Medicinal and Environmental Chemistry: Experimental Advances and Simulations

PART 1

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Bentham Books

Medicinal and Environmental Chemistry: Experimental Advances and Simulations (Part I)

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Experimental Advances and Simulations *(Part I)*

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ISBN (Online): 978-981-4998-27-7

ISBN (Print): 978-981-4998-28-4

ISBN (Paperback): 978-981-4998-29-1

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Singapore 068898
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FOREWORD

Environmental pollution (air, water and soil) and human health are inextricably linked. The developing countries are engaged in a wide range of activities that are causing enormous damage to the environment, ecosystems that sustain both our species and Earth's legacy of biodiversity, and human health. If our society takes constructive actions now, or at least soon, it will not be too late to prevent or repair many of these important environmental problems, which threaten the welfare of people and most other species. A more respectful attitude toward the natural world is also urgently needed, for the world is one family, "Vasudhaiva Kutumbakam".

This innovative book will attract scientists interested in environmental pollution and human health with a view to offer remediation techniques. The book chapters have been authored by experts from their fields, both scientists and academicians, and would benefit the readers.

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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, the novel coronavirus 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 separately medicinal chemistry and environmental chemistry have been widely explored, 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 as a whole.

The ten chapters included in this book are focused on diverse topics trying to blend the fields of environmental chemistry and medicinal chemistry and have been authored by experts, 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 so as 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, and plastics, which have become a major source of pollution, along with their remediation. The effect of environmental xenoesterogens on human health has been discussed in one chapter, while in another, the potential of natural curing agents to combat ecotoxicity has been explored. To further elaborate the importance of safe chemical practice, the concept of green chemistry has also 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 in making futuristic and accurate predictions to make drug discovery efficient, quicker and cost-effective. Chapters summarizing the challenges of medicinal chemistry as well as the advances of biomolecular simulations for drug designing with respect to ecotoxicity are also included.

The book will prove beneficial for academicians, students of environmental chemistry, pharmacy, researchers, scientists, computational chemists, pharmacologists, environmentalists, policymakers and postgraduate students. It would also provide researchers and medicinal chemists the information regarding 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

Environmental Chemistry: Applications, Interactions and Paradigm Shift in Futuristic Approaches

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Abstract: Environmental chemistry is an interdisciplinary science with multiple importance in the dynamic lifestyle and consumption pattern. Globally, the environmental regulatory agencies and research institutions feel the extreme need for environmental chemistry for the identification of the nature, source, monitoring, and remediation of pollutants. The pollutants may range from heavy metals, organometallics, polycyclic aromatic hydrocarbons, and nutrients, to the runoff of various other contaminants, their transportation, and interaction with living organisms. Their rapid and accurate separation, identification, quantification using sophisticated techniques, characterization, and understanding of the interactions and mechanisms are the key components of analytical chemistry, for better biochemical or physiological understanding. Contaminants generally have short or long-term toxic implications on the surrounding environment due to direct impact or through bioactivity. Management of environmental pollutants, with minimal impact on biodiversity and human population, is the desired objective of most of the Research & Development programs of International societal relevance. The coordination and effective implementation through sustainable, green, computational technologies may provide the best strategic solutions to the innovators, academicians, and stakeholders, amidst constraints on resources.

Keywords: Characterization, Environmental, Management, Strategic, Sustainable, Technologies.

INTRODUCTION

We need to attempt visualising the pathways and draw a roadmap for a sustainable future. We all know that newer materials/ alloys will lead to improved products, and novel processes may improve manufacturing efficiency and reduce

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energy usage, waste generation, and resultant pollution. The success of civilisation may thus depend on the ability to create such newer materials and novel applications [1 - 4]. It is projected that in emerging economies the production and sales of chemicals will continue to grow rapidly irrespective of the pandemic-related challenges. It will be going through a period of mergers, acquisitions, and several types of restructuring. Chemicals have a major role to play in global resource flow and value chain. China (approx. 37% of global sales) and the European Union (16% of global sales) remain the highest users of chemical products, followed by the United States and BRICS countries (Brazil, Russia, India, China, and South Africa). R&D experts feel that the pharmaceutical industry is highly innovative and competitive, with dependency on research funds, and is subject to strong government regulations. Moreover, the pharmaceutical industry has been shifting towards developing primary care and small-molecule medicines, transitioning to specialty medications for ageing populations.

In the post-Covid-19/ SARS-CoV-2 situations, it is expected that the thickly populated urban areas will always be susceptible to diseases, which may spread *via* airborne pathogens, surfaces, and human-to-human contact. They will be faced with immediate and long-term challenges [8 - 15]. The basic information collected and compiled regarding the dynamic properties of macromolecules may propel a shift to structural bioinformatics, from understanding single structures to analysing conformational ensembles. The molecular dynamic simulations have now evolved into a mature technique, which helps to understand the structure-activity relationship of macromolecules. Moreover, it helps in providing better insights into biological actions like enzyme mechanisms, regulation, transport across membranes, and building of large structures, such as ribosomes, viral capsids, transcriptions, *etc*.

INDUSTRIALIZATION AND CHEMICAL RESEARCH WORKS

Industrialization and globalisation are undergoing a paradigm shift and with an abundance of raw materials and comparatively economically priced manpower, our country is privileged to take the benefit of cost-effective manufacturing. Thomas Kuhn motivated for a change in interdisciplinary approaches originating from natural sciences and applied chemistry, with the utilization of computational techniques. Chemical research must aim to support new radical approaches and ground-breaking projects, through investigators who are exceptional leaders in terms of the originality and significance of R & D contributions.

Agency for Toxic Substances and Disease Registry (ATSDR) is an organisation for the dissemination of best solutions based on R & D findings, for trustworthy information with direct relation to health, to prevent harmful exposures and

preventing diseases associated with toxic substances [1]. It also offers an emergency response program for societal benefits, at a global level. Human exposures may be associated with chemicals or mixtures which are toxic and may originate from environmental and occupational sources. The exposures may be from other vital sources and drugs or indoor air pollutants and affect susceptible populations, communities, or indirectly associated tribal inhabitants.

PARADIGM CHANGES AND INNOVATIONS

In connection with the paradigm changes towards sustainability, the intensification of global agriculture practices must be interconnected with objectives that are directed to meet customer demands for resilience and biosphere protection. We need to take steps for eradicating hunger and at the same time securing food for an increasing global population of nine to ten billion, by 2050. This may require steady growth in food production amidst potential global environmental risks. The regulation of the usage of agrochemicals and synthetic fertilizers requires appropriate coordination and cooperation with agriculturists, institutions involved in R&D, civil society, and governments. All of this will become more critical in a global scenario of resource constraints, health hazards, and the dynamic requirements of a growing population. Modern technology, and its competent use for mitigating future pandemics or environmental crises, is the most effective tool we have in our arsenal to protect communities.

We must take a lesson from the reduction in industrial activities and emissions during the recent lockdown; the government's restrictions on movement from one area to another has led to a significant reduction in global pollution levels, and rejuvenation of nature. This was evident from various publications of reputed journals of science and technology. It has affected societies and economies around the globe and is expected to reshape the activities of professional life. The crisis fallout is both amplifying familiar risks and creating new avenues for managing systemic challenges to build an improved climate for coming generations in a universal scenario. Efforts are needed for a reduction in the release of irritating toxic gases affecting the pulmonary system. It is vital to address niche areas holistically *viz.* drug development, trade, governance, health, education, and labour, to mention the few where the balance of risk and opportunities exists after strength, weaknesses, opportunities, and threats (SWOT) analysis. We may utilise artificial intelligence and machine learning to provide momentum to a series of economically feasible activities in the field of environmental chemistry, with intelligent analysis applications. Preparedness, thus, becomes the strongest weapon in the anticipated disasters or natural calamities. Revolutionary analytical chemistry and computational biology, with better insight, will have a great future. The passive sampling devices, *in situ* methods, and specially designed assay

CHAPTER 2

Medicinal Chemistry: Opportunities and Challenges

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Abstract: Medicinal chemistry is a modern branch of the pioneer subject chemistry. Medicinal chemistry is primarily associated with drug discovery and design in search of New Drug Entities (NDEs). There are different sources, such as natural and synthetic products, animals, marine invertebrates, microorganisms, and recombinant DNA approaches which have been recognized as potential reservoirs for bioactive compounds or drugs. Medicinal chemistry has made several technological innovations, such as computational chemical biology, trial-and-error approach, and bioinformatics, which have greatly improved and accelerated the efficient and competent drug development process. Although with hi-tech innovations in medicinal chemistry, there are several diseases for which treatment is still not available, including the very recent dreadful occurrence of novel coronavirus (COVID-19), which originated from Wuhan city of China. At present, there is no vaccine or drug to cure it. Moreover, the drug development process starting from the identification of a new chemical entity (NCE) to the regulatory approval of NDE is relatively complex, costly, and time-consuming. It can take 10−15 years or even longer to develop and design an NDE. The present chapter intends to discuss and emphasize the different drug sources and drug development processes in medicinal chemistry along with understanding the associated opportunities and challenges.

Keywords: Animals, Artificial intelligence, Bioinformatics, Computer-aided drug design, Challenges, Drug design, Drug development, Drug repositioning, High throughput screening, Medicinal chemistry, New chemical entity, Natural products, Opportunities, Recombinant DNA technology, Synthesis.

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INTRODUCTION

The International Union for Pure and Applied Chemistry (IUPAC) in 1974 has defined Medicinal chemistry as, *"Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemist is not restricted to drugs but includes bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of drugs and related compounds"* [1]. The word drug is derived from the French word 'drogue', which means a dry herb, and it is defined as 'any substance used for diagnosis, prevention, relief or cure of some disease in a man or animal' [2]. Medicinal chemistry is primarily associated with drug discovery and design which creates a stimulating link between many scientific disciplines in search of New Drug Entities. Moreover, the field of medicinal chemistry has been revolutionized by several technological innovations, such as computational tools and bioinformatics, which have speeded up drug developments and design procedure. Drug discovery and design is the process through which potential new medicines are identified which are further used for the treatment of different diseases. It involves a wide range of scientific disciplines, including biology, chemistry, and pharmacology. Medicinal chemistry is concerned with this interaction, focusing on the organic and biochemical reactions of drug substances with their targets.

Medicinal chemistry is an interdisciplinary science combining the chemical sciences with life sciences and medical sciences at the interface to develop a potent drug. It involves biochemistry, pharmacology, molecular biology, genetics, immunology, pharmacokinetics, and toxicology on one hand, while on the other hand there are physical chemistry, crystallography, spectroscopy, computational techniques, data analysis, and data visualization [3]. The discovery of an NDE has always depended on creative and rational thinking, high-quality science and serendipity. An NDE is expected to meet an unmet medical condition or therapy where treatment modalities are not available or because of the incompatibility of existing drugs. The purpose of this book chapter is to demonstrate and discuss the possible drug sources, drug development process, advancements in drug discovery, and a robust understanding of how the medicinal chemist instigates the right experiments/strategy with the opportunities and challenges in medicinal chemistry.

SOURCES OF A DRUG

World Health Organization (WHO) describes a drug as any substance used in a pharmaceutical product that is intended to modify or explore the physiological

systems or pathological states for the benefit of the recipient [4]. A drug is a substance or product that affects the physiology or pathology of living cells. In simple words, it is used as a medicine to diagnose, cure, and prevent the occurrence of a disease and disorder and prolongs the lives of patients suffering from serious or incurable diseases.

Before the twentieth century, the main sources of drugs were plants. Later, microorganisms and minerals were also recognized as potential sources of drug candidates. Nowadays, most of the drugs are obtained from synthetic, semi-synthetic and biosynthetic sources. Nature has served as a potent source of all medicaments and has been continuing since ancient times as an important source of novel bioactive compounds. These bioactive molecules are used either directly as medicinal agents or act as leads for synthetic structural modifications and optimization. There are mainly six sources, *viz*. plant, animal, mineral/earth, microbiological, semi-synthetic/ synthetic, and recombinant DNA technology (Fig. **1**) which are the potential sources of drugs which will be elaborated in detail in this chapter along with the challenges associated with these sources.

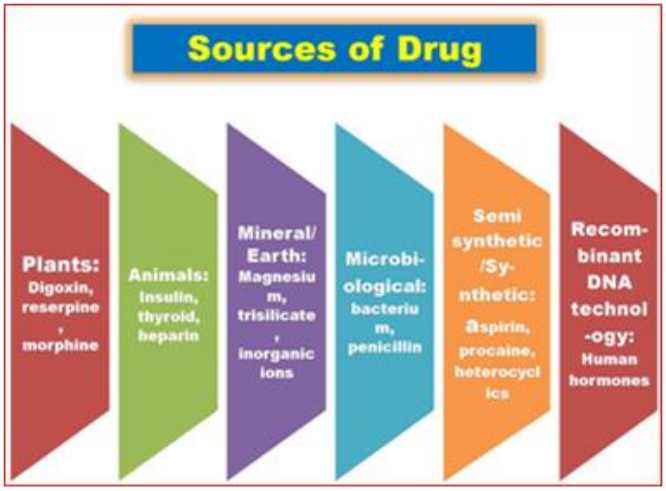

Fig. (1). Sources of a drug.

SYNTHETIC SOURCES

Synthesis is a core part of drug discovery and development. The birth of organic synthesis goes back to the early part of the 19th century, as marked by the serendipitous preparation of urea, a naturally occurring organic compound, from ammonium isocyanate, an inorganic compound. The case of medicinal chemistry and process chemistry, as it applies to drug discovery and development, is perhaps the most compelling demonstration of the impact of synthetic organic chemistry on society. Modern drug discovery and development rely on a biology-chemistr-

CHAPTER 3

Environmental Xenoestrogens: Developmental Effect On Changing Environment, Molecular Mechanisms, and Human Health

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Abstract: Estrogens, including estrone, estradiol, and estriol, are the female sex hormones conscientious for the regulation and play a significant role in the developmental process of the feminine reproductive organs. It is used for hypogonadal, postmenopausal, and hormone replacement therapy, as drugs in oral contraceptives and the cure of hormone-dependent cancers, such as breast cancer, ovarian cancer, and prostate cancer, and many other hormone-based complications such as osteoporosis. Environmental xenoestrogens may be classified into two categories- natural (derived from plants or fungi) and synthetic, which include steroidal estrogens, pesticides, and industrial waste. Phytoestrogens are thought to be beneficial for humans, but many environmental pollutants, including pesticides, plastics, and chemicals, which can mimic estrogen compounds, may act like estrogen or could interfere in the mechanism of action of natural estrogens and thus disturb the endocrine processes; such substances are called endocrine disruptors. In the last decade, concentrations of synthetic estrogens have increased rapidly in soil and water worldwide; synthetic xenoestrogens have attracted significant attention. In this chapter, the severe effects of xenoestrogens on human health have been highlighted.

Keywords: Breast cancer, Carcinogenesis, Early adolescence, Endocrine disruptors, Endometrial cancer, Environmental pollutants, Menopause, Mycoestrogens, Osteoporosis, Phytoestrogens, Steroid hormones, Xenoestrogens.

INTRODUCTION

Estrogens

The term ‘estrogen’ in American English or ‘oestrogen’ in British English is named after its importance in the oestrous cycle. Estrogens are steroidal hormones

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or similar compounds which are responsible for the development of women's reproductive system and other sexual characters. They are responsible for a wide range of physiological functions. Along with progesterone, the estrogen hormones control menstruation. They play a very significant role in preventing infection and inflammation, reducing mental stress, strengthening bones, controlling cholesterol, and increasing sex drive. They also increase the glow of skin and hair, because estrogen increases the level of collagen of the skin, which reduces wrinkles and makes the woman look attractive and helps in blood clotting, and maintains the smoothness of the vagina [1, 2]. The term estrogen can also be used for any compound that is either natural in origin or synthetic but exhibits a similar effect as natural hormones. Estrogens, such as estrone (1; E1), estradiol (2; E2), estriol (3; E3), and estertrol (4; E4), which is another type of estrogen produced only during pregnancy, are steroidal core molecules (Fig. **1**). The steroid core represents a structure that contains a C18 nucleus, consisting of four fused rings out of them three are six-membered (rings A, B, and C) and one is five-membered (ring:D) [3, 4]. Estrogen is usually formed in women in the placenta and ovary. The most important form of estrogen is the 17β-estradiol with estrogenic hormonal activity, produced and secreted by the ovaries of conceiving women, which plays an important role in the development of the baby and then protecting it from miscarriage. Estrone and estriol are primarily formed in the liver from estradiol [5].

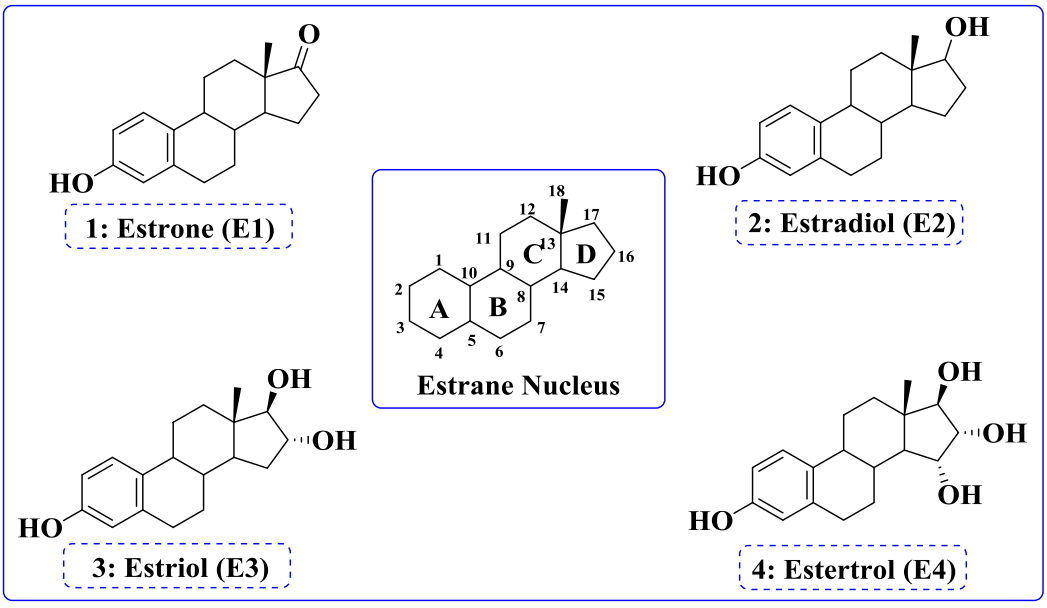

Fig. (1). Molecular structures of estrone (E1), estradiol (E2), estriol (E3), and estertrol (E4). The estrane nucleus is shown for reference.

Biosynthesis of Estrogens

The syntheses of sex hormones are regulated by the Gonadotropin-releasing hormone. The Gonadotropin-releasing hormone when released regulates the synthesis of sex hormones. The production of steroid hormones begins with cholesterol. When in the pituitary gland, GnRH induces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), after this process LH binds to its target cells and increases the expression of steroidogenic acute regulatory proteins (StAR). Biosynthesis involves cytochrome P50 and hydroxysteroid dehydrogenase (HSD) members. In corpus luteum, P450scc and 3beta-HSD, act as catalysts to reach progesterone from cholesterol, and they also catalyze P450arom (aromatase) in granulosa cells, from 19-carbon (C19) compounds to estrogens paves the way for biosynthesis, initiating the synthesis of theca cells at P450 [6, 7]. In the biological system, estrogen syntheses follow two routes:

Glandular Estrogen Synthesis

This type of synthesis occurs in granulosa as well as theca cells present in the ovaries. This type of synthesis also occurs in the corpus luteum. Luteinizing hormone stimulates granulosa cells to produce pregnenolone. Pregnenolone reaches the surrounding cells via these cells. After which Theca cells express 17, 20-lyase and 3-beta-hydroxisteroid dehydrogenase (3β -HSD), then metamorphose into androstenedione contraception via dehydroepiandrosterone.

Very often most of the androstenedione returns to granulosa cells, after which it is converted to estrone by the aromatase enzyme. After this process, the estrone is converted into 17β -estradiol with the help of a 17β -hydroxysteroid dehydrogenase enzyme. The expression of aromatase and 17β -hydroxysteroid dehydrogenase requires stimulation of follicle-stimulating hormone) (Fig. **2**).

Extra-glandular Synthesis

It occurs with the expression of aromatase in non-gonadal sites and facilitates peripheral aromatization of androgens to estrone. The detailed chemistry of biosynthesis of estrogens is depicted in Fig. (**2**).

CHAPTER 4

Persistent Organic Pollutants: The Ancient Intruders of Our Environment

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Abstract: Persistent organic pollutants (POPs) are chemicals compounds that directly affect human and animal health and accumulate in the environment leading to continuous exposure. They have the properties like bioaccumulation, persistence, and biomagnification, which give them the advantage of getting transported by wind and water. POPs were introduced with an intent to benefit the human population, but their excessive usage had made their presence everywhere that turns them to be toxic compounds. Some of the POPs are even generated as a byproduct of chemical and thermal processes. The toxicity evaluation of the POPs moved it towards the class of toxicants that are carcinogenic by nature and imposes a threat to animal and human both. The various analytical approaches had been made to quantify the POPs in various matrices using different sophisticated analytical tools like high-resolution GC-MS and LC-MS/MS. The limit of detection (LOD) and limit of quantification (LOQ) are proposed to be lower as they need to be quantified and detected in biological samples as well.

Keyword: Bioaccumulation, Biomagnification, Carcinogenic, High-resolution GC-MS and LC-MS/MS, Persistent.

INTRODUCTION

In the worldwide scenario, persistent organic pollutants (POPs) are responsible to cause adverse effects on the environment and human health due to their toxicity. The major issues associated with POPs are their easier transportation by both wind and water affecting people and wildlife in a wide range of areas. Therefore, it is difficult to locate the actual source of POPs contamination as it can be generated in one country and shows its effects even in an area far from where they are released. POPs are volatile compounds under environmental temperatures,

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therefore gets volatilize from various sources they are being used in like soils, vegetation, and aquatic system. POPs resist the breakdown reactions in atmospheric air consequently and they travel to long distances before getting re-deposited and show their presence in regions far from where they were used or discharged. POPs can persist in the environment for a longer time and their bioaccumulation can be observed which leads to the transportation of POPs from one organism to another *via* the food chain. POPs can move through the food chain by getting accumulated in the body fat of living organisms and their concentration level increases at each tropic level that leads to "biomagnifications". Contaminants found in small concentrations at the lower level of the food chain can lead to biomagnifications thereby resulting in the catastrophe of the entire food web and therefore small release of POPs is responsible for remarkable results. This was confirmed by the analysis of the sample collected from the Antarctic region. The sample of melted glaciers shows a high concentration of POPs and proves the theory of distant migration of POPs through the air and concluded that melting glaciers are a secondary source of POPs [4].

Many sources like effluent waste releases, runoff from agricultural lands, and atmospheric deposition are responsible for the settlement of POPs in marine and freshwater ecosystems because of which these sediments act as reservoirs or "sinks" for POPs. Lower solubility in water made it possible for POPs to bond strongly to particulate matters in aquatic sediments. POPs have both hydrophobic (water repellant) and lipophilic (fat attracting) properties due to which they show strong binding capacity with solids, mainly organic matters, and can easily enter into the lipids of organisms and get stored in fatty tissues. This stockpiling of POPs in various types of fatty tissues makes them rich in these compounds and gets them preserved in the biota due to slow metabolism because of which, POPs move upwards in the food chain pyramid [2].

After World War II when the whole world was moving towards fast-pacing industrialization, the use of synthetic chemicals increased as they proved to be beneficial in pest and disease control to increase crop production and flourish the new industry. These chemicals besides providing a strategy for increasing crop production also put forth unforeseen effects on human health and the environment. With the increased risk of POPs exposure and harmful effect, an effort was made on a global level through the Stockholm Convection. The Convention has played an important role in combating harmful chemicals worldwide.

The major classification of POPs is:

1. Intentionally produced POPs: These chemicals were produced with a positive intention of using them in various fields according to their effectiveness. These chemicals include agricultural pesticides, disease control sprayer's reagents, and industrial important chemicals. Foe example: DDT is used as a mosquito repellent and PCBs are used in a variety of industrial applications. They are also used in the heat exchange and paint industry.
2. Unintentionally produced POPs: They include chemicals generated as byproducts of some other processes. These are not produced with any motive but are generated along with main compounds. For example: Dioxins are produced as a result of industrial processes and waste combustion.

Environmental Protection Agency (EPA) and the USA had notably lowered the release of POPs generated through combustion processes like dioxins and furans into the environment. Along with the assessment of dioxins like POPs, EPA had worked attentively on the reduction of DDT globally from primary sources. To reduce the emissions of POPs, different countries have signed an agreement to implement the elimination process of toxicants. The convention aims at reducing the generation of POPs, therefore in this context, the trade of POPs is prohibited to combat their production and use. The export of POPs is allowed under the convention only when the exporting countries certify that they would minimize the harmful release of POPs to the environment and attention would be paid to their destruction or disposition in an environment-friendly manner.

Through several studies conducted to assess the toxicity level of POPs, the findings showed abnormalities and decrease in the number of wildlife organisms such as certain kinds of fish, birds, and mammals, reproductive and developmental defects, behavioural changes, neurological, endocrine, and immunological problems in human beings. The sensitive groups comprising children and old aged people have a lower immune response that makes them more vulnerable to different POPs. They also cause reproductive toxicity in both men and women [1]. The possible route of exposure to POPs includes primarily contaminated food, whereas drinking water and direct contamination are lesser-known for POPs toxicity. The low levels of POPs exposure to humans are even dangerous because they can lead to increased chances of cancer, reproductive disorders, alteration in the immune response, degeneracy in neurobehavioral, disruption of endocrine functioning, genotoxicity and increased birth defects which are discussed in detail in the later part of the chapter.

To trace the body burdens of POPs, the matrices chosen are human milk, maternal blood, and adipose tissue. Biomonitoring of human milk gives detailed

CHAPTER 5

An Experimental and Simulation Study to Address Variabilities and Uncertainties in Risk Assessment of Lead and Cadmium Ingestion for a Vegetarian Diet

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Abstract: The risk of adverse health effects of heavy metals, lead (Pb) and cadmium (Cd), was characterized by considering dietary intake of food items and resulting levels of biomarkers, blood Pb levels (PbB), and urinary Cd levels (CdU). Specifically, 35 food items (cereals, pulses, vegetables, and fruits), used in a vegetarian diet in India, were considered. Samples of food items were taken in the winter and autumn seasons and were analysed for Pb and Cd. The observed concentrations were translated into probability density functions (PDF) and Monte Carlo simulation was used to generate levels of chronic daily intake (CDI) that accounted for variability in (i) body weight, (ii) concentration in food and (iii) amount of food intake. The CDI levels were translated into equivalent PDF and the probabilities of exceedance of WHO-suggested provisional tolerable weekly intake of Pb and Cd were estimated. The probability of exceedance of the WHO tolerable limit was 5.55×10^{-3} for Pb and 7.36×10^{-4} for Cd. Further, CDIs were translated into PbB levels using a physiologically based pharmacokinetic model. The estimated health risk from (i) ingestion of Pb (*i.e.*, probability of exceedance of safe PbB level of 10 μg/dL) was 9.24×10^{-3} and (ii) ingestion of Cd (*i.e.*, probability of exceedance of 5 μg/g creatinine) was 4.21×10^{-5}, suggesting that Pb in the environment still poses a substantial risk despite its phasing out from gasoline.

Keywords: Biomarker, Cadmium, Exposure, Lead, Risk.

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INTRODUCTION

Lead (Pb) and cadmium (Cd) metals and their compounds are used in industrial and domestic products. Pb is used in Pb-based paints, Pb-containing pipes in water supply systems, battery recycling, plastics, ceramics, *etc* [1]. Cd is used in nickel-Cd batteries, as a pigment, for corrosion-resistant plating on steel, and to stabilize plastic [2]. Both the heavy metals find their way in the environment and show ubiquitous presence, even far from their emitting sources (mining, smelters, refining, incineration, and waste disposal). These metals are persistent and toxic and have no useful biological function in the human body. Even small quantities of these metals may pose a health risk to humans and the environment.

Pb is listed as one of the hazardous heavy metals by the Agency for Toxic Substances and Disease Registry (ATSDR) [3]. The main source of Pb in the air was through vehicular emissions, but after the introduction of unleaded gasoline in 2000, the air Pb levels have significantly dropped in Indian cities. For example, in Kanpur (Latitude 26.4670° North and Longitude 80.3500° East), the Pb levels during the pre-unleaded period were 2.0-2.75 $\mu g/m^3$, which have dropped to about 0.70 $\mu g/m^3$ [3 - 6]. However, Pb is still found in various environmental media (air, water, and soil) due to its stable and persistent nature. Once Pb enters the food chain, it continues to be found at all trophic levels and poses a significant health risk. In Japanese cities, it continues to be present in various food items even after 20 years of the development of unleaded gasoline [7].

The biomarker useful in estimating Pb body burden is blood lead (PbB) level. In response to increasing epidemiological evidence, the Centres for Disease Control and Prevention (CDC) gradually lowered the acceptable PbB level in the US from 60 μg/dL before 1975 to 10 μg/dL, in 1991. As per the CDC, there is no safe level of PbB below which there may not be any adverse effects [8]. The World Health Organization (WHO) has also proposed an acceptable PbB level of 10 μg/dL, which has been adopted by several countries for developing air quality standards [9]. There is poor intellectual development in children at PbB levels even below 10 μg/dL [10, 11]. Prenatal Pb exposure is reported to have a more lasting impact on child development than postnatal exposure [11]. The study by Schnaas *et al*. [11] also suggests that PbB levels in expectant mothers should be well below 10 μg/dL.

Physiologically based pharmacokinetic (PBPK) models are frequently used to assess the risk of exposure to metals and other toxins. The PBPK models describe the relationships among critical biological processes using mathematical mass balance equations that account for the disposition and uptake of chemical substances [12]. Estimates of the chemical-specific physicochemical, physio-

logical, and biological parameters are required to apply the PBPK model for any substance. A PBPK model for Pb has been developed to estimate the PbB (the biomarker for Pb exposure) concentration and assess the health risk due to Pb [5, 13].

Cd and its compounds have been established as toxins having adverse health effects by the US Department of Health and Human Services and the International Agency for Research on Cancer [14, 15]. Cd exists as vapours and/or particles in the air and it may be deposited either by wet or dry deposition onto soil and water surfaces. Cd present in the soil is largely immobile since it binds strongly to the organic matter and enters the food chain. In water, the soluble form migrates, whereas the insoluble part gets accumulated in sediment [14]. The biological indicators of Cd exposure are Cd levels in the blood, urine, kidney, liver, hair, faeces, and other tissues. Cd level in urine (CdU) reflects the total body burden of Cd [16]. The biological half-life of Cd is over 13 years [17].

To assess the risk due to heavy metal exposure, it is important to account for variability in metal concentration in food, water, and air. Information on the average level is of little use in risk assessment. A probabilistic assessment of exposure to heavy metal through ingestion and inhalation, exceeding the safe exposure level (*e.g.*, provisional tolerable weekly intake (PTWI)), by Herman and Younes [18] indicates the underlying risk [19]. The estimation of the probability of interest depends on the tail behaviour of the statistical distribution of exposure, more precisely on the extreme exposures [20]. Under the complexity of the distribution of different variables, exposure can be assessed through Monte Carlo simulation, which accounts for several variables at a time [21]. The variables include body weight, food consumption quantity and metal concentration in various food items. As the numbers of food items are many, there is a need to group them; notably, those grown under and above the ground. The present research objective is to characterize the risk of the adverse health effect of Pb and Cd for the vegetarian population of Kanpur city. The specific objectives of this research were to (i) measure concentrations of Cd and Pb in food products (fruits, vegetables, cereals, pulses, milk) and water, (ii) estimate product-wise food consumption, and (iii) develop statistical distributions of intake of Pb and Cd and characterize the risk through their biomarkers, PbB and CdU, by employing the Monte Carlo simulation.

STUDY AREA, MATERIALS, AND METHOD

The study area for the present research was Kanpur city (population – over 37,00,000; area - 3,029 km^2) (Fig. **1**), which is characterized by many industries (leather, paint, soaps, and detergents, *etc*.), including a 220 MW coal-based

CHAPTER 6

Safety Evaluation of Coloured Plastic Tiffins/Bottles and Medical Strategies to Mitigate Additive Toxicity

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Abstract: Over the last 50 years, plastics have become an integral part of our day-t--day life. They seem to be the material of choice, being inexpensive, lightweight, resistant to chemicals, flexible, and mouldable. Over 350 million metric tons of plastics are produced the worldwide and about 50% are discarded within the first year of usage. With plastics being non-biodegradable, their safe disposal is a major challenge. Although one can argue that it is recyclable, its indiscriminate disposal clogs up our rivers, oceans, and land. Some of the chemical components of plastics such as plasticizers, stabilizers, monomers, and colourants are known to leach out from the finished plastics into the stored commodity. They can also be released during various recycling processes. In the present study, undergraduate students were involved in analysing a few representative samples for the estimation of the overall leaching of plastic constituents and heavy metals into food and drinking water. Toxic effects of heavy metals, phthalates and BPA, probable mechanism of toxicity, and some medical strategies have been discussed. Findings from a survey carried out by the students to gauge awareness about leaching in plastics, segregation, and disposal of plastic wastes practised by the community are presented. This experiential learning is aimed at inculcating behavioural change about the judicious usage and proper waste disposal of plastics.

Keywords: BPA, Heavy metals, Judicious usage, Leaching, Medical strategies, Phthalates, Safety Evaluation, Toxicity.

INTRODUCTION

The past hundred and fifty years have witnessed an unbelievable pace of scientific and technological developments. Modern science has attempted and to a great extent succeeded in realizing the dreams of the scientists of the previous centuries. Ranging from the packaging of drinking water, foodstuff, and pharmaceuticals to biomedical implants, kitchenware, tabletops and alternate building materials,

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plastics and polymeric products have become an integral part of our day-to-day life. They are materials of choice due to their inertness in the finished state, lightweight, high strength, amenability for quick and mass production, and ease of fabrication into complex shapes in a variety of colours. Over 350 million metric tons of plastics are produced annually worldwide and about 50% of them are discarded within the first year of their usage [1]. The chemical structure of plastics makes them resistant to various natural degradation processes. These two factors together have led to a huge accumulation of plastic waste in the world. Almost all water bodies form a web and eventually flow into the oceans. Thus, these rich natural resources act as conveyor belts for our trash. An overview of plastic toxicology is given in Fig. (**1**).

Fig. (1). Plastic toxicology- An overview [2].

As most of the floating plastic waste is non-biodegradable, it does not decompose and keeps floating for years leading to overtime lowering of oxygen level in the water. Moreover, when marine creatures and birds accidentally consume plastic waste, they choke on it, thus leading to a steady decline in their population. Another worrying aspect of plastic usage is the migration of additives from plastic containers into the stored commodity. Most of the additives like plasticizers (*viz.* Phthalate Esters), colourants and stabilisers (*viz.* organo-tin, lead, and barium compounds) added to plastics to improve their physicochemical properties are not chemically bound to the polymers. These being small, are liable to dissolve in the aqueous environment and leach out over time from the containers into the foodstuff and water stored in them. They can also be released from the plastics during various recycling processes and from the products manufactured from

recyclates. Various studies [3 - 5] have shown that heavy metals leach out from the plastics and get accumulated in the human body and additives like Di(2-Ethylhexyl)phthalate(DEHP) and Bisphenol A (BPA), which are toxic, have been found in traces in human blood, urine and sweat [6, 7].

Due to a large demand for inexpensive brightly coloured plastic tiffin boxes, bottles, and toys for children, several small-scale industries are involved in manufacturing these plastic products from both fresh and recycled plastics. Often to make the articles attractive, additives, more than the prescribed limit, are added to attain the desired quality. In India, 60-65% of the recycling industry falls in the unorganised sector, thus fewer or no quality checks are performed before the finished products are sold in the market.

Children carry tiffin boxes and bottles to school daily; often hot food is packed in these tiffin boxes and the water bottles are left in the sun. The overtime leaching of additives could be detrimental to their health. DEHP and BPA are well-known endocrine disruptors. Since hormones control and coordinate activities throughout the body, even a small disruption can interfere with the child's growth and development. A brief review of the toxic effects of common migrating additives and some medical interventions to mitigate additive toxicity is presented here.

HEAVY METAL TOXICITY

Some heavy metals like zinc, copper, chromium, iron, and manganese are naturally found in our body and are necessary for regular body functioning but when their levels cross the critical limit [8] in the body tissues, toxicity is observed (Fig. **2**). These elements gain access into our bodies *via* food, air, or water. General symptoms of mild metal toxicity can be diarrhoea, nausea, abdominal pain, shortness of breath, weakness, and increased chances of miscarriage. Copper is essential for haemoglobin formation and carbohydrate metabolism. In excess, however, it causes cellular damage [9]. Exposure to very high levels of lead in children has been found to decrease attention span, increase irritability, and lower intelligence [10]. Further, lead is reported to be primarily stored in the bones and teeth which accumulate over time to affect the bones, kidney, and liver [11]. Long-term exposure may result in degenerative changes leading to multiple sclerosis, Parkinson's disease, muscular dystrophy, and Alzheimer's disease.

TOXICITY MECHANISM

The majority of heavy metals facilitate the formation of ROS (Reactive oxygen species/free radicals) and reduce the level of antioxidants like glutathione in the body leading to oxidative stress in the body (Fig. **2**). This increased level of

CHAPTER 7

Natural Compounds with Anticancer Therapeutic Potential for Combating Ecotoxic Carcinogens

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Abstract: Cancer is a disease characterized by uncontrolled proliferation of cells, and it is caused due to the complex interaction of many cancer-causing factors that change the normal functioning of some genes; these factors may be internal causing mutation, or they may be ecotoxic carcinogens. Ecotoxic carcinogens are the agents that are present in our environment and exposure to them can increase the risk of cancer. These include aflatoxins, arsenic, asbestos, coke-oven emissions, tobacco smoke, wood dust, and indoor emissions from the household combustion of coal, *etc*. Nature has provided us with an enormous source of natural compounds which have application in various fields such as medicine, cosmetics industry, food, and nutrition, *etc*. Nature and the natural compounds are serving as a boon to mankind. The medicinal application of natural compounds is one of the most prominent applications of plant products. Plant products have been playing a very important role in the treatment of cancer, as many anticancer drugs have been developed from plant products, such as vinca alkaloids (vinblastine, vincristine, and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptothecin and irinotecan), *etc*. The plant-derived anti-cancer drugs have benefits such as easy availability, cost-effectiveness, and fewer side effects. This book chapter will emphasize the various ecotoxic carcinogens and numerous plant-derived anti-cancer drugs, with their mechanism of action.

Keywords: Amphiboles, Anthropogenic, Apoptosis, Chromosomal aberrations, DNA adducts, DNA methylation, Genotoxic, Nitropolyaromatic, Oncogenes.

INTRODUCTION

Cancer is a serious health issue across the globe and one of the major reasons for deaths reported globally. According to the World Health Organisation (WHO), cancer is defined as uncontrolled growth and spread of cells, which can affect any

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part of the body. Apart from this, cancer is characterized by the invasion of the surrounding tissue and tends to metastasize the distant sites too [1]. The cancerous cells differ from the normal cells in the following manner:

1. Cancer cells show uncontrolled proliferation, and this is accomplished in many ways, such as by the generation of autocrine stimulation, not responding to the inhibitory signals and apoptotic signals, lacking contact inhibition. Normal cells are genetically stable, as they have machinery that works to rectify the mutations that occur during cellular processes, while the cancerous cells have mutations and chromosomal aberrations as well, which makes the cancerous cells genetically unstable. Cancer cells are immortal, while normal cells show cellular senescence *i.e.*, they die after performing a particular number of cell divisions, the cancerous cells keep on dividing. This happens due to the presence of telomerase enzyme in cancerous cells which lacks in the case of normal cells. The telomerase enzyme in cancer cells helps to maintain the length of telomeres.

2. Cancer cells have the property of tissue invasion and metastasis which is not the property of normal cells [2, 3]. Our body is made up of billions of cells grouped to form tissues. The tissues are grouped to form organs; as different organs of our body are involved in doing different activities, so the cells of different organs differ from each other as well. Depending on the cell from where cancer originates cancer is divided into 5 categories [3, 4].

• Carcinoma: is the cancer of epithelial tissue, which forms the covering and lining of body organs and the body cavity. Carcinoma is further classified as adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, and transitional cell carcinoma.

• Sarcoma: sarcoma is cancer that affects the connective tissue of the body and it is of two types, namely bone sarcoma and soft tissue sarcoma.

• Leukaemia: it is the cancer of blood-forming tissue.

• Lymphomas and myelomas: these are the cancer of the lymphatic system, which works to fight against infections.

• Brain and spinal cord cancer: cancer can also occur in the brain cells and cells of the spinal cord as well [4].

Cancer is caused due to alteration in gene function which occurs due to mutations and chromosomal aberrations [5]. These changes result in the cumulative effect of both internal and external factors, the internal factors being the cellular machinery plays a role in crucial cellular processes, like DNA replication, cell cycle

progression, *etc*. while the external factors are the substances that act as carcinogens [6]. Carcinogens are compounds that have the potential to cause cancer in humans and model organisms [7]. Our environment also serves as a reservoir of many ecotoxic carcinogens. Due to the high levels of pollution, many contaminants are present in our environment that are genotoxic, which make them carcinogenic; even scientific reports have been published that state that the environment plays a role in the development of cancer [8]. However, our environment is not just the culprit; rather it has provided a way to fight against cancer as many anticancer drugs have been developed from plant-based sources [9].

ENVIRONMENT: A RESERVOIR OF ECOTOXIC CARCINOGENS AND SOURCE OF ANTICANCER DRUGS

Ecotoxic Carcinogens

The environment constitutes the surroundings in which an organism lives, it includes both biotic and abiotic components [10], and the organisms interact with different components of the environment. Likewise, humans interact with their surrounding environment to fulfill their specific needs that impose an adverse effect on environmental conditions [11]. The level of contaminants has increased in the environment and these contaminants affect human health as we are in direct contact with our environment [12]. Cancer is a disease characterized by uncontrolled proliferation of cells; causative agents of cancer include both genetic and ecotoxic carcinogens present in our environment. In other words, the development of cancer depends on the deposition of both genetic and epigenetic changes in the cell. The environment also influences the occurrence of cancer [13, 14]. The term ecotoxic carcinogen is used for pollutants and contaminants present in our environment having the potential to cause cancer [15]. The ecotoxic carcinogens include arsenic, asbestos, benzene, cadmium, smoke, gasoline, hair dye, nickel, radon, *etc* [13, 16]; some of them are explained below:

Aflatoxins

Aflatoxins are the secondary metabolites obtained from polyketides produced by different species of *Aspergillus* (*Aspergillus flavus, A. parasiticus*, and *A. nomius)*. Being highly toxic, these fungi are the contaminants of several important cereal crops, such as wheat, walnut, corn, cotton, peanuts, tree nuts, *etc* [16, 17]. Aflatoxins are reported to cause several health issues in humans and animals [17]. Aflatoxins (Aflatoxin B1) are one of the ecotoxic carcinogens which cause hepatocellular carcinoma [18]. People get exposure to aflatoxins when they come in contact with the crops that are contaminated with the fungi *Aspergillus* or when they encounter the affected animals. The four more common types of aflatoxins

CHAPTER 8

Basics of Drug Designing Through Small Organic Molecules and Their Toxicological Impact on The Environment

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Abstract: In the most basic sense, drug design involves designing molecules that are complementary in shape and charge to the biomolecular target with which they interact, and therefore will bind to it. The therapeutic potential of an organic molecule-based chemotherapeutic candidate is influenced by the basic functional groups, where the stereo-arrangement and stereo-selectivity of groups enhance the therapeutic benefits. Stereo-selective organic molecules in different configurations show diverse activity, such as (R) and (S) enantiomers of ibuprofen are effective pain killers but only (S) naproxen has inflammatory activity. Similarly, the transformation of diethyl stilbesterol has potential estrogenic activity and not the cis form. The softness or hardness of drugs depends on the functionality of organic molecules; mostly, the presence of hydroxyl and carboxylic groups improves the softness. This chapter deals with effective drug designing, including the structure-activity relationship and the influence of various functional groups on the activity of a drug compound. The toxicological impact of drugs on the environment has also been explored. In recent times, it has been successfully studied that residue of drugs could enter the ecosystem through the water channel. It directly or indirectly impacts soil, groundwater, and surface water, and creates environmental and health problems.

Keywords: Drug, Environment, Functional group, Organic, Stereochemistry, Therapeutic, Toxicological.

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INTRODUCTION

Drug Design and Development of New Drugs

Drugs play an essential role in the prevention and treatment of human diseases. Human life is constantly threatened by diseases, such as cancer, and fungal, bacterial, and microbial diseases. Therefore, ideal drugs have great demand for the treatment of diseases. The chemists face the challenge to develop the patent drug design. For meeting these challenges, several multidisciplinary approaches are required for the process of drug development; collectively these approaches form the basis of rational drug designing. Rational drug designing for tailor-made compounds is the inventive process of finding new drugs with a high degree of chemotherapeutic index and specificity of action, based on the knowledge of the biological target [1]. Mostly, the small organic molecules are used to derive drugs, which activate or inhibit the targeted protein function, with a resultant therapeutic benefit to the patient. The selection of organic molecules in drug design depends on their shape and charge concerning the biomolecular target, having its interaction and binding properties [2]. Frequently but not necessarily, computer modelling techniques are used to study the three-dimensional structure of the biomolecular target and are known as structure-based drug design [3]. Mainly, computational methods have been used to enhance the bioavailability of small organic molecules for improving the affinity, selectivity, and stability of protein-based therapeutics. On a large scale, small molecules are an important class of drugs in terms of biopharmaceutical and therapeutic agents. Currently, small molecules or drugs have been showing great efficacy as new cardiovascular agents, antineoplastics, drugs for endocrine diseases, and acting on the central nervous system [4]. Attention should be given to which drug is better for the body and, also what the body does to the drug when it is administered to a patient. The drug must travel a journey in the body before it reaches the target site and performs its work, which is related to pharmacokinetics, and after the drug reaches the target site the mechanism is referred to as pharmacodynamics [5]. During the development of new drugs, drug targets are also identified. These targets include carbohydrates, lipids, proteins, and nucleic acids [4].

The Procedure Followed in Drug Design

The discovery of a new drug is used for the cure or prevention of diseases or the recovery of physical or mental health. Nowadays, several methods are used for rational drug designing [2 - 4]. The principal ones are Computer-Assisted Drug Design (CADD) which is primarily concerned with physicochemical parameters involved in drug activity, quantitative structure-activity relationships (QSAR), and quantum chemistry models (molecular orbital calculations) to determine the

most promising drug candidate [3]. Molecular graphics refers to the visualization of molecular objects, and this term is also used as a synonym for molecular modelling. The molecular shape and design of a drug are determined with the help of Single-Crystal X-ray crystallography and spectroscopy techniques [5].

Concept of Lead Compounds and Lead Modifications

A chemical entity may show pharmacological activity to be useful in therapeutics, but some optimal properties are required in the drug structure for better interaction with the target [6]. The chemical structure is used for chemical modifications to improve the potency, selectivity, and pharmacokinetic parameters of drugs [7]. Furthermore, the newly invented organic molecule may have poor drug activity and may require chemical modification to become a pharmacologically active drug, which is confirmed on basis of biological or clinical tests [8]. Natural products are a rich source of potential lead compounds. Plants, snakes, lizards, frogs, fungi, corals, and fish have all yielded potent lead compounds which have either resulted in clinically useful drugs or have the potential to do so. Recently, drug discovery has significantly increased due to the availability of 3D X-ray or NMR structures of biomolecules and docking tools, and the development of computer-aided methodologies.

Concept of a Prodrug, Double Prodrug, and Soft Drug

a. Prodrugs

After administration, prodrugs are used as pharmacologically active drugs. A prodrug is metabolized within the body and may be used to improve how a medicine is absorbed, distributed, metabolized, and excreted (ADME) [9]. Prodrugs are often designed to improve bioavailability when a drug itself is poorly absorbed from the gastrointestinal tract [10], especially in chemotherapy, it can reduce the adverse or unintended side effects of the drug [11].

Drug latentation consists of chemically transforming an active drug (parent drug) to an inactive form, which is converted to parent drug within the body before exhibiting its pharmacological action. The latent form of the drug is known as prodrug [12]. Prodrugs are prepared to minimize the unpleasant odour and taste, pain at the site of injection, and gastrointestinal irritation. For example, to mask the bitter taste of the chloramphenicol and lincomycin, they were converted to the form of palmitates, which are tasteless and release the active antibiotics *in vivo* [13].

A few drugs do not exert any physiological action in the body and require conversion in the body to give one or more active metabolites, such drugs are

CHAPTER 9

Advances in Biomolecular Simulations for Rational Drug Designing and Ecotoxicity

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Abstract: This chapter emphasizes the advances in structure-based drug designing to accelerate the drug discovery process. This chapter discusses the various *in-silico* techniques, such as molecular docking, virtual screening, and molecular dynamics simulations, giving insight into quantum-chemical methods and quantitative structure-activity relationship (QSAR) techniques, which are some of the most popular methods in predicting drug efficiency that helps in designing novel molecular structures. It presents a clear concept of state-of-the-art computational techniques in molecular biology, pharmacology, and molecular medicine, using quantum-chemical techniques. Also, this chapter covers advances in environmental toxicity and its effect on human health. Pharmacological techniques, including pharmacokinetic and pharmacodynamic approaches, have been discussed to predict the effect of drugs on the environment and the human body, including the effects of toxic compounds on the environment and the human body. This chapter will be of immense value to readers of different backgrounds ranging from engineers and scientists to consultants and policymakers. It will be an invaluable resource for students, researchers, and industrial laboratories working in the areas related to medicinal chemistry, cheminformatics, pharmaceutical chemistry, pharmacoinformatic and environmental toxicology

Keywords: Drug design, Molecular docking, Molecular dynamics, PBPK, Pharmacodynamics, Pharmacokinetics, Physiology-based pharmacokinetics, QSAR, Quantitative Structure-Activity Relationship, Virtual screening.

INTRODUCTION

Bioinformatics, an interdisciplinary subject, has emerged as an essential discipline towards providing scientific and novel insights into various biological studies. It helps in better understanding the biomolecules through quantum and molecular-level analysis to complex systems biology approaches. Bioinformatics helps biologists to make use of the advances in computational technologies in various

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biological applications, ranging from genomics and proteomics to advanced molecular dynamic simulations, systems biology, metabolomics, and pharmacokinetics. In this chapter, we have included various bioinformatic techniques such as molecular docking, virtual screening, molecular dynamics, QSAR, and pharmacokinetic modelling. As environmental pollution has proven to be a major hazard to the ecosystem, the applications of these bioinformatic techniques in the allied field of environmental sciences have been emphasized. These techniques help in understanding the effects of environmental pollutants on the human body and the ecosystem as a whole.

VIRTUAL SCREENING

Virtual screening is a technique to identify novel structural hits that show activities, such as inhibitory functions towards the specified proteins, from a large dataset of chemical libraries, using computational methods to identify drug candidates from a wide range of chemical libraries. The virtual screening technique employs similarity searching based on substructures, QSAR, and pharmacophore generation. Primarily, the virtual screening approach uses molecular docking and drug-likeliness analysis in finding the molecules that show biological activities towards the target. A schematic representation of various steps involved in virtual screening is shown in Fig. (**1**).

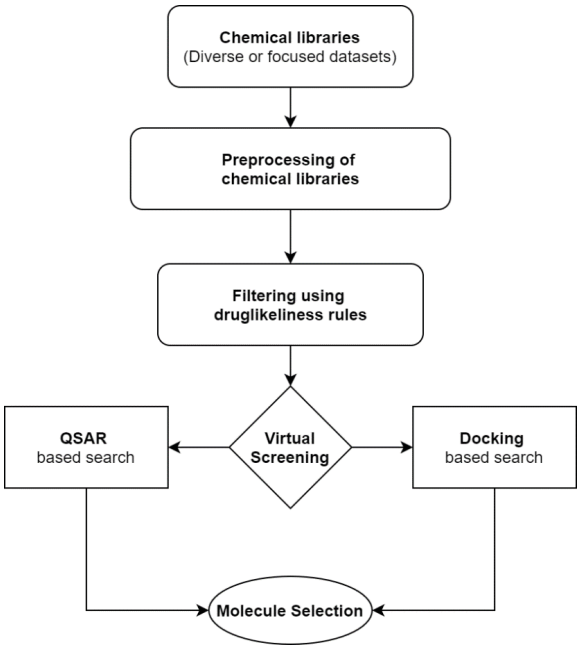

Fig. (1). A schematic representation of the steps involved in virtual screening.

MOLECULAR DOCKING

Molecular docking is a critical approach to achieve rational drug designing. It helps in understanding the molecular mechanisms involved in interactions between various biological and chemical structures, helping in analyzing their binding energies and affinities. It provides us with an overview of interactions between protein-ligand (Fig. **2**) or protein-protein complexes, ranking the candidate by their affinity scores. Molecular docking aims to evaluate the binding conformations of a ligand with a protein structure whose 3D conformation is known. The binding conformations of the ligand, known as binding pose, help in understanding the positioning and conformational state(s) of the ligand relative to the receptor. Therefore, docking methods can be used to rapidly screen a large number of small molecules into the binding site of a receptor, evaluating them in terms of binding energy between ligand and receptor.

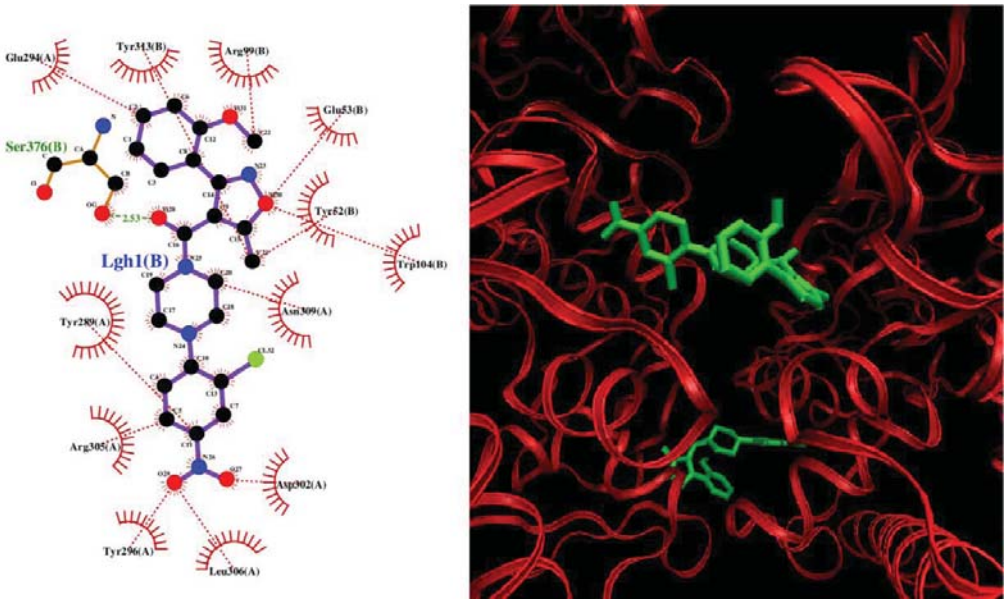

Fig. (2). Ligand bound to influenza A virus nucleoprotein.

Fig. (**2**) highlights the interactions between ligand and the nucleoprotein. The hydrogen bonds between the ligand and the protein are shown in green while the hydrophobic interactions are shown in red.

Docking can be used to predict the interactions between a ligand and a receptor (Fig. **2**). Generally, the ligand is a small biological molecule, but a peptide or a protein can also be used as a ligand [1]. The receptor is usually a protein of interest. Docking can be broadly classified into three types based on the flexibility

CHAPTER 10

Green Chemistry: Making Chemistry Environment-Friendly

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Abstract: Chemistry is all around the universe. Green chemistry underpins the enormous social and technological changes in the future. Beginning from eco-friendly chemical synthesis to green catalyst *via* green chemical reactions, it finds a good correlation with the environment, taking biosynthesis and biomimetic principles into consideration. Widespread interest in this field is seen today among scientists. Considering the present scenario of "The age of tools", the compatibility with technology today is of utmost importance. Green chemistry is one of the powerful tools to cut the Gordian knot of pollution by reducing chemicals in the surroundings to make them eco-friendly. This chapter emphasizes the various aspects of green chemistry, from its principles to its applications, leading to a sustainable eco-friendly future.

Keywords: Chemistry, Environment, Green chemistry, Pharmaceuticals, Solvent, Sustainable.

INTRODUCTION

Green Chemistry

Keeping an eye on the past and looking at the present, the fact that chemistry is often misused, cannot be denied. The increase in the percentage of pollutants, toxic substances, and non-biodegradable materials all around, has resulted in imbalanced biodiversity. Applications of chemistry on living systems to increase productivity without damaging our natural resources are a very important aspect today. Chemical industries are of utmost importance in the world's economy; however, their success has defaced the environment to some extent. Fortunately, scientists are moving steadily towards attaining an eco-friendly approach by

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practising resource sustainability. The chemistry community has been active for the last few years in developing various chemical strategies that have a less hazardous impact on biodiversity. This new approach of chemistry, called Green Chemistry, is also known by different names like Clean Chemistry, Environmentally Benign Chemistry, *etc*. The practice of chemistry in a manner that maximizes its benefits while reducing its adverse impacts has come to be known as green chemistry.

In a nutshell, green chemistry is an approach of promoting technologies or methodologies adopted for the generation/production of unhazardous chemical products essential for living systems, thereby removing pollutes from the environment. It is thus a potential driver of a sustainable ecosystem.

Green chemistry primarily involves the reduction of hazardous chemicals responsible for environmental damage. Green chemistry can also be defined as a sustainable process of minimizing hazardous substances, affecting biodiversity, from the environment economically. Today, green chemistry has generated some new terms *viz.* sustainable chemistry, atom economy, eco-efficiency, inherent safety, atom efficiency, ionic liquids, renewable energy resources, alternate feedstocks, *etc*.

Thus, today the need of the hour is developing various easy and economical methodologies for the production of harmless essentials required for mankind and the environment.

Principles of Green Chemistry

The twelve principles of green chemistry were introduced by Paul Anastas and John Warner in 1998. These principles provide guidelines for designing a chemical reaction to reduce the use of hazardous reagents and solvents and also avoid the formation of any toxic by-products. The principles are summarized below.

1. Prevention: It is well-known that many synthetic procedures involve the use of toxic reactants and solvents, and also produce a large number of toxic by-products. Many such reactions are carried out in industries. The chemical industry produces several million tonnes of such waste every year, which then requires clean-up. According to the green chemistry approach, it is better to prevent waste than to treat or clean up waste after it has been created. However, the absolute prevention of waste generation is virtually impossible in practice as the raw material cannot be fully utilized. Therefore, it is necessary to first consider whether the prevention of waste generation is possible and if not, methods should

be devised to utilize the waste produced in the best possible way, so it becomes useful [1, 2].

2. Atom economy: Barry Trost introduced the concept of synthetic efficiency in 1990. Atom economy or atom efficiency refers to the concept of maximizing the use of raw materials [3, 4]. It is a theoretical value used to assess how efficient a reaction will be [5].

The ideal reaction would incorporate all the atoms of the reactants. Synthetic methods should be designed to maximize the assimilation of all materials used in the process into the final product. In this way, there is minimum waste formation. For example, cycloaddition reactions or multi-component coupling reactions constitute one category of efficient reactions (Fig. **1**).

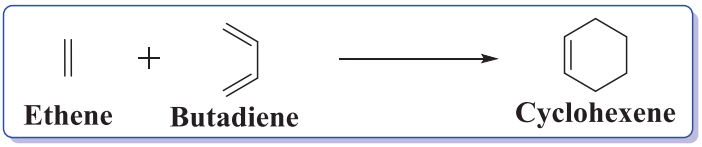

Fig. (1). Diels Alder reaction showing 100% atom efficiency.

3. Less hazardous chemical synthesis: Synthetic procedures should be designed in such a way that less harmful reagents and solvents. Cascade or tandem reactions and enzymatic reactions are good examples of cleaner and more efficient synthetic pathways [5 - 13]. Harmful chemicals are now being replaced by cleaner and cheaper biological enzymes in many industrial processes [14]. For example, Dehydrogenases can be used for synthetic procedures involving dehydrogenation, like oxidation of alcohols. Enzymes like Oxidoreductases, Transferases, Hydrolases, Lyases, Dehydrogenases, and Isomerases, are now used in industries, such as pharmaceuticals, food, agrochemicals, cosmetics, *etc*. Also, the use of solvents and separation agents should be avoided wherever possible. For example, chromatographic separations use large quantities of solvents, which cause environmental pollution. Most traditional organic solvents are toxic, flammable, and corrosive, and their recycling is associated with considerable energy loss [1]. Therefore, green solvents like water should be used wherever possible.

4. Designing safer chemicals: One of the most challenging aspects of designing safer products is minimizing their toxicity while maintaining efficacy. For this, an understanding of not only chemistry but also toxicology and environmental science is required. Chemists often use highly reactive chemicals in synthesis procedures as they are useful in causing molecular transformations. However,

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