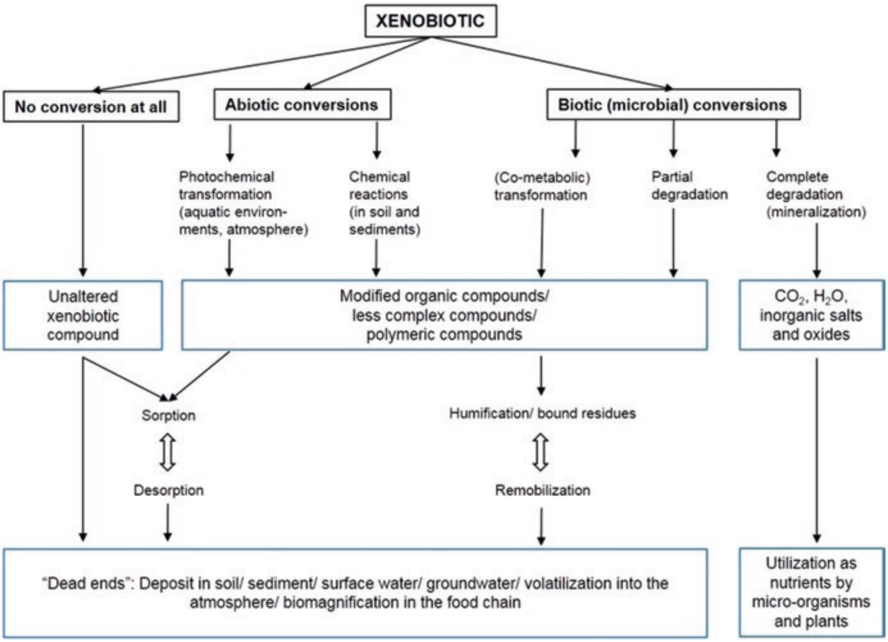

Fig. 1.1 Possible environmental fate of a xenobiotic compound

1.5 Common Xenobiotic Compounds Based on Its Course of Action

Xenobiotics are designed to target specific metabolic and molecular pathways in humans and animals in the ecosystem. However, when xenobiotics are introduced into the environment, they may affect the same pathways in animals having identical or similar target biomolecules, organs, tissues or cells. The current ecotoxicological effects of pharmaceuticals deal mainly with the acute toxicity in standardized tests and it is generally focused on aquatic organisms. The influence of environmental parameters such as pH on toxicity has only rarely or not yet been investigated. More studies have focused on acidic pharmaceuticals that may induce different toxicities depending on speciation at different ambient pH. Moreover, till date less research has been done on the effects of drug metabolites. The following are the common pharmaceutically based xenobiotic compounds that pose such environmental concerns. Figure 1.2 illustrates the different types of pharmaceutical xenobiotics.

1.5.1 Analgesics and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The widely used non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen and diclofenac and some of their metabolites such as hydroxyl-ibuprofen and carboxy-ibuprofen are widely used and usually can be detected in surface and

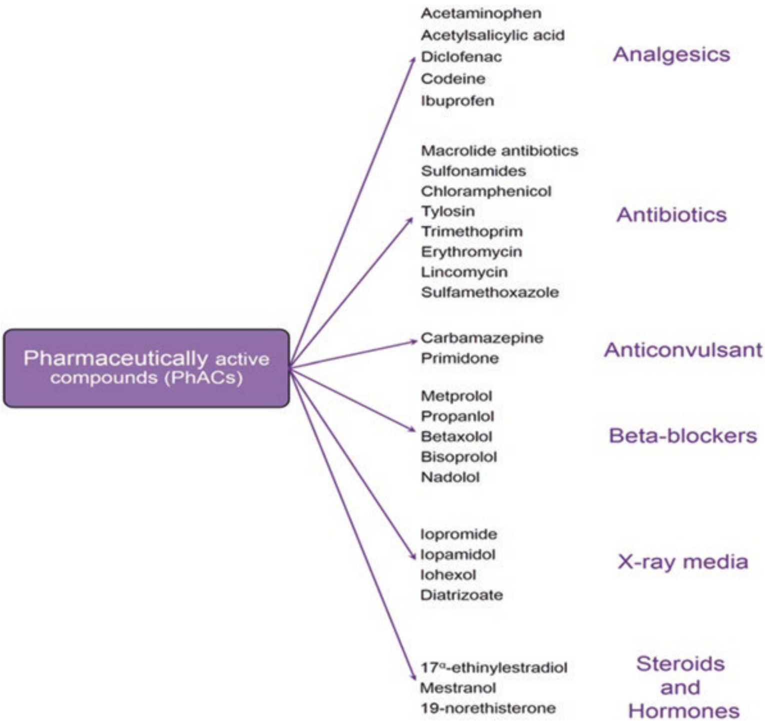

Fig. 1.2 Different types of pharmaceutical xenobiotics

water sewage. Gross et al. (2004) reported that NSAID levels exceed in sewage system to 1 µg/L, and it can exceed the concentration to 0.1 µg/L in the effluent of conventional sewage plants (mechanical clarification and biological treatment) in the USA. The deacylated which is a more active form of acetylsalicylic acid has detected in many municipal wastewaters at the levels up to 4.1 µg/L, 13 µg/L or even 59.6 µg/L. Similar to acetylsalicylic acid, acetaminophen (paracetamol) is well removed from STP. However, Kolpin et al. (2002) reported that up to 10 µg/L (median 0.11 µg/L) acetaminophen is spotted in 24 % of samples from US streams (Kolpin et al. 2002). Also, the analgesic codeine was detected in 7 % of samples (median 0.01 µg/L). Moreover, in many countries, diclofenac was frequently detected in the wastewater and also in lower levels of surface water.

Wiegel et al. (2004) have reported that in Norway, ibuprofen and its metabolites have been found in all sewage samples and in seawater at the concentrations of 0.1–20 µg/L. Kolpin et al. (2002) detected ibuprofen in 10 % of stream water samples in high concentrations up to 1 µg/L (median 0.2 µg/L). Moreover, several other NSAID compounds have been detected in sewage and surface water as well as in drinking water samples and groundwater.

1.5.1.1 Mode of Action

NSAIDs (non-steroidal anti-inflammatory drugs) are frequently used to treat inflammation and pain and to relieve fever, and sometimes they are also used for long-term treatment of rheumatic diseases. NSAIDs act by inhibiting factor either reversibly or irreversibly one isoform of the cyclooxygenase enzyme (COX-1 and COX-2), which catalyse the synthesis of different prostaglandins from arachidonic acid. COX-1 and COX-2 inhibit by classical NSAID at different degrees, whereas new NSAID act more selectively on COX-2, the inducible form which is responsible for the inflammatory reactions. Differences in binding site size are in charge for the selectivity of these drugs. NSAID inhibit nonspecifically.

In the kidney, prostaglandins are elaborate in maintenance of the equilibrium between vasoconstriction and vasodilatation of the blood vessel that supply glomerular filtration.

At times, after chronic NSAID treatments, renal damages or renal failure seems to be triggered by the lack of prostaglandins in vasodilatation-induction. Inhibition of both COX isoforms can cause gastric damages. In contrast, liver damages are apparently due to building of reactive metabolites (e.g. acyl glucuronides) rather than inhibition of prostaglandin synthesis (Bjorkman 1998). The mode of action of paracetamol is not yet fully elucidated. However, it has been found that this drug acts mainly by inhibiting the cyclooxygenase of the central nervous system, and it does not have anti-inflammatory effects, because of the lack of inhibition of peripheral cyclooxygenase involved in inflammatory processes. Adverse effects of paracetamol mainly occur when the availability of glutathione is diminished in liver cells which could be due to formation of hepatotoxic metabolites, primarily *N*-acetyl-*p*-benzoquinone.

1.5.2 Blood Lipid Regulators

The most frequently reported pharmaceutical in monitoring studies is clofibric acid which is an active metabolite from a widely used blood lipid regulators such as clofibrate, etofylline clofibrate and etofibrate. These compounds have been found in numerous wastewaters, surface waters and seawater and at rather high concentrations in drinking water (0.07–0.27 μg/L) and groundwater (4 μg/L). Bezafibrate and gemfibrozil which are lipid-lowering agent have been found in maximal concentrations of up to 4.6 and 0.79 μg/L, respectively, in wastewater and surface water, respectively (Kolpin et al. 2002). In addition, other drugs which act as metabolite of fenofibrate such as gemfibrozil, clofibric acid and fenofibric acid have also been detected in sewage up to the μg/L level and in surface water (Heberer 2002).

1.5.2.1 Mode of Action

There are basically two types of antilipidemic drugs, namely, statins and fibrates, which are used to decrease the concentration of cholesterol (statins and fibrates) and triglycerides (fibrates) in the blood plasma. These drugs have been targeted analytically more often in the aquatic environment. Statins as inhibitors of cholesterol synthesis act by inhibiting the 3-hydroxymethylglutaril coenzyme A reductase (HMG-CoA), responsible for the limiting step in the cholesterol synthesis, namely, the conversion of HMG-CoA to mevalonate. Due to interactions of statins with mevalonate metabolism, multiple additional effects occur (anti-inflammatory, anti-oxidative). Studies also show that statins affect juvenile hormone synthesis in insects as fluvastatin completely suppressed its biosynthesis in vitro and in the mandibular organ of lobsters. The effects of fibrates lead to alterations in transcription of genes encoding for proteins controlling lipoprotein metabolism and they also activate the lipoprotein lipase enzyme, which is mainly responsible for the conversion of very-low-density lipoprotein (VLDL) to high-density lipoproteins (HDL), decreasing therefore plasma triglyceride concentration.

Moreover, fibrates stimulate cellular fatty acid uptake by conversion to acetyl-CoA derivatives and catabolism by the beta-oxidation pathways. Hence, these processes are combined with a reduction in fatty acid and triglyceride synthesis that decreases in VLDL production. Studies on animal (rat) show that hepatic damages can occur after chronic exposure to fibrates and which could be due to the inhibition of mitochondrial oxidative phosphorylation. Fibrates caused in rodents a massive proliferation of peroxisomes. Strong correlation between fibrate exposure and hepatocarcinogenicity in rodents was found, while this was not observed in humans (Cajaraville et al. 2003). These findings increase the interest for ecotoxicological impact of this therapeutic class of drugs. Activators of PPARα genes (found in fishes) include different endogenously present fatty acids, leukotrienes and hydroxyeicosatetraenoic acids and drugs, such as fibrates.

1.5.3 Beta-Blockers

Several beta-blockers such as bisoprolol, propranolol and metoprolol were identified in wastewater showing 0.59, 2.9 and 2.2 μg/L, respectively. Also in lower concentration, other beta-blockers, namely, nadolol (in surface water) and betaxolol (0.028 μg/L in surface water), were detected (Ternes 1998). Moreover, Sacher et al. (2001) reported the presence of propranolol, metoprolol and bisoprolol in surface water and sotalol in groundwater.

1.5.3.1 Mode of Action

Beta-blockers act by competitively inhibiting beta-adrenergic receptors. They are employed for the treatment of high blood pressure (hypertension) and the prevention of heart attacks in high-risk patients. Regular body processes like heartbeat regulation and oxygen supply, vasodilatation of blood vessels and bronchodilation are the functions of the adrenergic system. Furthermore, it is important for the metabolism of carbohydrates and lipids in cases of starvation. Beta-blockers could selectively impede one or more β-receptor types based on their needs. For instance, β2-blockers are employed for the treatment of hypertension preventing impending cardiac arrests, as this receptor subtype is not present in the heart. Beta-blocker propranolol, a beta1-adrenoceptor antagonist, has the ability to stabilize cell membranes, unlike metoprolol which does not have that property (Doggrell 1990). Side effects of these beta-blockers are mostly bronchoconstriction and disturbed peripheral circulations. They are supposed to pass the blood-brain barrier and to act in the central nervous system because of their lipophilicity (Heberer 2002). Clenbuterol or ractopamine that functions in mammals as β-agonist had a different reaction in rainbow trouts. The different structures and function of the receptors may be responsible for varied affinity with β-blockers and mechanisms triggered by these drugs.

1.5.4 Neuroactive Compounds (Antiepileptics and Antidepressants)

Antiepileptic carbamazepine was detected most frequently and in highest concentration in wastewater (up to 6.3 μg/L) (Ternes 1998) and at lesser concentrations in other media (Heberer 2002). Carbamazepine was found in all effluent samples of the Canadian STP at concentration up to 2.3 μg/L. This substance was reported to be present in all samples of German river Elbe and streams (Wiegel et al. 2004), exceeding 1 μg/L in other surface waters (Ternes 1998; Heberer 2002) and also occurred in groundwater (Sacher et al. 2001). Carbamazepine was also reported at average levels of 20.9 ng/mg solids of STP. Diazepam was noted in 8 out of 20 treatment plants in Germany at relatively low concentrations of up to 0.04 μg/L (Ternes 1998), whereas in Belgium it was recorded at concentration up to 0.66 μg/L (van derVen et al. 2004). The antidepressant fluoxetine was also recorded in Canadian effluent samples, and in US streams, median concentrations of 0.012 μg/L were estimated (Kolpin et al. 2002). In addition to these, an antiepileptic drug, primidone (0.6 μg/L), was also identified in sewage (Heberer 2002).

1.5.4.1 Mode of Action

Antiepileptic drugs decrease the overall neuronal activity. This can be achieved either by blocking voltage-dependent sodium channels of excitatory neurons (e.g. carbamazepine) or by enhancing inhibitory effects of the GABA neurotransmitter by binding on an exact site in the gamma subunit of the corresponding receptor (e.g. diazepam, member of benzodiazepine family). The uptake of serotonin is inhibited by a very common antidepressant, fluoxetine. It is a neurotransmitter that has to do with hormonal and neuronal mechanisms, and it is vital for sexual behaviour and food intake. Fluoxetine, sertraline, norfluoxetine and desmethylsertraline have been discovered in fish sampled from the wild in the USA and therefore reflect a bioaccumulation potential (Brooks et al. 2005).

1.5.5 Various Other Compounds

Effluents of the sewage treatment plants and surface waters which have been contaminated by drugs are comprised of caffeine and cotinine (a nicotine metabolite).

In the USA, caffeine was found in streams at high levels of 6.0 µg/L (median 0.1 µg/L) (Kolpin et al. 2002) which can serve as an anthropogenic marker in aquatic systems as a result of its ubiquity in surface water, in seawater (Wiegel et al. 2004) and also in groundwater. Cimetidine and ranitidine (antacids) were estimated to occur at concentrations of 0.58 and 0.01 µg/L, respectively, in streams in the USA (Kolpin et al. 2002). Iopamidol has been detected in municipal wastewater at very high concentrations (15 µg/L), in surface water (0.49 µg/L) and in groundwater.

The antidiabetic compound metformin was observed in 5 % of stream water samples with estimated levels of 0.11 µg/L (Kolpin et al. 2002). Bronchodilators (β2-sympathomimetics terbutaline and salbutamol) were also detected in sewage not exceeding 0.2 µg/L (Ternes 1998).

1.5.5.1 Mode of Action

Cimetidine and ranitidine are compounds, which act by hindering the histamine receptor type 2 in the gastric system, thus inhibiting the acid secretion (antacid). These drugs are for the treatment of gastric ulcer. Metformin is an antidiabetic agent, whose mechanisms of actions have not been fully studied. It has been reported that this drug acts by increasing the cellular use of glucose and inhibiting the gluconeogenesis. Metformin acts on insulin receptor by direct stimulation of the insulin receptor or indirectly through inhibition of tyrosine phosphatase (Holland et al. 2004).

1.5.6 Steroidal Hormones

Steroidal hormones have been reported in wastewater and surface waters in a number of countries in Europe, Canada, the USA, Japan, Brazil, etc. A study in the USA showed that the average oestrogen concentration was 73 ng/L and levels of mestranol were 74 ng/L (Kolpin et al. 2002). They were detectable in 16 and 10 % of the streams sampled. Typical wastewater effluent concentrations are 0.5 ng/L and they are even lower in surface water.

1.6 Effects of Xenobiotics on Ecosystem

Every year, more than 13 million deaths and 24 % of world diseases are said to be as a result of environmental pollutants/exposures which can be avoided. Today, detectable levels of pharmaceutical preparations either as parent drug or metabolite are present in foodstuffs and water, i.e. both rivers and seas (Bonjoko 2014). Medications for humans and animals have severe consequences extending far beyond the traditional objectives of conventional medical care. The healthcare industry is the major source of active pharmaceutical ingredients (API) from medications, residues of which could lead to environmental pollution.

1.6.1 Effects on Aquatic Ecosystem

Aquatic organisms are significant biological indicators of pollution. Fent et al. (2006) conducted a comprehensive study on the occurrence; end result of pharmaceuticals in the aquatic environment, discussed potential mechanisms of action based on knowledge from mammalian studies and described the acute and chronic ecotoxicological effects on organisms. Pharmaceuticals are most often released back into the environment either in their original form or as metabolites. In humans, the main pathway is ingestion following excretion and disposal via wastewater. Municipal wastewater is the largest source of human pharmaceuticals. Hospital wastewater, wastewater from manufacturers and landfill leachates may contain significant concentrations of pharmaceuticals. Pharmaceuticals that are nondegradable in the sewage treatment plant (STP) are being released into treated effluents resulting in the contamination of rivers, lakes, estuaries and, rarely, groundwater and eventually drinking water. There is also likelihood of contamination when sewage is applied in agriculture. In addition, drugs meant for animals enter the waterways during surface application for agriculture purposes and runoff and also via direct application in fish farming. Pharmaceuticals of environmental significance oftentimes have high production volume in addition to environmental persistence and biological activity, especially after long-term exposure.

In recent studies, it has been observed that the increasing amounts of pharmaceuticals found in surface waters worldwide have raised concerns especially with respect to their effects on the aquatic flora and fauna. It would therefore be a huge task to initiate a strategy for prioritizing drugs on which to focus the most expensive environmental research efforts on. Among aquatic organisms, fish most often share drug targets with humans. Not much is known about the long-term effect of drugs in aquatic organisms. Diclofenac influences the expression of genes in fish and organ histology when exposed to a concentration of 1 μg/L of this drug (Cuklev et al. 2012). A study in India on surface water from 27 locations of the Kaveri velar and Tami rapani rivers in southern India revealed the presence of a number of nonsteroidal anti-inflammatory drugs (NSAIDs): naproxen, ibuprofen, diclofenac, acetylsalicylic acid and ketoprofen. This situation poses risks of direct toxicity to all consumers of the water (Shanmugan et al. 2013). Another case, likewise, effluents from a treatment plant in Hyderabad, India, was observed to be the cause of deleterious effects on water organisms. An embryo toxicity test that was carried out observed that as little as 0.2 % of the effluent reduced tadpole growth by 40 %; however, zebra fish (*Danio rerio*) growth was not impeded. Although the study focused on fish, it also increased knowledge about how aquatic vertebrates are possibly affected by effluent exposures, which substances in the effluent are causing the toxic effects and their threshold dilutions (Shanmugan et al. 2013).

Streams and rivers have been identified to be exposed to combinations of different drugs. Antidiabetic and antihistamine diphenhydramines were observed to cause significant disruption to the biofilm community which is important to the ecosystem. Biofilms are aggregates of microorganisms in which cells that are frequently embedded within a self-produced matrix of extracellular polymeric substances