Medicinal and Environmental Chemistry: Experimental Advances and Simulations

PART 2

Editors:
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Medicinal and Environmental Chemistry: Experimental Advances and Simulations (Part II)

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FOREWORD

In recent years, our environment has deteriorated at an alarming rate. Be it the air we breathe, the water we drink, or the food we eat—the hazards are hitting closer to home. Consequently, there has been a deluge of diseases and disorders associated with environmental pollution, industrialization, lifestyle changes, etc. From cardiovascular diseases and growth defects to neurological disorders and stress, these environmental diseases have been coupled with other environmental threats like pollution, climate change, food shortage, and novel infections and have made the study of environmental chemistry indispensable in present times. In the development of more effective and safer therapies that would cater to diseases both old and new, the study of medicinal chemistry is vital to determine accurate knowledge of drugs, their structure, synthesis, pharmacology, and pharmacokinetics.

Environmental diseases have brought about a close association between these two branches of chemistry as well as pharmaceutical chemistry. It gives me great pleasure that this book brings them together on one platform. This book aims to provide a better comprehension of environmental problems as well as remedial strategies to amend them and includes an assorted collection of topics presented by experts from academia, research, and development.

I think that the authors can be confident that readers will gain a broader perspective of the disciplines of environmental chemistry, medicinal chemistry, and pharmaceutical chemistry as a result of their efforts.

Imran Ahmad
Jina Pharmaceuticals Inc.
USA

PREFACE

With the drastic disturbance in environmental harmony and balance, there has been a rise in global deaths and diseases, calling for the exploration of novel remediation strategies for innovative drug action mechanisms and target identification. The fine balance between human and ecological health is getting disturbed, leading to serious implications including the occurrence of new pathogens and diseases, including the novel corona virus SARS-CoV-2, being the most recent instance having gripped the entire globe.

Environmental diseases are non-communicable and are caused by chronic exposure to toxic pollutants. Other contributory causes of environmental diseases include radiation, pathogens, allergens, and psychological stress. Their increasing occurrence is due to industrialization, changes in farming protocols, and the increase in exposure to chemicals released into the environment. Lifestyle changes, including the increased use of tobacco and processed foods also greatly contribute to the environmental/lifestyle diseases burden.

Though medicinal chemistry and environmental chemistry have been widely explored separately, yet their close association and interdependence have been overlooked. By exploring the association between these two focal areas, the present book aims to provide solutions and curative strategies for the well-being of humans and the environment.

The twenty-one chapters included in the book are focused on diverse topics trying to blend the fields of environmental chemistry and medicinal chemistry and have been authored by expert scientists and academicians from renowned institutions. A wide range of topics has been explored in the book, to make it relevant to environmental chemists and students. The chapters have been designed to introduce environmental contaminants and techniques for their quantification and removal. Also, a medicinal perspective for remediation of environmental hazards, from therapeutic strategies available to the design of new and safer drugs, is introduced through experimental and simulation approaches.

Specialized chapters have been dedicated to persistent organic pollutants, heavy metals, antibiotics, and plastics, which have become a major source of pollution, along with their remediation. The biochemical aspect of Cytochrome P_{450} and its association with mitigation strategy upon the exposure of smog on the human body, the effect of environmental xenoestrogens on human health, and the potential of natural curing agents to combat ecotoxicity have also been explored. Experimental techniques like the use of quantification methods for pharmaceuticals and persistent organic pollutants, chemosensors and polymeric ceramic composite membranes, and the concept of nanotechnology for the synthesis and use of gold and silver nanoparticles from plant-based sources have also been elaborated. To further elaborate on the importance of safe chemical practise, the concept of green chemistry has been introduced.

As we are aware that drug discovery for a particular disease is a time taking endeavour, therefore, a few chapters have also been dedicated to *in-silico* predictions like molecular docking and virtual models for biological properties, the software used and their utility to make futuristic and accurate predictions to make drug discovery efficient, quicker and cost-effective. Chapters summarizing the advances of biomolecular simulations for drug designing with respect to ecotoxicity, drug degradation, use of bioisosteric groups, and advances in pharmaceutical and modelling interventions for the treatment of COPD are also included. An interesting chapter has also explained the ligand identification for effective drug development through virtual screening by taking the example of COVID-19.

The book will prove beneficial for academicians, students of environmental chemistry and pharmacy, researchers, scientists, computational chemists, pharmacologists, environmentalists, policymakers, and postgraduate students. It would also provide researchers and medicinal chemists, information about the latest research done and the modern techniques used to develop more effective and safer drugs that would not be harmful to the environment. In this way, the proposed book would be highly beneficial to the audience it hopes to cater to.

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CHAPTER 1

Air Pollution and its Impact on Respiratory Health

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Abstract: Air pollution is a major environmental health threat due to the increasing rate of morbidity and mortality associated with it. The World Health Organization (WHO) classified particle pollution (PM_{10} and $PM_{2.5}$), tropospheric ozone (O_3), carbon monoxide (CO), sulfur oxides (SO_x), nitrogen oxides (NO_x), and lead as six major air pollutants. Particulate matter (PM) can penetrate the respiratory system, causing respiratory and cardiovascular diseases. Stratospheric ozone plays a protective role against ultraviolet irradiation, but ozone is harmful when present in the troposphere, affecting the respiratory and cardiovascular systems. Nitrogen oxide, sulfur dioxide, carbon monoxide, and lead are harmful to humans causing respiratory problems, such as Chronic Obstructive Pulmonary Disease, asthma, bronchiolitis, lung cancer, and cardiovascular events. The only possible way to cope with this problem is through public awareness coupled with a multidisciplinary approach by scientific experts. The Government of India made the Pollution Prevention and Control Act, 1981, for the prevention of air pollution. Prime Minister Narendra Modi launched the Ujjwala scheme on 1st May 2016, from the Balia district in Uttar Pradesh. The scheme is aimed at replacing unclean cooking fuels. The Ministry of Environment, Forest, and Climate change has started the National Environment Health Profile (NHEP) study, involving 20 cities, to assess health effects associated with environmental exposure. The National Clean Air Programme (NCAP) has also been launched for pan-India implementation to tackle the increasing air pollution problem in the country (102 cities); the tentative national level target is 20%–30% reduction of particulate concentration by 2024.

Keywords: Air pollution, Asthma, Cardiovascular disease, Environment, Health, Particulate matter, Pollutants.

INTRODUCTION

The interactions between humans and the surrounding environment have been extensively studied. The environment is an interplay of the biotic (living organisms) and the abiotic (hydrosphere, lithosphere, and atmosphere) components. Pollution is described as the addition of hazardous substances in the

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environment that decreases the quality of the environment for living organisms. Human activities have the biggest adverse impact on the environment by polluting air, water, and soil. The industrial revolution has added a huge concentration of pollutants by emissions, which are harmful to human health. Globally, air pollution is considered as the major environmental health risk by the WHO [1]. Various studies have regularly revealed the detrimental effects of air pollution on human health. Air pollution leads to 7 million deaths globally due to its health hazards. In India also, 1.2 million deaths are attributed to it. The air we breathe consists of emissions from various sources like the industrial sector, automobiles, power industry, chemicals from factories, radioactive substances from nuclear power plants and household fuels along with tobacco smoke. Human lungs are the organs of respiration and are responsible for the delivery of oxygen to all the tissues. This oxygen that we breathe is given by plants and trees. Around 10,000 litres of air pass in and out through the lungs every 24 hours, and 10,000 litres of blood passes through the lungs every 24 hours; out of this 10,000 litre of air and 350 litres of oxygen is delivered every day to our body (Fig. **1**). We humans breathe 25,000 times a day. We can live without food for 3 weeks; we can live without water for 3 days, but we can live without air for only 3 minutes. That is why oxygen is called ‘Pran-Vayu’.

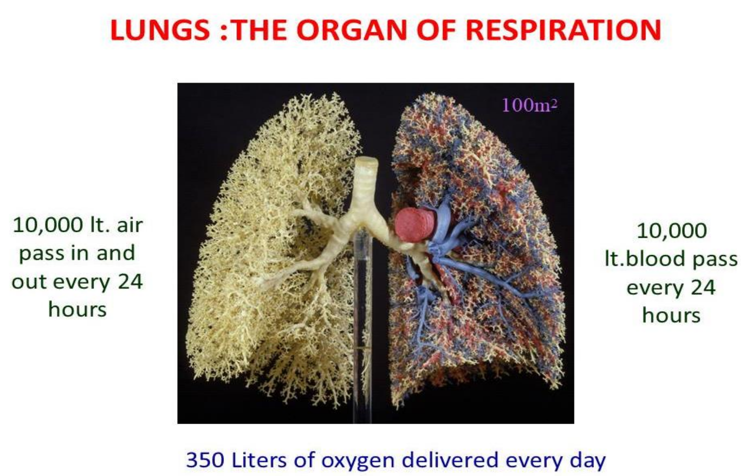

Fig. (1). Representation of the human lungs.

Air pollution has a huge impact on the normal morphology and functioning of the lungs. Air pollution’s impacts on health have been extensively studied in recent years. Various studies show that air pollution is harmful to human health and predominantly for those who are already susceptible individuals, like children and the elderly or people having chronic health problems. The epidemiological studies suggest that harmful health effects are based on the concentrations of the pollutants and the time of exposure to them. The effect of long-term exposure is more hazardous than short-term exposure to air pollution [2, 3].

MAJOR AIR POLLUTANTS

Air pollution has been defined as chemicals added in high concentrations to the atmosphere by natural events or human activities, enough to be harmful. Annually, various substances are released into the air from both natural sources and man-made (anthropogenic) activities. The use of fossil energy sources, growth of the manufacturing industry, and the use of chemicals result in growing air pollution [4]. Deforestation is also a major cause for the increase in air pollution; 50% of forests have been destroyed in the last 50 years in India which is leading to an imbalance in various environmental cycles and 6500 million trees are destroyed every year in our country. Smoking is also a significant contributor to air pollution.

TYPES AND SOURCES OF AIR POLLUTION

There are two categories of air pollutants-

Primary Air Pollutants

These are the harmful substances emitted directly into the atmosphere, for example- CO, CO_2, NO, NO_2, SO_2, most hydrocarbons, and most particulates.

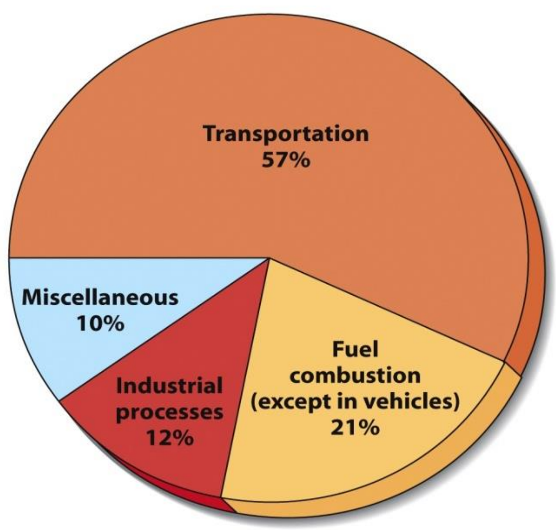

Fig. (2). Important sources of air pollution.

CHAPTER 2

Cytochrome P_{450} and Health Hazards of Smog

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Abstract: The rising levels of smog, blanketing northern parts of India during October-January in recent years, have pushed pollution levels to an extremely hazardous point. The pollutants and the particulate matter (PM) generated by various activities have a very harmful effect on human health. This has resulted in an increase in human diseases, especially of the respiratory and cardiovascular organ systems. Combustion results in the formation of redox-active metals and aromatic hydrocarbons, which stay in the environment long after the activity has ceased. These moieties form air-stable, environmentally persistent free radicals on entrained particles that harm the pulmonary and cardiovascular systems. The protective mechanisms of the broncho-pulmonary tract are unable to stop the ultra-fine air pollutants from invading the body. The various by-products of smog enter the human body *via* several different routes, finally reaching the liver for detoxification by Cytochrome P_{450} (also known as CYPs). Negative health effects of air pollutants have been shown on the cardiovascular system resulting in multiple respiratory diseases, including respiratory infections, asthma, chronic obstructive pulmonary disease (COPD), lung cancer, even in combination with stroke and heart diseases. The CYPs are endoplasmic reticulum resident enzyme systems that are involved in the metabolism of xenobiotics as well as drugs. The free radicals have a deleterious effect on these enzymes and have been found to inhibit six forms of P_{450} in rat liver microsomes. These free radicals are thought to inhibit CYP2B4-mediated substrate metabolism by physically disrupting the CPR•P450 complex.

Keywords: Cardiovascular, COPD, Cytochrome P_{450}, Particulate matter, Pollution, Pulmonary, Smog.

INTRODUCTION

Smog is a man-made haze, comprising air pollutants, that is seen over most parts of the world, especially with the onset of the winter months. The term is derived from the words smoke and fog and was used for the first time by H.A. Des Voeux,

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a Glasgow public health official in 1905, to describe the atmospheric conditions over many British towns. The Air Quality Index (AQI) world ranking puts India in the 4th spot, behind Mexico, Spain, and Romania, with an AQI of 367. This emphasizes the seriousness of the situation, even as the whole country has been in lockdown due to the novel coronavirus pandemic since March 2020.

The main components of smog are sulfur oxides, which are the by-products of the combustion of coal, residual particulate matter that wafts into the air when coal is burnt, volatile organic compounds (VOCs) from automobiles, nitrogen oxides, ozone, and peroxy-acyl nitrates (PANs) [1].

TYPES OF SMOG

There are two types of smog formed in different weather conditions. They are known as sulfurous smog and photochemical smog (Fig. **1**) [2]. Sulfurous smog is also known as 'London smog,' as it was first observed in London. It has a high concentration of sulfur oxides and is formed due to the use of sulfur-bearing fossil fuels, especially coal. It is found in areas that have a heavy concentration of industries using coal as their major source of fuel. This type of smog is characterized by atmospheric dampness and an unusually high concentration of suspended particulate matter in the air.

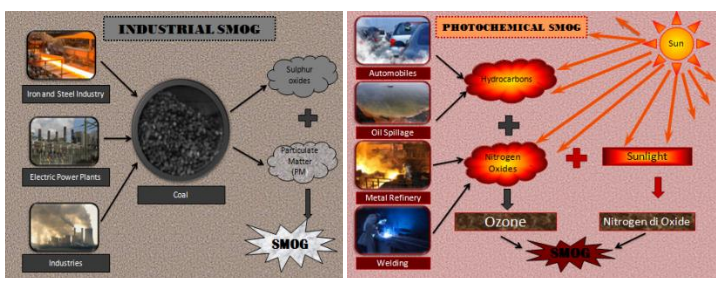

Fig. (1). Industrial and Photochemical Smog and their method of formation.

On the other hand, photochemical smog, which is also known as 'Los Angeles smog,' occurs in predominantly urban areas that have many vehicles. This type of smog has a high concentration of nitrogen oxides and hydrocarbon vapours emitted by automobiles and other sources, which then undergo photochemical reactions in the lower atmosphere. The highly toxic gas, ozone, is formed when nitrogen oxides react with hydrocarbon vapours in the presence of sunlight. Nitrogen dioxide is also produced from the reaction of nitrogen oxide with sunlight. The resulting smog has a light brown colour and it results in reduced visibility, plant damage, irritation of the eyes, and respiratory distress. Exposure to surface-level ozone concentrations is detrimental to human health, especially if the concentration is above 70 parts per billion, for eight hours or longer. These conditions are encountered in areas experiencing photochemical smog.

HEALTH HAZARDS OF SMOG

Smog has been known to cause a range of diseases in humans, affecting many organ systems. Major among these are coughing, respiratory problems like COPD, asthma, respiratory tract infections like influenza, bronchopneumonia and purulent bronchitis, irritated eyes, a range of cardiovascular diseases like acute myocardial infarction, heart failure, cardiac arrhythmias, atherosclerosis, cardiac arrest, cerebrovascular diseases, skin diseases like atopic dermatitis and even a significant number of cases of cancer.

CYTOCHROME P_{450}

Cytochrome P_{450} enzymes (E.C.1.14.14.1) belong to a superfamily of monooxygenases that have a cysteine thiolate-ligated heme (Fig. **2**). A hemoprotein is classified as belonging to the P-450 group depending on its absorption spectrum. The Fe (II)-CO complex gives a characteristic absorption maximum (Soret band) near 450nm due to axial ligation with a cysteine thiolate of the protein (with or without substrate protein). The important cysteine residue can be found in a relatively well-conserved region, ~80% into the protein from the N-terminus [3]. These enzymes catalyze the reaction in which an oxygen atom from molecular oxygen is transferred to several biological substrates to make them more water-soluble and to aid in their excretion from the human body. The second oxygen atom from the molecular oxygen is reduced by two electrons to a water molecule [4, 5]. These enzymes are involved in hydroxylation, epoxidation, heteroatom oxidation, and heteroatom de-alkylation reactions. The stoichiometry of the hydroxylation reaction catalyzed by CYPs can be written as equation **1.**

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+ \qquad \textbf{(1)}$$

Here RH refers to the substrate which binds to the CYP enzymes.

CYPs are found in almost all organisms, from unicellular yeasts and bacteria to multi-cellular birds, fish, plants, insects, and even mammalian tissues. These monooxygenase enzymes are involved in drug metabolism, biotransformation of naturally occurring molecules, the oxidative metabolism of xenobiotics, and synthesis of certain molecules like steroid hormones, cholesterol, some fatty acids, and bile acids. There are approximately 60 cytochrome P450 genes in humans.

CHAPTER 3

Pharmaceutical and Modelling Interventions for Environmental Pollution Related Chronic Obstructive Pulmonary Disease

Tahmeena Khan[1], **Alfred J. Lawrence**[2], **Iqal Azad**[1], **Shalini Dixit**[3,*] and **Saman Raza**[2]

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Abstract: Chronic obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD), are causing an extreme burden on societal health, affecting above 500 million people worldwide and affecting lung physiology at a multi-biological level. The increasing burden of air pollution is a major contributing factor to the disease, other than smoking and living conditions. Over the years, several studies have been undertaken to understand lung function, airflow mechanisms, and impairment for better therapies and therapeutic interventions. Still, it is very unlikely to predict the morbidity and mortality associated with COPD due to limitations of early and timely prediction and progression which calls for personalized treatment interventions to avert exacerbation and refractory symptoms. This chapter presents an overview of the status of COPD worldwide with a special emphasis on Indian statistics, along with the drug and pharmacological advancement, and computational medicinal modelling, its applications, and limitations. Though experimental models may predict the prerequisites for the system medicine approach, they are unable to analyse the finer details, calling for more advanced molecular technologies. A computational model of system medicine mimics the functioning of a complex system and can predict future functioning as well. Working with large data sets, computational models may have greater benefits to minimize patient risk and assist in clinical decision-making.

Keywords: Chemistry, COPD, Environment, Lung, Modelling, Pharmaceutical, Pollution.

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INTRODUCTION

Exposure to air pollutants is rampant in cities because of the increasing population and emitting sources. The essential air quality assessment parameters are depicted in Fig. (**1**). The health effects of pollutants are numerous, ranging from short-term like cough, throat irritation, and asthma [1], to long-term, including chronic obstructive pulmonary disease (COPD) and cardiovascular health problems [2]. The particulate contamination which has a size smaller than 2.5 µm is especially detrimental for health because of its penetration in lungs and bloodstream and deposition in the brain and heart [3]. Chronic obstructive lung diseases, including asthma and COPD, are causing an extreme burden on societal health [4, 5]. Though a significant amount of work has been done on asthma, much must be explored when it comes to COPD [6, 7]. The existing challenge is to identify molecular interactions involved in the pathophysiology to work on treatment therapies. The exact contribution of air pollutants in the total COPD burden is very unclear at the present stage [8], though presently it is the fourth leading cause of death and by 2030, would become the third. Hence dealing with COPD and its consequences is a huge and momentous challenge for the scientific fraternity. Smoking is another important factor leading to COPD though it can also have other etiologies.

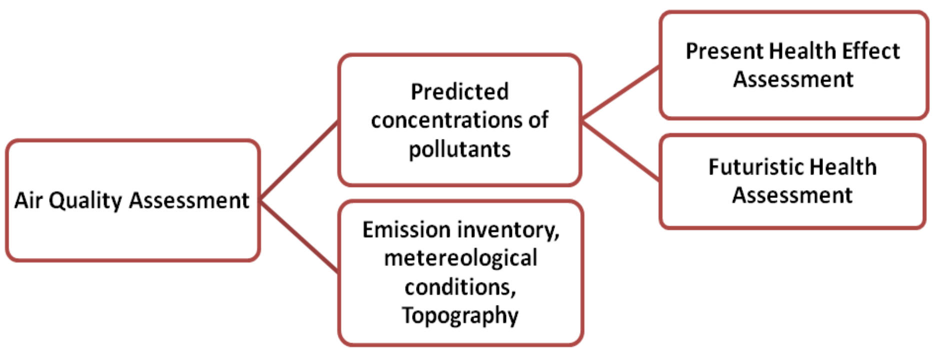

Fig. (1). Key parameters of air quality assessment.

INFLUENCING FACTORS FOR INITIATION AND MODULATION

The overall assessment has shown that COPD is initiated by exposure to hazardous particles and gases. Passive exposure to tobacco, smoke from fuel burning, occupational hazards, and outdoor pollution also contributes significantly to COPD spread [9]. Respiratory toxicants containing complex mixtures of several thousands of compounds and their composition vary depending upon the source of origin [10]. There are also factors that do not directly contribute but influence the magnitude and progression of the disease. Women are more prone to the risk of COPD than men and have different comorbidities [11]. Diet and physical activity also modulate COPD to an appreciable extent. Food rich in vitamin C, vitamin E, and β-carotene is found to improve lung function and protects against COPD [12]. Proper and healthy functioning of the cardio-respiratory system is linked with lower occurrences and improved working in childhood and adolescence, leading to greater lung volume [13].

COPD AND ITS ASSOCIATION WITH COMMON AIR POLLUTANTS: A WORLDWIDE PERSPECTIVE

COPD exacerbations have been linked with emergency hospital admissions and are associated with increased mortality and decreased quality of life. Patients have reportedly experienced one or more exacerbations [14]. A German study on the influence of Air Pollution on Lung, Inflammation, and Aging (SALISA) conducted for five years showed that the five-year average concentration of particulate matter with a diameter of 10 μm had a negative correlation with FVC and FEV1 and a positive relationship with the possibility of the occurrence of COPD [15]. In several time-series studies conducted in the USA, a nominal association between PM_{10} and COPD related complaints and hospital visits has been found [16], though the studies did not consider delayed effects and temporal lags of the dependent variables in the progression. A good correlation between the PM_{10} and $PM_{2.5}$ levels and frequent hospital visits has been established in several studies [17, 18]. Overall analysis showed a stronger correlation with $PM_{2.5}$ than with PM_{10} because smaller particles penetrate deeper into the lungs. The influence of $PM_{2.5}$ was stronger in Asian countries with a great deal of heterogeneity involved. Doubly high concentrations of $PM_{2.5}$ than Europe have been reported in Asia, whereas these concentrations were four times higher than North America, where the $PM_{2.5}$ limit was lower than the WHO permissible limits. The meta-regression analysis hinted at the nonlinear relationship between COPD-related hospital visits and exposure to ambient air pollution. Though the association is quite clear, it still needs to be interpreted carefully because of the limited number of studies conducted to ascertain the close association. Regarding the effect of PM_{10}, very scarce information is available to assess seasonal variation and health outcomes, although a study conducted in a tropical climate has suggested a higher impact in the winter season [19]. A 2.7% rise in chances of COPD-related hospital admissions has been observed for a 10 μg/m^3 increase in the concentration of PM_{10} [20]. Not only particulate matter but gaseous pollutants have also contributed significantly to the rise of COPD. An association has been developed between CO and SO_2 levels and COPD exacerbations. The two pollutants have been found to have acute or short-term effects up to 2-3 days, respectively. The association was more prominent in Asian countries with an OR of 1.03; 95% CI, 1:00-1.06. Apart from geographical variation, a seasonal variation in SO_2 has also

CHAPTER 4

Arsenic Toxicity of Groundwater and Its Remediation for Drinking Water

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Abstract: Due to the overall industrial development and human activities, the demand for clean water in India is continuously on the rise. There already exists a danger to the geochemical environment owing to the indiscriminate withdrawal of groundwater, resulting in the release of Arsenic (As). In some localized areas this level of As has already exceeded the World Health Organization's (WHO) permissible limits (10µg/L or 10ppb) for drinking water, leading to serious environmental and health consequences. Arsenic is predominantly present as inorganic species either as arsenate As (V) or arsenite As (III) in natural systems. In oxygen-rich environments where aerobic conditions persist, As (V) exists as mono-valent $(H_2AsO_4)^-$ or divalent $(HASO_4)^{2-}$ anion, whereas, As (III) exists as an uncharged molecule (H_3AsO_3) and anionic $(H_2AsO_3)^-$ species in moderately reducing atmosphere where anoxic conditions persist. The concentration of arsenic above its permissible level results in skin sclerosis. Arsenic gets deposited in the tissues of the vital organs and may cause cancer of the liver, lung, and urinary bladder. This study is an attempt to (a) review the arsenic problem in Uttar Pradesh, (b) to bring out the health issues due to arsenic, and (c) find sustainable solutions to address the issue.

Keywords: Arsenic, Cancer, Environment, Groundwater, Heavy metals, Inorganic, Remediation.

INTRODUCTION

Inorganic substances are being mobilized and modified by human activity. These substances are not distinguished by the ecosystem as natural or anthropogenic, but rather as nutrients or at higher levels, as toxins [1]. Adverse effects of metal in their certain forms and specific doses cause metal toxicity or metal poisoning. The toxicity term generally refers to heavy metals but certain lighter metals like beryllium and lithium also become toxic under certain circumstances. Certain metalloids, like arsenic (As), are well known for their toxic effect. Even the trace elements, if present in abnormally high doses cause toxicity. Radioactive metals

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have both radiological toxicity and chemical toxicity. All heavy metals are not necessarily toxic. Bismuth is mildly toxic and some metals, like iron, are also required essentially in the biological systems. For some metals, an oxidation state which is abnormal to the body may also cause toxicity. For example, chromium (III) is an essential trace element, but chromium (VI) is a carcinogen [2].

Some metals become toxic in the form of soluble compounds. Metals like lead, in any measurable amount, pose a negative impact on health. To summarize, metal toxicity or metal poisoning is the toxic effect of certain metals, in some specific forms and doses, on life. Therefore, for convenience, metals can be classified as essential and non-essential depending on their roles in biological systems.

ESSENTIAL METALS

These metals play a crucial role in the biological system (Fig. **1**). They are required essentially for various biochemical and physiological activities [3]. Their deficiency and excess both are detrimental to the biological system resulting in a variety of deficiency syndromes and metal poisoning. For some metals like chromium and copper, there is a very narrow difference between the beneficial and toxic concentrations [4 - 6].

NON-ESSENTIAL METALS

The metals which do not play any biological role are termed non-essential metals (Fig. **1**). Since no biological functions have been established for these metals, hence the term non-essential is used for them [7]. Such metals have a negative impact at all concentrations.

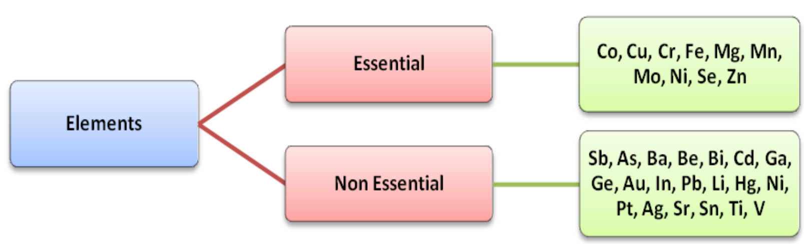

Fig. (1). An overview of essential and non-essential elements.

CONCEPT OF TOXICITY

The toxicity of metals can be due to their accumulation in the vital cells or sometimes it is because of the imitation of the action of an essential element by some other metals in the body, interfering with the metabolic process and resulting in illness. Toxicity depends on the following factors:

1. Solubility of the Metal Complexes

Toxicity is a function of solubility. Insoluble compounds, as well as the metallic forms, often exhibit negligible toxicity.

2. Oxidation State of the Metal

Metals like chromium are non-toxic in lower oxidation state (III) but become carcinogenic at higher oxidation state (VI) [2]. Arsenic is less toxic in the oxidation state of +3 as compared to +5.

3. Ligand Attached to the Metal Atom

Toxicity of any metal decreases or increases depending on the ligand attached to it. For example, mercury (Hg) becomes more poisonous by coordinating to methyl group forming methyl mercury (Eq. **1**).

$$Hg + 4\,CH_4 \rightarrow Hg\,(CH_3)_4 + 2H_2 \quad \textbf{(1)}$$

The same is the case with lead (Pb), which becomes extremely toxic as tetraethyl lead (Eq. **2**).

$$Pb + 4C_2H_6 \rightarrow Pb(C_2H_5)_4 + 2H_2 \quad \textbf{(2)}$$

At the same time, the reverse is seen with cobalt (Co), the formation of its organometallic derivative, cobaltocenium cation (Eq. **3**) makes the metal less toxic.

$$Co + 2C_5H_5 \rightarrow [Co(C_5H_5)_2]^+ \quad \textbf{(3)}$$

Metals bioaccumulate in the body through the food chain and cause adverse and chronic effects. These accumulated metals start interfering with various biological activities. One such example is shown by the radioactive heavy metal radium, which imitates calcium and gets incorporated into human bones.

CHAPTER 5

Studies on Polymeric Ceramic Composite Membranes for Water Treatment

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Abstract: Environmental chemistry is the study of chemical processes occurring in the environment for understanding the diverse issues related to human health and resource conservation. These significant effects may be felt on a global scale, through the presence of water pollutants or toxic substances arising from chemical waste. The increasing world population, rapid industrialization, and human activities have resulted in higher water demand throughout the world. The fast spread of contamination problems worldwide and their effects on the natural resources of water led to the evolution of environmental chemistry. This evolution relies on the different membranes technology to facilitate the scientific investigations on the contamination extent and optimize remediation efforts. Polymeric ceramic composite membranes comprise a captivating field of membrane separation technology. Rapid development and innovation have been done in the modification of these membranes. These membranes have superiority in terms of high temperature and chemical resistance, higher chemical, and mechanical stability, and have higher longevity. All these outstanding features have made these membranes ideal for water treatment and desalination applications. This chapter is a review of the development, and the use of polymer composite membranes in treating wastewater. A brief description of synthesizing these membranes through different routes is given and is reviewed critically.

Keywords: Ceramic membrane, Desalination, Polymer, Sol-gel process, Water treatment.

INTRODUCTION

Water is the main source of life; from being the basis of human survival to the economic development of a country. One of the major issues our society faces today is the shortage of fresh water. Increasing global population, periodical

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droughts, and rapid industrialization have resulted in higher water demand around the world. To complicate the issue, fresh water resources are reducing year after year throughout the world.

With the increase in world population, the gap between the supply and demand for water is growing and reached at such an alarming rate in some parts of the world that it is threatening the very existence of humans [1]. With the increase in population, the demand for drinking water has increased seven times [2]. Over the next 30 years, it is estimated that the population will grow by 40% and demand for domestic, agricultural, and industrial water sources will be increased, especially in developing countries where the need for water is greater than the population [3]. Lack of fresh water is a growing problem worldwide as only 1% of the earth's fresh water is available for people to consume [4]. It was reported by the United States geological survey that 96.5% of the earth's water is in oceans and seas and 1.7% in icebergs. The remaining percentage is in the form of salty water, brackish water, which is found as surface water in an outfall, and groundwater in salty sinkhole [5]. Demand for clean water is at the top of the global agenda of critical issues. India has 16% of the world's population and 4% of fresh water reservoirs [6]. Due to rapid urbanization, industrialization and development, there is an increased chance of recycling unsafe water in developing countries such as India. Although India occupies only 3.29 million square kilometres, making up 2.4% of the world's arid land, it carries more than 15% of the world's population.

The population of India as of March 31, 2011, was 1,210,193,422 (Census, 2011). The livestock population grew by 4.6% from 512 million in 2012 to 536 million in 2019 in India, which is about 20% of the world's total livestock. However, the total annual water consumption in the country is 1086 km^3, which is only 4% of the world's water assets [7]. The total annual water supply for groundwater and surface water is 396 km^3 and 690 km^3, respectively [8]. As a result of rapid population growth and increasing water challenge, stress on India's water supply is increasing and the availability of water per capita is declining day by day. In India, surface water levels in 1991 and 2001 were 2300 m^3 and 1980 m^3 respectively, and this is estimated to have dropped to 1401 m^3 and 1191 m^3 in 2025 and 2050 respectively [9]. The national water demand by 2050 is estimated to be1450 km^3 higher than the current availability of 1086 km^3. To overcome the water scarcity and the need for clean drinking water, there is a need for the development of new water resources and the protection of existing water resources through appropriate water treatment strategies [10].

The hydrosphere contains more than 75% of the earth's surface, including all types of water resources such as oceans, seas, rivers, lakes, streams, lakes, glaciers, icebergs, and groundwater. About 97% of the world's fresh water is in the form of oceans, which is inaccessible for human consumption due to its high salt content and total dissolved solids (Table **1-2**). About 2% of water resources are available in ice-cold areas and glaciers, while only 1% is available as clean water for human use and other uses. Fresh water is also available in the form of rain, snow, dew, and so on. The main use of water is in irrigation (30%), thermal power plants (50%), and other uses including domestic (8%) and industrial use (12%). Insecticides, pesticides, fertilizers, humans, animals, as well as industrial wastes, pollute the surface water.

Table 1. Classification of water according to its concentration of solids.

Description	>Dissolved Solids (mg/L)
Drinking water	Less than 1000
Mildly brackish	1000 – 5000
Moderately brackish	5000 – 15000
Heavily brackish	15000 – 35000
Average seawater	35000

Table 2. Palatability of water according to concentration of its total dissolved solids.

Palatability	Dissolved Solids (mg/L)
Excellent	Less than 300
Good	300 – 600
Fair	600 – 900
Poor	900 – 1200
Unacceptable	More than 1200

WATER POLLUTION

Of all-natural resources, water is essential to the existence of living organisms; civilization has polluted it and is facing its consequences. A decrease in physical, chemical, and biological properties of water can be defined as Water pollution caused due to natural weathering of rocks, minerals, soil sediments, nutrients, and organic matters of soil transported by erosion. This deterioration in the quality of water has increased in the last few decades mainly due to human activities in industrial and agricultural processes. In a few decades, there has been a growing global concern about the widespread distribution of pollutants from human activities, industrial and agricultural activities, and the potentially harmful effects of these pollutants on humans or ecosystems.

CHAPTER 6

Chemosensors For Anions Of Biological and Environmental Relevance

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Abstract: Anions are prevalent in nature and have important roles in many biological, medical, industrial, and environmental processes. These processes lead to the release of anions in the environment, which act as pollutants at higher concentrations. The proper management of these anions requires adequate detection techniques. Anion sensing, a branch of supramolecular chemistry, deals with chemosensors that are capable of selective recognition and detection of anions through optical or electrochemical response. Further, these compounds are also used for the construction of sensory devices and the extraction and separation of anions. Chemosensors are very useful for the detection of potentially toxic (*e.g.*, fluoride, cyanide) and environmentally hazardous (*e.g.*, phosphate, nitrate) anions as well as in medical diagnostics. Consequently, anion sensing has become one of the most active areas of supramolecular chemistry. The design and synthesis of anion-selective receptors and sensors are challenging, as compared to cation counterparts, due to their different sizes, shapes, high hydration energies, and pH-dependent properties. Three approaches have been used for the detection of anions by chemosensors *viz.* binding site-signalling subunit approach, displacement approach, and chemodosimeter approach. This chapter focuses on small molecular optical chemosensors and the mechanisms adopted for the detection of anions.

Keywords: Anion-π interaction, Calix [4] pyrrole, Chemodosimeter, Colourimetric, Displacement approach, Electrostatic interaction, Fluorescence sensors, Halogen-bonding, Hydrogen-bonding, Hydrophobic interaction, Lewis acid, Metal complexes, Molecular assembly, Naked-eye detection, Non-covalent interactions, Optical sensor, Recognition, Self-assembly.

INTRODUCTION

Anions play many important roles in biological, chemical, and industrial processes, and find widespread use in catalysis, medical diagnostics, and environmental chemistry. Deviation from the required concentration of anions has

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adverse effects on biological systems as well as on the environment [1]. Anions are released from the living systems and industrial effluents in the environment and cause pollution; if not managed properly, this can have devastating effects. Certain anions are important for plant growth and development and are added in fertilizers *e.g.*, nitrate, sulfate, phosphate, and chloride ions. Overuse of fertilizers and soil erosion leads to the release of these anions into the environment. Phosphate ions, along with other ions, are the principal cause of eutrophication [2]. Sulphate ions contribute to the permanent hardness of water, and along with the nitrate ions, are a prominent constituent of acid rain. Likewise, cyanide ion which is used in gold mining, electroplating, production of organic chemicals and polymers, including nitriles, nylon, and acrylic plastics, increases the risk of its unwanted release in the environment [3]. Therefore, efficient techniques which can detect the anions selectively under real-world conditions, in the presence of other anions, are desirable.

Biological Significance of Anions

A few important anions which are responsible for maintaining the normal functioning of life are DNA (carrier of genetic code), phospholipids (involved in the formation of the cell membrane), and ATP (the energy currency of biological systems). Carboxylate ions such as citrate, succinate, maleate, *etc*. are present in different steps of Kreb's Cycle.

Many fruits and vegetables contain oxalate, which is an essential nutrient. However, overconsumption of oxalate is associated with the development of kidney stones [2a]. Citrate salts are used as flavouring agents and preservatives in the food industry and as local anticoagulants in clinical practices [4]. Citrate ions inhibit the crystallization of calcium ions; therefore, secretion of less than 320 mg of citrate per day in urine is also associated with renal stone [2b].

Iodide anion is an essential micronutrient and is involved in the synthesis of thyroid hormones T_3 and T_4. These hormones are responsible for cell differentiation, cell growth, and metabolism. Deficiency of dietary iodide results in the enlarged thyroid gland (goitre) and permanent brain damage in foetuses and children. These disorders can be prevented by adequate iodine intake. However, excessive intake of iodine is also detrimental, triggering goitre and Hashimoto disease [5].

Fluoride is a widespread, non-biodegradable, and biologically important anion and is a comparatively persistent pollutant [2d, 6]. Fluoride is added to drinking water to prevent dental caries and is used for the treatment of osteoporosis. The recommended concentration of fluoride in water should not exceed 2 ppm [2c, 2d]. Fluoride assists in maintaining the teeth' health by inhibiting the acid-assisted demineralisation, promoting remineralisation, interference in the functioning of plaque microorganisms, and alteration in tooth morphology. The primary and most important action of fluoride is topical. The main constituent of tooth enamel is hydroxyapatite (HAP). In the presence of fluoride ions (present in saliva), HAP is converted into fluorohydroxyapetite (FHAP) by substitution of OH^- by F^-. Owing to the decreased solubility of FHAP compared to HAP, the process of demineralization is inhibited, while during the formation of the tooth, FHAP incorporates into the tooth enamel and assists in remineralisation of tooth enamel and alters the tooth morphology. In addition to mineralization and demineralization, fluoride ions interact with oral plaque bacteria and inhibit the production of lactic acid formed by the fermentation of carbohydrates. So, in this way, under recommended doses, fluoride assists in maintaining the health of skeletal tissues. However, excessive levels of fluoride in water lead to the diseased condition fluorosis, caused by the accumulation of fluoride in teeth and bones, along with other clinical consequences [2c, 2d].

Other anions of biological significance are chloride and bicarbonate which, in combination with sodium ions, are responsible for the regulation of Anion Gap (AG) in serum and maintaining cellular pH [7]. In addition to regulating electrical neutrality, chloride helps to regulate the distribution of water in the body while bicarbonate plays an important role in the transportation of CO_2. Any variation in AG levels results in acute illness, which includes mental disorder, acute renal failure, and disorders in lungs, kidneys, and other organs. Furthermore, an elevated level of chloride anions in sweat chloride test is used to diagnose cystic fibrosis (CF), which is a lethal genetic disease characterized by the production of thick and sticky mucus. CF is caused by dysregulation of chloride channels of epithelial cells [2e, 2f]. Cyanide ion is a neurotoxic agent and is lethal in a very small dose. It binds strongly to the active site of the cytochrome oxidase, leading to inhibition of the mitochondrial electron-transport chain, and decreases oxidative metabolism [2g, 3].

Thus, the diagnosis of some diseases can be established by the detection and analysis of certain anions. Therefore, developing novel methods for anion detection will not only improve the management of anion induced environmental hazards but may also offer efficient diagnostic tools. Much research is being focused on finding inexpensive, reliable, and simple ways of detecting anions in solution and biological samples.

The present chapter gives a brief introduction of the important techniques available for detection of anions, along with a detailed study of small, molecular optical chemosensors, the use of which is one of the most explored and practically applicable techniques for detection of anions of biological and environmental

CHAPTER 7

Antibiotic Pollution: Challenges and Strategies

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Abstract: Antibiotics have been used as antimicrobial agents to fight a variety of infectious diseases, for the past more than 100 years. Apart from this, they are also extensively used in animal farming, agriculture, and aquaculture, all over the world. However, this frequent and large-scale overuse and incorrect use lead to the excessive dispersal of antibiotics in water and soil, resulting in their accumulation in the environment, which is known as antibiotic pollution. The removal of antibiotics from water and soil is complicated due to their non-biodegradable nature, and special techniques must be used for the same. This pollution has serious implications on both human health and the ecological balance. The major adverse effect is antibiotic resistance, wherein, microbes become less susceptible to treatment with antibiotics, posing problems for both the patient and the physician. This chapter describes the causes and consequences of antibiotic pollution, the challenges it presents, and the strategies to counter them.

Keywords: Adjuvant-therapy, Antibiotic, AOP, Beta-lactam, Efflux, Inhibitors, Non-biodegradable, Non-target, Permeabilizers, Pollution, Resistance, Wastewater.

INTRODUCTION

Ever since Alexander Fleming discovered penicillin in 1929, antibiotics have become the most significant medical discovery of the twentieth century. This is because antibiotics were able to treat a variety of microbial infections, many of which were fatal and had no treatment earlier [1]. By the 1970s, over 160 new antibiotics and their semi-synthetic derivatives were introduced for the treatment of infectious diseases [2].

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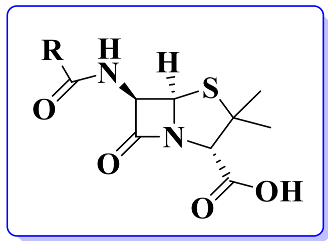
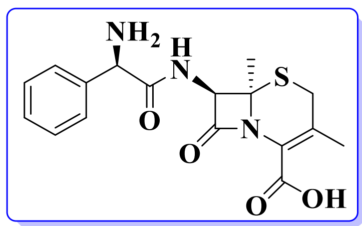
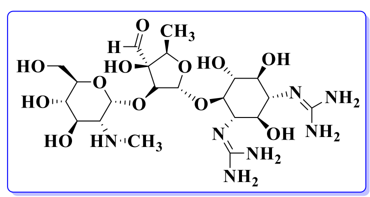
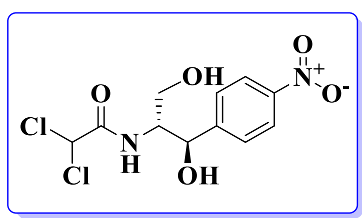
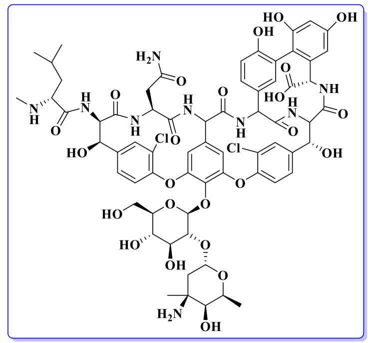
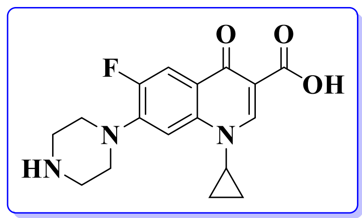
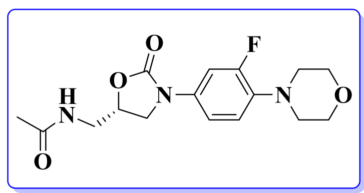
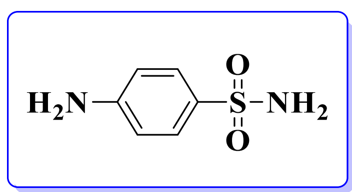
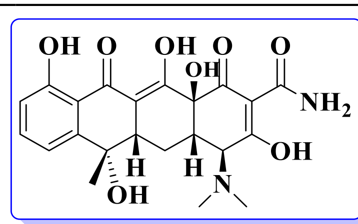
Antibiotics can be classified based on their structure, mode of action, spectrum of activity, etc. Table **1** gives the classification of antibiotics based on their structure. The structure and mode of action of the important classes of antibiotics have also been described in the table.

Table 1. Different classes of antibiotics based on the structure.

Class of Antibiotics	Examples	Structure	Mode of Action
ß-Lactams	Penicillins such as amoxicillin and flucloxacillin		Inhibit bacterial cell wall biosynthesis
	Cephalosporins such as cefalexin.		Inhibit bacteria cell wall biosynthesis
Aminoglycosides	Streptomycin, neomycin, kanamycin, paromomycin.		Inhibit the synthesis of proteins by bacteria
Chloramphenicol	Chloramphenicol		Inhibits the synthesis of proteins by bacteria

(Table 1) cont.....

Class of Antibiotics	Examples	Structure	Mode of Action
Glycopeptides	Vancomycin, teicoplanin.		Inhibit bacterial cell wall biosynthesis
Quinolones	Ciprofloxacin, levofloxacin, trovafloxacin.		Interfere with bacterial DNA replication and transcription
Oxazolidinones	Linezolid, posizolid, tedizolid, cycloserine.		Inhibit the synthesis of proteins by bacteria
Sulfonamides	Prontosil, sulfanilamide, sulfadiazine, sulfisoxazole.		Do not kill bacteria but prevent their growth and multiplication.
Tetracyclines	Tetracycline, doxycycline, limecycline, oxytetracycline.		Inhibit the synthesis of proteins by bacteria

CHAPTER 8

Analytical Advancement for Pharmaceuticals Quantification in Environmental Matrices

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Abstract: The pharmaceutical residues and their metabolites present in soil and water have been considered as active pollutants, posing various health risks to humans. Major sources from where pharmaceutical compounds enter the environment are hospitals, pharmaceutical industries, domestic wastes, and improper disposal of medicines. Metabolism of drugs in humans is sometimes incomplete, resulting in their excretion in either the unchanged form or in the form of metabolites. However, biodegradation of pharmaceutical compounds and/or their metabolites in the environment is not easy; therefore, their repeated addition to the environment makes them even more persistent. The pharmaceuticals, based on their physicochemical properties, bind to soil particles or enter the aquatic system. The most adverse effect of increasing the concentration of pharmaceuticals in environmental matrices is the development of resistance in certain bacteria against antibiotics, which is a serious health concern. Steroidal hormones can alter the steroidogenesis of aquatic and terrestrial life and cause endocrine disruption, leading to cognitive and brain development problems. The concentration of pharmaceutical residues in the environment is very low; therefore, highly sensitive instruments for their quantification are required like liquid chromatography coupled with mass spectroscopy (LS-MS/MS) and gas chromatography with mass spectroscopy (GS-MS). The techniques allow the identification of various analytes with improved detection limits. The pharmaceutical residues are considered lethal pollutants, even if present in ng/kg or ng/l, and can cause potential harm upon exposure. This chapter aims to review various analytical approaches for pharmaceutical residue analysis and recent advancements made in analytical techniques.

Keywords: Active pollutants, Analytical techniques, Biodegradation, Gas chromatography, Liquid chromatography, Mass spectroscopy, Pharmaceutical compounds.

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INTRODUCTION

In recent years, there has been a momentous increase in the use of pharmaceuticals in the field of medicine and personal care products to counter various health-related problems, and to improve the quality of life. The improper handling and disposal of these pharmaceuticals lead to an increase in the concentration of pharmaceutical residues in various environmental matrices [1]. Pharmaceutical residues in the environment are considered as one of the active pollutants, even in trace amounts, causing severe health-related issues to the wildlife and producing toxic effects to the ecosystem. These pharmaceutical compounds show the same behaviour as several harmful xenobiotics, that can accumulate in the environment, to produce a negative impact on living organisms [2]. Water and soil are most contaminated, as a large amount of pharmaceutical waste is dumped or disposed of inappropriately, into these matrices. The identification and determination of pharmaceutical residues are one of the major concerns to detect their contamination level in the environment [3].

There are several classes of pharmaceuticals that are extensively targeted for the development of analytical methods, to enhance their traceability in different environmental compartments. Pharmaceuticals are categorized into the following eight classes that include hormones, antibiotics, lipid regulators, nonsteroidal anti-inflammatory drugs, beta-blockers, antidepressants, anticonvulsants, and antineoplastics [4]. The use of these pharmaceuticals on a broad spectrum, for medication, has led to the contamination of the environment. Hormones like estrogens, at their polluting levels, are responsible for causing breast cancer in females and prostate cancer in males, as well as altering the physiology of fish and reproductive patterns of domestic and wild animals [5]. The increasing antibiotic pollution in the environment results in developing resistance in certain bacteria, against a particular dose of antibiotics, which is a serious health concern [6]. In a study, the European pharmaceutical review (EPR) found that around 10% of pharmaceutical compounds, that have been disposed into the environment, can cause damage to it. Amongst the compounds that are of major concern are hormones, painkillers, and antidepressants [7]. Due to the complex nature of the matrix and their low level of occurrence, rigorous quantification of pharmaceutical residues in the environment is an analytical challenge. There have been various methods for the quantification of pharmaceutical residues, even at their trace level, such as nanograms (ng) or picograms, in different environmental matrices. Presently, gas chromatography (GC) and liquid chromatography (LC), along with several steps of extraction, derivatization, clean-up method, and detection using mass spectroscopy (MS), are used to detect and quantify various pharmaceutical compounds as well as their metabolites, in different environmental matrices. For the analysis of pharmaceuticals, there is another method known as capillary electrophoresis (CE). CE is less complicated and cost-effective; however, it is less sensitive in comparison to GC and LC, having detection limits in micrograms. To enhance the analytical approaches towards the detection of pharmaceutical residues, various advancements have been made in the instrumentation and the sample preparation, derivatization, and clean up processes [8].

Before the instrumental analysis, there is an essential step of sample preparation that allows the removal of all the possible interferences and matrix effects. The sample preparation is tedious and time-consuming yet an important and compulsory step, for the determination of pharmaceutical residues or any other compounds present in the environment. The method of sample preparation involves the preservation, extraction, and clean-up procedures that help in processing an extract with a high concentration of analytes, that must be detected or analysed on a particular instrument. Several sample preparation techniques have been used for the determination of pharmaceutical compounds, of which the most used techniques are liquid-liquid extraction (LLE), dispersive liquid-liquid micro-extraction (DLLME), solid-phase extraction (SPE), solid-phase micro-extraction (SPME), and stir bar sorptive extraction (SBSE). Recently, with the emergence of new advancements in sample preparation techniques, several new techniques, such as pressurized liquid extraction (PLE) or ultrasonic extraction (USE) have been used, either individually or coupled with SPE clean-up, to prepare samples for solid matrices of the environment.

For the analysis of pharmaceuticals in environmental samples, both GC and LC are considered suitable methods. GC is applicable to analyse the non-polar and volatile compounds whereas LC helps to separate polar organic compounds. Mass spectrometry, coupled with LC or GC, has been used to detect numerous pharmaceutical compounds along with various detectors, such as fluorescence, UV (ultraviolet detector), PDA (Photo Diode array), FID (Flame ionization detector), ECD (electron capture detectors), *etc* [8].

Analytical Methods for the Determination of Pharmaceutical Residues in the Environment

In the present day, advancements in analytical methods have made it possible to detect complex pharmaceutical compounds and their metabolites in the environment, even at low concentrations or trace levels. Chromatographic techniques such as GC and LC are used to analyse the environmental samples to detect the pharmaceutical residues. However, every analytical method involves

CHAPTER 9

Use of Bioisosteric Functional Group Replacements or Modifications for Improved Environmental Health

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Abstract: Bioisosteres are chemical substituents, groups, atoms, or moieties that have similar physical and chemical properties, producing analogous biological effects but with greater impact and potency. Bioisostere replacement is an impactful concept in medicinal chemistry. Bioisostere replacement is used for attenuation of toxicity, enhancement of the activity of the lead compound, or alterations in pharmacokinetics and toxicity of the lead. This chapter deals with the degradation or minimization of ecotoxic waste through bioisostere replacement. The chapter details bioisosteric replacements for the degradation of eco-hazardous wastes in two ways, *i.e.*, direct way and indirect way. The direct way involves bioisosteric changes in insecticides, which directly affects the environment, while the indirect way involves bioisosteric modifications in drug molecules to increase their bioavailability and half-life period so that maximum drug is consumed within the body, providing better efficacy against the disease and release of a minimum amount of waste into the environment. These modifications prove to be eco-friendly. Some important bioisosteric groups used for replacement are -fluoro, -deutero, -nitro, -t-butyl, and others. This chapter gives an insight into the plausible alterations with improved functional groups in bioisosterism to improve the eco-detrimental effects of compounds or drugs.

Keywords: Bioisosteres, Drugs, Ecofriendly, Half-life period, Insecticides, Medicinal chemistry, Metabolites.

INTRODUCTION

The interactions between molecular interfaces of two or more biomolecules, like receptor (DNAs, RNAs, proteins, peptides, and polysaccharides) and ligand (physiologically active substances) play a major role in molecular recognition, which is important for metabolic events of life action [1]. The specific interaction

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of binding site and substrate is an important concern for drug targeted action in medicinal chemistry which are often comparable to the 'Lock-and-Key model'. These interactions are attributed to various intermolecular forces, such as hydrogen bonding, ionic bonding, van der Waals force, and dipole interaction, generated due to specific functional groups, atoms, or chemical moieties. Improvement in drug efficacy, *in vivo* stability of drugs, their oral absorption, membrane permeability, and ADME (absorption, distribution, metabolism, excretion) properties can be achieved by bioisosterism. The modification of drug candidates by their corresponding bioisosteres is the best alternative for drug discovery investigations [2, 3]. In the present scenario, a large amount of work is being done for environmental sustainability and thus, greener alternatives are being explored, whether in terms of synthesis or degradation. Bioisosterism *via* computer-aided drug design is one such alternative that serves the purpose of environmentally safe drugs in terms of synthesis as well as degradation [4]. In this chapter, we have discussed bioisostere replacement in chemical compounds with improved functional groups to enhance their degradation characteristics or to reduce their toxicity, for safer and lesser hazardous environment waste. The chapter details bioisosteric replacements for the degradation of eco-hazardous wastes in two ways, *i.e.* direct way and indirect way. The direct way involves bioisosteric changes in agricultural insecticides and pesticides entering the metabolism of insects and pests, while the indirect way involves bioisosteric modifications in drug molecules to increase their bioavailability, half-life period, and *in vivo* stability, so that maximum drug is consumed within the body, providing better efficacy against the disease and release of a minimum amount of waste into the environment.

BIOISOSTERISM - DIRECT EFFECT ON ENVIRONMENT

Bioisosteric modifications directly affecting the environment include changes or modifications in chemical compounds like insecticides and pesticides, in terms of bioisostere replacement. Synthetic insecticides and pesticides play a major role in the integrated pest management system, limiting pests that are harmful to crop yields. However, long-term usage of conventional synthetic insecticides and pesticides is posing a serious threat to the environment, creating eco-biological problems. Therefore, to overcome this grave threat to the environment, there is a pressing need to search for novel compounds (insecticides/pesticides) which are potent, follow a modified mode of action, bear eco-friendly properties, such as easy biodegradability to non-toxic residues and minimize or cause no metabolic disturbances in human biological systems [5].

BIOISOSTERIC MODIFICATIONS FOR ANTHRANILIC DIAMIDES

Most of the insecticidal bioisosteric modifications were performed on the established class of compounds; anthranilic diamides. Anthranilic diamides are portrayed through three chemical moieties: A) aromatic bridge amide moiety, B) N-pyridyl-pyrazole moiety and C) terminal aliphatic amide moiety. Bioisosteric modifications were made on these three groups, especially amide functional groups, to produce novel compounds with better efficiency and lesser toxicity [6, 7]. Major work done on this class of insecticides, to reduce eco-detrimental effects of insecticides, has been discussed in detail in this chapter.

BIOISOSTERIC MODIFICATIONS AT AROMATIC BRIDGED AMIDE FUNCTIONAL GROUP

Wang *et al*. worked on bioisosteric replacements in anthranilic diamides, yielding novel pyridyl pyrazole acid derivatives as a potent alternate insecticide. Anthranilic diamides are an important and potent class of conventional insecticides. The ryanodine receptor is considered to be an important receptor class for insecticidal compounds. Chlorantraniliprole and Cyantraniliprole (Fig. **1**) are important and established anthranilic diamide class of insecticides. These compounds exhibit good insecticidal activity on a broad range of insects such as Lepidopterans, Coleopterans, Dipterans, and Isopterans. Wang and his co-workers explored the bioisosteric replacement of the amide functional group or moiety for improved, novel insecticidal compounds.

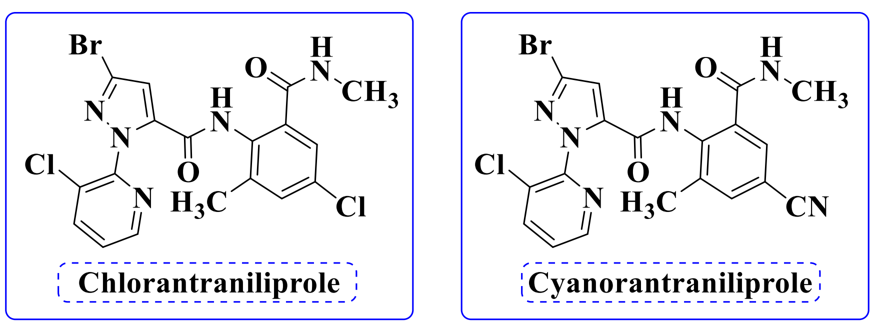

Fig. (1). Structures of anthranilic diamide class of insecticides.

Bioisosteric changes were made in these two anthranilic diamides to yield potent molecules with greater efficacy. The changes made in the molecule are represented through schemes. The modifications were mainly concerned with benzene moiety or amide terminal functional group or amide bridge-group [8].

Scheme **1** details the bioisosteric replacement alterations at benzene moiety and

CHAPTER 10

Gold and Silver Nanoparticle Synthesis by *Pyrus* and *Eurya*: Environment-Friendly Therapeutic Agents

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Abstract: Two new metal-containing biosources *i.e*. *Pyruspaschia* fruits and *Eurya acuminate* leaves were used in the preparation of gold and silver nanoparticles.*Pyruspashia* has many medicinal uses as it is used in gastrointestinal disorders, fever, and headache, hysteria, and epilepsy. The fruits are sedative, febrifuge, and laxative. *Eurya acuminate* leaves are used as a treatment for cholera, diarrhoea, and other stomach diseases. The leaves are applied as a poultice on skin eruptions. These bio-sources are metal chelators used for binding natural dye to textile. These both metal-bearing plant parts were first time used to produce nanoparticles which further can be used therapeutically based on their size. This approach can add results to an environment-friendly medicinal agent. The nano-particles so generated were characterized by UV-Visible spectroscopy, FESEM (field emission scanning electron microscopy), TEM (transmission electron microscopy), and AFM (atomic force microscopy) techniques. The particles were found to be crystalline and both Au and Ag nanoparticles were pure and their mother liquor did not have significant sedimentation as impurities. FT-IR (Fourier transformed infrared spectroscopy) analysis authenticates the role of phytochemicals in this work. The synthesis of silver and gold nanoparticles using the above biological resources suggests an eco-friendly/green possibility, in comparison to many available methods based on chemical or physical techniques. Their application as therapeutic agents in various diseases and cancerous growth is of great prospect.

Keywords: AFM, *Eurya acuminate* leaves, FESEM, FT-IR, gold and silver nanoparticles, *Pyruspaschia* fruits, TEM.

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INTRODUCTION

The current field of synthetic and medicinal chemistry has now gained a significant impetus in terms of research into the preparation of small and sub small level molecules beneficial for the human race. Nanotechnology in this respect has gained much attention and found a respectable place in the therapeutic arena as well. It involves the synthesis and maintenance of such nano/small molecules to almost any structure. These methods are used today to produce a wide variety of useful chemicals such as pharmaceuticals or commercial polymers [1]. Nanoparticles present an exciting and potential tool to operate at a cellular level as almost all physical reactions in the human body involving enzymes and biochemical/biomolecules manoeuvres at the nano-scale. Successful management of these procedures with manufactured nano-scale molecules gives rise to a new and very powerful arena for future therapeutics, especially where deadly/lethal diseases are involved. In this regard, metal nanoparticles (NPs) are of great importance due to their specific role, determined by their size, shape, composition, and crystallinity [2]. The green/eco-friendly chemistry process involving the production of specially design nanoparticles will eventually rise as an attractive technology to chemists, researchers, and industrialists for innovative chemistry research and applications involving medicinal/therapeutic demands [3]. It also connects to another branch of chemistry *i.e*., environmental chemistry. This green chemistry is fundamental for the improvement of sustainable chemistry involving such small biomolecules [4]. Biosynthesis of metal nanoparticles using biological/green sources will produce and sustain methods/procedures which allow the procurement of uncommon shapes in nanoparticles such as nano-triangles and prisms [5]. The physical [6] and chemical processes [7] are the classical general methods used for the fabrication of nanoparticles, but due to the presence of non-environment friendly effects, these methods are not ecologically compatible [8] and can lead to unwanted results in the biomedical applications [9]. These shortcomings can be met or overcome by a microbe-mediated and plant-mediated biological process and this bio-route appeals to a larger perspective of eco-friendliness and biocompatibility [10]. A rapidly growing area of nanoscience and nanotechnology by green route has been widely recognized and gained quite an attention in recent years [11]. Thus, the controlled synthesis of metal nanoparticles with well-defined shapes and sizes is among one of the most fascinating aspects of nanoparticle research. In recent years, compared to bulk metals or metal ions, metallic nanoparticles, including silver (Ag), gold (Au), platinum (Pt), and palladium (Pd), have been extensively studied because of their unique properties, particularly the effect of quantum size and large surface area. Besides, metallic nanoparticles are compatible with the biological system, and therefore, they have been used for drug delivery, diagnostic imaging, labelling, and biosensors [12].

Therefore, a clean/green or environment-friendly method of synthesizing gold and silver nanoparticles that exhibit biological functions is demonstrated herein. It satisfies the need for developing environmentally friendly and sustainable methods for the synthesis of nanoparticles. There is a current drive to incorporate all the eco-friendly methodologies in designing environmentally benign tools and procedures. The utilization of various plant resources for the biosynthesis of metallic nanoparticles is called green nanotechnology, and it does not utilize any harmful chemical protocols. In this respect, a method of preparation of gold nanoparticles by the reduction of Auric chloride by aqueous extract of *Mirabilis jalapa* flowers has been reported [13].

The following study reports the plant-mediated synthesis of gold and silver nanoparticles using the plant leaf extract of *Eurya acuminate* and dried fruit extract of *Pyruspaschia*, in which plant extract are reductants. These nanoparticles were characterized by ultraviolet-visible spectroscopy, FTIR, scanning electron microscopy, AFM, and TEM.

The plant part of the study was *Pyruspaschia* fruit (Fig. **1**) which was used in the dried state. *Pyruspaschia* or the wild pear tree grows commonly at altitudes of between 700 and 2000 meters. *Pyruspaschia* is native to the Himalayas, west China and Myanmar, and Afghanistan [14]. The fruits of *Pyrus paschia* are used by local tribal people for eating. *Pyruspaschia* fruit contains about 6.8% sugars, 3.7% protein, 1% ash, and 0.4% pectin [15]. It also contains a low content of Vitamin C. *Pyruspaschia* also contains minerals, such as potassium, magnesium, phosphorous, calcium, and iron [16]. It is assumed that the presence of a little amount of Vitamin C is responsible for its reducing capability.

Fig. (1). Fruits of *Pyrus paschia.*

Eurya acuminate (Fig. **2**) is a shrub and 130 species of this plant are available

CHAPTER 11

Novel Drug Development Strategies- A Case Study With SARS-CoV-2

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Abstract: The current epidemic of Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) has led to a major health crisis in 2020. SARS-CoV-2 has spike protein, polyproteins, nucleoproteins, and membrane proteins with RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins. These are probable targets to be explored for the discovery of antiviral agents, still, to date, no definite treatment or vaccine has been discovered. Virtual screening with molecular docking has its advantage to speed up the drug development procedure in an accurate manner. In this chapter, novel computational strategies for drug discovery have been elaborated. Docking tools and drug filtering rules which may efficiently assist the drug development procedure and channelize the whole process in the right direction have also been discussed. A case study with 322 natural, semi-synthetic, and synthetic derivatives of citric acid (2-hydroxy-1,2-3-propane tricarboxylic acid), in search of a potential lead molecule to combat the novel coronavirus SARS-CoV-2, has been elaborated. The derivatives were explored from the PubChem database. The obtained library of compounds was filtered through Lipinski's rules, out of which, 74 obeyed the rule and were further subjected to molecular docking investigation against the SARS-CoV-2 replicase polyprotein 1a or pp1a (ID: 6LU7), with AutoDock Vina and iGEMDOCK. Deptropine possessed the highest binding affinity, in terms of released binding energy (-7.4 kcal/mol), against the SARS-CoV-2 replicase polyprotein 1a.

Keywords: Citric acid, Computational strategies, Drug, Docking, Repurposing, SARS-CoV-2, Virtual screening.

INTRODUCTION

Three coronaviruses responsible for zoonotic diseases *viz.* Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and SARS-CoV-2, have caused lethal

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pneumonia in humans by crossing the species barrier in recent times [1]. In 2002, SARS-CoV originated in the Guangdong region of China and was transmitted through the air to adjacent regions, leading to approximately 8,098 infections and 774 deaths [2, 3]. MERS-CoV outbreak took place in 2012 in the Arabian Peninsula and became a major public health issue. MERS-CoV reached 27 countries, infecting ~2,494 people and causing 858 casualties [4]. In December 2019, in Wuhan, a novel coronavirus (SARS-CoV-2) was discovered, spreading all over the world within few months [5]. It is linked with lethal pneumonia infecting over one crore people worldwide and causing more than five lakh deaths, till 13th July 2020 (Table **1**). MERS-CoV was found to be originated from bats [6]; similarly, SARS-CoV and SARS-CoV-2 which are closely associated, also originated from bats. SARS-CoV-2 is a positive-sense ssRNA virus. It is a β-coronavirus like MERS-CoV and SARS-CoV. The initial viral 30 kb RNA genome is termed as an open reading frame (ORF1a/b) part and interpreted through polyproteins (pp1a and pp1ab). The remaining portion of the viral RNA genome encrypts accessory proteins as well as four important structural proteins, namely spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein [7].

FACTORS AFFECTING THE SPREAD OF SARS-COV-2

Environmental Factors

SARS-CoV-2 is a positive-sense ssRNA virus that mainly causes respiratory failure [8]. In the spread of the virus, numerous factors are involved, associated with the environment and the human correlation [9], in which migration, community interactions, dispersal of the human population, agricultural development, climate transformation as well as interaction with animals find a prominent place [10]. The correlation between the viral spread with major environmental factors like humidity, ambient temperature, and wind speed, *etc*. has not been satisfactorily explored. How the virus crosses the nose, ears, eyes, and mouth, *etc*. is not well recognized, and the release of SARS-CoV-2 as droplets and aerosols have also not being investigated thoroughly [11]. Owing to the versatility and mutation of COVID-19, control and prevention have drawn serious and urgent concern [12].

Concerns have originated to establish a clear relationship between environmental factors and SARS-CoV-2 cases [13]. According to the World Health Organization (WHO) (2020), sunlight, pH variations, and high temperature may curb viral growth [14]. A study conducted in China and Italy described the association between the SARS-CoV-2 spread with several environmental factors, such as humidity, wind speed, and temperature [15, 16]. Some researchers have described the resistance of the SARS-CoV-2 at low and high temperatures and found that at 4 °C its survival is for a longer period, whereas at 70 °C the virus survived only for 5 minutes. Wang *et al*. in their study conducted in 26 areas in China with a sample size of 24,139 positive SARS-CoV-2 cases, showed that a 1 °C rise in the minimum ambient air temperature decreased the cases by 0.86% [16, 17].

Table 1. Total cases of SARS-CoV-2 in top 10 countries (https://news.google.com/covid19) till 13th July 2020.

S. No.	Country	Confirmed Cases	Recovered Cases	Deaths
1	United States	33,66,515	9,88,656	5,71,444
2	Brazil	18,66,176	12,13,512	1,37,191
3	India	8,78,254	5,53,470	72,151
4	Russia	7,33,699	5,04,021	23,174
5	Peru	3,26,326	2,42,474	11,439
6	Chile	3,15,041	2,83,902	11,870
7	Mexico	2,99,750	1,84,764	6,979
8	United Kingdom	2,90,133	No data	35,006
9	South Africa	2,76,242	1,34,874	44,830
10	Iran	2,59,652	No data	4,079
11	**Worldwide**	**1,29,45,505**	**70,01,675**	**5,71,444**

Food Materials, Handlers, and Packaging

Center for Disease Control and Prevention (CDC) has reported that the spread of SARS-CoV-2 through food materials, handlers, and packages has not been recognized till yet [17]. Recently, Seymour *et al*. (2020) described the perseverance of the SARS-CoV-2 on surfaces ranging from an hour to a few days [18].

Water and Wastewater

Adopting good personal hygiene plays a crucial role in supporting human health [17]. Bhattacharjee (2020) has reported that SARS-CoV-2 also causes intestinal infection [19]. Some recent studies have also shown that around 2-10% of the active SARS-CoV-2 cases suffer from diarrhoea [13]. In sewage, the occurrence of the SARS-CoV-2 virus has been confirmed as well as its persistence in water and wastewater resources. Its occurrence in water and wastewater resources is based on important factors like sunlight, temperature, and organic content [17].

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Tahmeena Khan

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