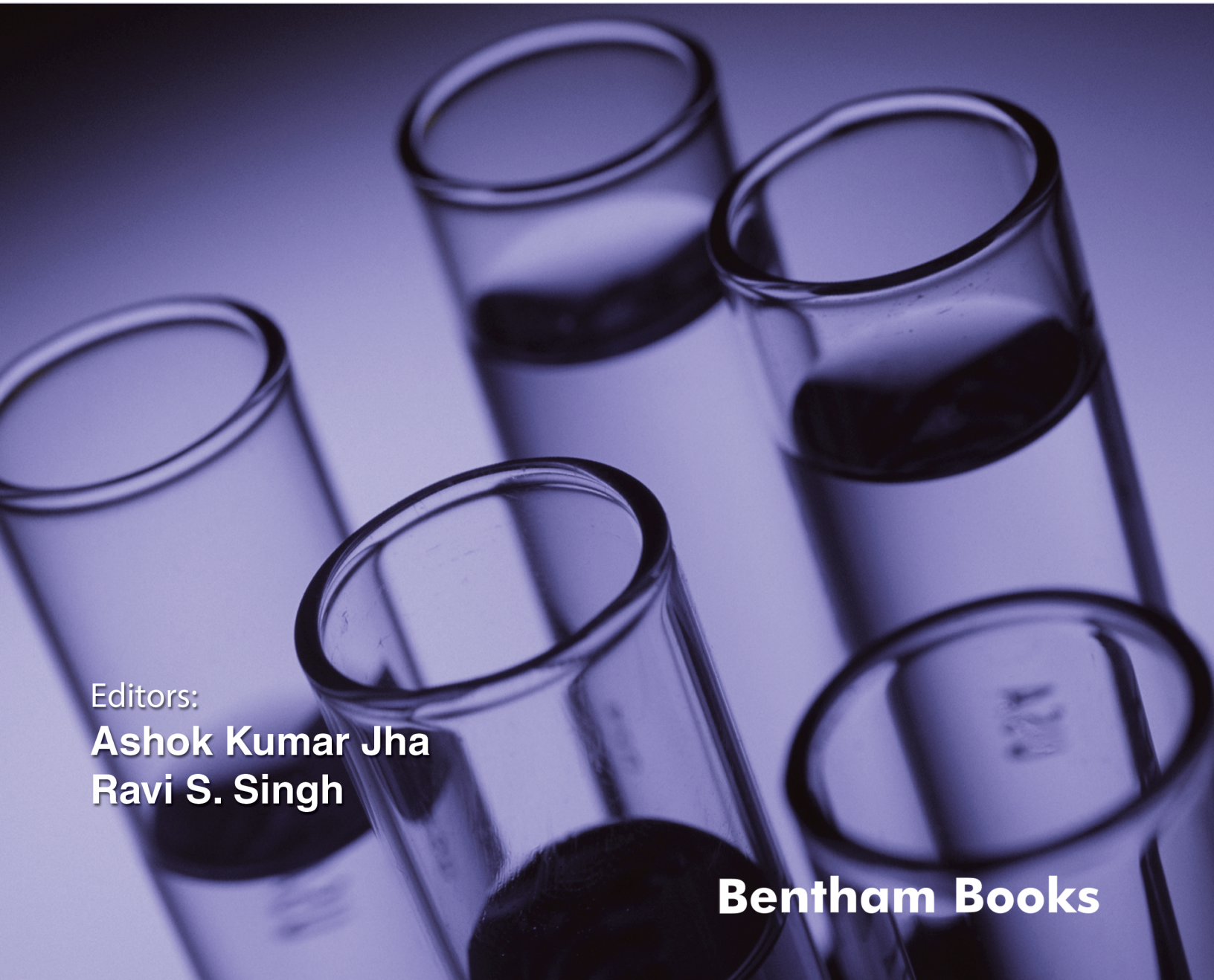
Frontiers

in Medicinal Chemistry



Editors:
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Frontiers In Medicinal Chemistry

(Volume 10)

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FOREWORD

I am extremely happy to find that Dr. Ashok Kumar Jha, Department of Chemistry, Tilka Manjhi Bhagalpur University, Bhagalpur, has ventured to edit a book titled **"Frontiers in Medicinal Chemistry".** Such a treatise is a long-standing requirement for those engaged in research and teaching the subject.

Medicinal Chemistry in Chemical Science has been serving humankind from the very beginning by way of the discovery of potentially bioactive molecules in the treatment of various ailments. Everybody would agree that the role of medicinal chemists is pivotal in the medical sciences. The development of recent therapeutic agents, secondary metabolites from plants and nano drugs, along with drug delivery targets, has added a new dimension to the field of medicinal chemistry. Methods of computational approaches in drug repositioning have emerged as effective techniques recently to cope with the devastating effects of mysterious diseases and pandemics, too. Different databases such as DrugBank, OMIM, ChemBank, and PubMed are worth mentioning in many drug repositioning prospects. A few discoveries have also taken place on isoxazole derivatives as a potential pharmacophore for new drug development. A lot of biological activities such as antimicrobial, antitubercular, antiepileptic, anthelmintic, and antimalarial have been found in heterocyclic compounds.

Cancer, arising from uncontrolled cell division, has emerged as a prominent cause of death around the globe. Carcinogenic agents and toxic heavy metals cause lung, breast and liver cancer in general, and cases of lung cancer among workers in chromium-related industries have already been established due to the ingestion of hexavalent chromium. Different types of chemotherapeutic agents and phytochemicals have been investigated for anticancerous activities.

In addition, nature has a vast treasure of medicinal plants that have not been explored for their therapeutic values till now, and so the mystery has to be unveiled for their medicinal value. From time immemorial, people have been using them as folk medicines to treat ailments. Intensive research is required to characterize the phytochemicals, which are instrumental in the cure of diseases. Some of the chapters on cancer treatment and causative agents, along with the mechanism of uncontrolled cell growth due to metal toxicity, will prove very beneficial for scientists who want to pursue advanced research in the field. Articles in the book "Frontiers in Medicinal Chemistry" have been contributed by experienced and recognized experts in the area of medicinal chemistry with a view to enrich the existing knowledge of those who are engaged in teaching and research in the field.

I do hope that this book will be appreciated by the faculties, researchers as well as students.

D.C. Mukherjee
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PREFACE

In recent times, Medicinal Chemistry has emerged in Chemistry as a very fascinating and challenging area to cope with mysterious diseases, as a result of which this branch of Chemistry has attained prime importance. From the beginning of civilization in ancient times, Chemistry has been designed to serve humankind through Ayurveda, herbal medicines and metals in nano-size for drug delivery. In the Himalayas, there were very good and well-known plants used for the treatment of severe ailments. The ancient concept of Swarna bhasma, iron bhasma, and other bhasmas is nothing but modern time nano drugs. Lead and silver bhasmas were also in practice. There is no doubt that Medicinal Chemistry plays a significant role in the discovery of therapeutic agents or bioactive molecules for use in the treatment of various human ailments. It generally involves chemical, synthetic and computational aspects of identification and modification of molecules known as drugs either from natural or synthetic products.

This book, titled "Frontiers in Medicinal Chemistry," contains diverse topics from different areas of Medicinal Chemistry, including developments in drug discovery and design, identifying new targets for existing drugs through drug repurposing, along screening new and emerging drug targets. In addition, carcinogenicity due to hexavalent chromium and arsenic with a probable mechanism of mismatch DNA repair and proteotoxic stress have been discussed in the chapter of the book. Biosynthetic pathways, biotechnology, biochemistry, molecular biology and related topics from food science have also been incorporated in the book.

I do hope that this book will serve as an important repository of scientific information on Medicinal Chemistry to students, researchers and a broad scientific spectrum. We had long sittings in the calmness of the night and even under the fading stars of dawn, completely away from the din and bustle to complete this monumental treatise. We express our sincere thanks to Senior Research Fellow Sri Sachin Verma “Heavy Metal Remediation Laboratory’’ for providing his computer skills and expertise. I also express my thanks to Dr. Ujjwal Kumar, AIIMS Patna, for showing interest in the present book.

Last but not least, we express our deep sense of gratitude to Prof. D.C Mukherjee for constant encouragement. We sincerely thank and appreciate Bentham Science Publishers for providing an opportunity to complete this project. Finally, we bow before the Almighty, Creator of the Universe, for instilling inner strength in us to complete this arduous task.

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CHAPTER 1

Isoxazole Derivatives as Potential Pharmacophore for New Drug Development

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Abstract: Isoxazoles are five-membered aromatic heterocyclic compounds in which oxygen and nitrogen atoms are present at positions 1 and 2 of the ring system. Isoxazole derivatives play a vital role due to their diverse biological activities, such as antimicrobial, antifungal, anti-viral, anti-tubercular, anti-epileptic, anti-diabetic, anticancer, anthelmintic, antioxidant, antipsychotic, antimalarial, analgesic, anti-inflammatory, *etc*. Isoxazole scaffold is present in various drug molecules, such as leflunomide (antirheumatic), valdecoxib (non-steroidal anti-inflammatory drug), and zonisamide (anti-convulsant). Similarly, isoxazole derivatives such as isocarboxazid act as monoamine oxidase inhibitors. It is used to treat symptoms of depression that may include anxiety, panic, or phobias. Whereas the isoxazole derivatives, including sulfamethoxazole, sulfisoxazole, and oxacillin, are used clinically for the treatment of bacterial infections. Isoxazole pharmacophore is also present in β-lactamase resistant antibiotics such as cloxacillin, dicloxacillin, and flucloxacillin. Cycloserine is a naturally occurring antibiotic that possesses isoxazole moiety with anti-tubercular, activity. This study focuses on the therapeutic potentials of isoxazole derivatives in new drug development.

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Ashok Kumar Jha & Ravi S. Singh (Eds.)

Keywords: Biological activity, Disease, Drug, Isoxazoles, Pharmacophore, synthesis.

1. INTRODUCTION

Heterocyclic compounds containing nitrogen and oxygen atoms play a significant role as medicinal agents due to their wide range of therapeutic activities [1]. Heterocycles are the common structural moiety present in various clinically available drugs [2]. The cyclic compound with at least two different atoms (one is carbon and the others are heteroatoms such as nitrogen, oxygen, and sulfur) in the ring system is called a heterocyclic compound [3]. Depending on the presence of a type of heteroatoms (N, O, or S), and ring size, the heterocyclic compounds are of different types, including three-membered (oxirane, thiirane, aziridine), four-membered (oxetane, thietane, azetidine), five-membered (oxolane, thiolane, azolidine, triazole, oxadiazole, thiazole, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole), six-membered (pyridine, pyrimidine), seven-membered (azepine), eight-membered (azocine), *etc* [4]. In addition to this, fused heterocyclic compounds are present such as quinoline, isoquinoline, indole, benzofuran, benzothiophene, coumarin, purine, benzimidazole, *etc* [4]. Due to the structural diversity of the heterocycles, these compounds possess a wide spectrum of therapeutic applications such as anti-bacterial, anti-malarial, anti-viral, anti-psychotic, anti-fungal, anti-tumor, anticonvulsant, anti-oxidant, antilipidemic, analgesic, and anti-inflammatory [5].

1.1. Isoxazoles

Nitrogen-containing heterocycles are considered a major class of compounds in medicinal research [6]. Among these, isoxazole derivatives play a vital role due to their diverse pharmacological activities such as antimicrobial, antifungal, anti-viral, anti-tubercular, anti-diabetic, anticancer, anthelmintic, antioxidant, anti-epileptic, antipsychotic, antimalarial, analgesic, anti-inflammatory, *etc* [7]. Isoxazoles (**1**) are unsaturated five-membered heterocyclic aromatic compounds containing three carbon atoms, one oxygen atom, and one nitrogen atom in a ring system, as presented in Fig. (**1**) [8].

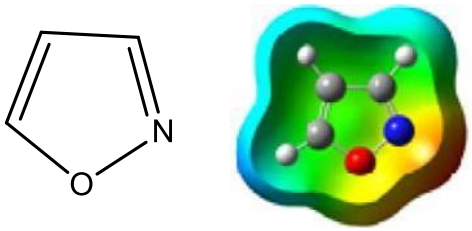

Fig. (1). Structure of isoxazole.

It is an azole in which oxygen and nitrogen atoms are present at positions 1 and 2 of the ring system [9], as presented in Fig. (**2**). The partially saturated analogs of isoxazole (**1**) are named isoxazolines (**2**) and the completely saturated analog is called isoxazolidine (**3**) [10].

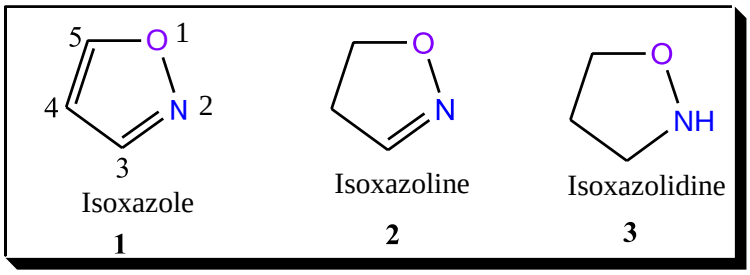

Fig. (2). Structure and nomenclature of isoxazole moiety.

1.1.1. General Methods of Synthesis

The chemistry of isoxazole and its derivatives have been developed extensively due to their diverse synthetic methodologies and potential pharmacological properties. The synthesis of isoxazole derivatives can be performed by the following methods.

The synthesis of isoxazole and its derivatives involves the cyclization of β-keto esters (**4**) with hydroxylamine (**5**) to produce 3-hydroxy-isoxazoles (3-isoxazolyl) (**6**). This method is called Claisen isoxazole synthesis (Fig. **3**) [11].

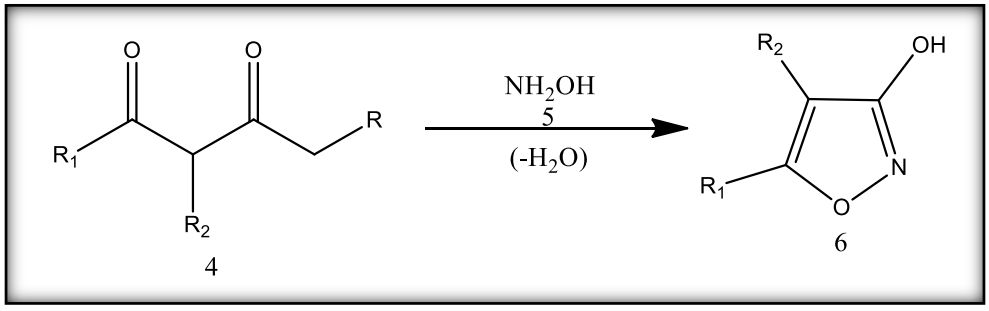

Fig. (3). Claisen isoxazole synthesis.

The synthesis of isoxazole derivatives (**8**) involves the cyclization of O-propioloyloxime (**7**) *(via* intermolecular arylidene group transfer using gold as a catalyst (Fig. **4**) [12].

CHAPTER 2

Contemporary Trends in Drug Repurposing: Identifying New Targets for Existing Drugs

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Abstract: Drug repurposing or drug repositioning has emerged as an efficient, very popular and alternative technique in modern drug discovery to identify old drugs for new targets cost-effectively and dynamically. This concept gets a tremendous boost, especially in the century's most challenging healthcare concern of the Covid-19 pandemic across the globe. In this approach, scientists seek new indications and clinical use of the drugs at minimum risk, which have previously already been pharmacologically established and approved. The methods developed for drug repositioning include computational approaches and biological methodologies, and with the fast technological advancement, various new drug-target- diseases are discovered, and thereby immense information is now available in the different databases, such as DrugBank, OMIM, ChemBank, KEGG, Pubmed, Genecard, and many more. The information available on all the above public domain databases has been utilized successfully in many drug repositioning projects. The present chapter discusses the concept of drug repurposing and its impact on academia, industries and, of course, their social implications. Besides this, the chapter will also cover details on tools and techniques to identify drugs for repositioning and their application in identifying drugs for various diseases and disorders. The current work will also foresee the recent market analysis and updates on the cost of drug discovery and development by drug repurposing, its comparison with traditional drug discovery approaches, challenges involved with drug repurposing, and future perspectives.

Keywords: Case studies, Drug repositioning, Drug repurposing, *in silico* approaches, Polypharmacology, Pharmacological approaches.

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Ashok Kumar Jha & Ravi S. Singh (Eds.)

1. INTRODUCTION

Drug repurposing or repositioning, or reprofiling, is an alternative and modern drug discovery approach that involves identifying the role of older drugs for newer targets or diseases. It is a cheaper and faster way of drug development for the disease [1]. The first example of drug repurposing goes back to the 1920s, when serendipitous incidents usually developed the drugs, and their history has been full of such stories. Herein if any drug was found to have a newly recognized effect or off-target effect, it was usually carried forward to take advantage of it [2]. Ashburn and Thor introduced the term — repurposing, which is the process to find the new use for existing drugs where drugs may or may not be part of public domain drugs comprised primarily of generic drugs [3]. This definition changed significantly with time, including active substances that either include failed drugs or drugs failed at the clinical level due to their profound toxicities and off-target effects. This widened definition excludes all the compounds that fall into the category of selective optimization of side activities (SOSA). In SOSA methodology, drugs withdrawn or failed drugs are chemically modified through chemical modification to be repurposed for a new indication [4]. The present chapter is put forth to expand the role of drug repurposing within the perspective of the scientific community working in academia and industry. Besides this, the chapter will also cover details on tools and techniques to identify drugs for repositioning and their application in identifying drugs for various diseases and disorders. The current review will also foresee the recent market analysis updates on the cost-effectiveness of drug discovery and development involving drug repurposing compared to traditional drug discovery, challenges involved with drug repurposing, and future perspectives.

2. BACKGROUND

One of the U.S. FDA reports showed that the number of new drugs approved by the FDA has declined since 1995. The report estimates that of the total approved drugs and vaccines, approximately 30% are repositioned drugs [5]. Some blockbuster drugs that have been discovered by repurposing methods include sildenafil, thalidomide, minoxidil, aspirin, methotrexate, and many more. Sildenafil was initially used as an antihypertensive drug, but Pfizer repurposes it to treat the erectile dysfunction-based condition. It is marketed as Viagra, which reveals great worldwide sales of approximately $2.05 billion. Thalidomide is yet another example that was marketed in 1957 for managing nausea in pregnant women. But due to skeletal defects in the newborn because of its teratogenic effect, it was discontinued from the market. However, thalidomide was then repurposed for erythema nodosum leprosum (ENL) and multiple myeloma and marketed successfully on the pharmaceutical drug market [6]. Drug repurposing,

in general, is based on the fact that all the drugs approved or declined by regulatory agencies have already undergone thorough trials and safety assessments; thus, their repositioning is quick and does not require substantial funds comparatively to conduct extensive trials [7].

In contrast, traditionally, when a drug exhibits biological activity on numerous receptors, also called "polypharmacology," it was considered negative in search of a promiscuous drug candidate. However, polypharmacological currently presents a broader scope for identifying off-targets that may be utilized if the disease pathology is quite complex [8]. The system biology insertion into polypharmacological assessment has further recolonized the area of drug repurposing [6]. Repurposing drugs is often considered attractive since the process is less risky, more economical, and time-saving. Drug repurposing is essential and also a hot topic in modern drug technology as it boosts the economy as well in a short time. Some certain advantages reflected by drug repurposing involves cut in research and development cost and time saving. Generally, five long steps are involved in traditional drug discovery, these includes **i.** discovery of lead followed by preclinical studies; **ii.** review of safety; **iii.** clinical trials; **iv.** review by USFDA; **v.** post market surveillance and long-term safety assessment. However, drug repurposing involves four steps that are relatively very less in contrast to traditional discovery. The major steps include **i.** compound identification from the approved leads; **ii.** acquisition of lead compound(s); **iii.** validation of new target; and **iv.** FDA approval and market surveillance for safety parameters. Traditional *de novo* drug discovery takes a long time, from drug identification to the marketing of the particular drug, and it also takes high cost and high risk that creates less interest for an investor to invest in the pharmaceutical industry. Compared to this, the drug repositioning strategy requires lesser time and money to launch the drug in the market for the disease. In this case, the *in vitro* and *in vivo* (also do not require phase 1 clinical trials) screening, validation, and efficacy studies require lesser time and reduced cost, which grows the interest of the investor. In this process, repositioned compounds have gone through different safety and pharmacokinetics studies for drug development with zero error or leakage and 100% accuracy. It is disclosed that repositioning drugs save cost and accomplishes profits of around 40% from the market [9, 10]. It is estimated that repurposing requires 3-4 years to undergo significant clinical trials and an investment of around 1.6 billion dollars in contrast to 12 billion dollars on an average requirement for novel drug discovery [11]. Currently, drug repurposing has been practiced for the treatment of orphan, rare or neglected diseases where cost investment is very scarce, along with pandemics that require rapid discovery of putative drugs in a short span of time [12].

CHAPTER 3

Pharmaceutical Potential of Pyrimidines as Antiviral Agents

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Abstract: Antiviral drugs are a class of medicines particularly used for the treatment of viral infections. Drugs that combat viral infections are called antiviral drugs. Viruses are among the major pathogenic agents that cause a number of serious diseases in humans, animals and plants. Viruses cause many diseases in humans, from self-resolving diseases to acute fatal diseases. The strategies for the development of antiviral drugs are generally focused on two different approaches, *i.e.*, targeting the viruses themselves or the host cell factors. Antiviral drugs that directly target viruses include the inhibitors of virus attachment, inhibitors of virus entry, uncoating inhibitors, polymerase inhibitors, protease inhibitors, nucleotide reverse transcriptase, inhibitors of nucleoside and the inhibitors of integrase. The inhibitors of protease (ritonavir, atazanavir and darunavir), viral DNA polymerase (acyclovir, tenofovir, valganciclovir and valacyclovir) and integrase (raltegravir) are listed among the top 200 drugs by sales during the2010. Still, there are no effective antiviral drugs available for many viral infections. There is a couple of drugs for herpes viruses, many for influenza and some new antiviral drugs for treating hepatitis C infection and HIV. This chapter gives an overview of the pyrimidines and hetero annulated pyrimidines that have been reported to be active against viral infections; identification of novel pyrimidine leads may be used in the designing of new potent, selective and less toxic novel therapeutic agents having promising antiviral activity. An effort has been made to compile all the possible information regarding antiviral pyrimidines and bring them together to make easy availability of the existing literature on the subject. The objective of this chapter is to provide the structural and antiviral activity information as well as methods being used for the screening of the antiviral activity and antiviral potential $IC_{50}/ED_{50}/CC_{50}$ values of the reported active pyrimidines are briefly discussed.

Keywords: Antiviral drugs, Antiviral pyrimidines, Inhibitory actions, Mechanisms of action.

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Ashok Kumar Jha & Ravi S. Singh (Eds.)

1. INTRODUCTION

The treatment of specific viral diseases requires specific antiviral drugs, *e.g.*, antibiotics for bacteria. In contrast to the complex structure of protozoa, fungi, and helminths, in viruses, the nucleic acid, protein coating and viral enzymes, including the coating of lipids, simply constitute the viral structural framework. Moreover, for replication, viruses utilize all the machinery of the cell and are hence treated as typically obligate intracellular pathogens. Under such conditions, it is a very difficult task for scientists to design and synthesize potential antiviral agents, which are only selectively toxic against viruses [1], as viruses are very tiny agents either made up of DNA or RNA and are also causal organisms of various diseases in animals and plants. Hence, in order to combat humans and viruses, different strategies are needed to adopt against each other. Antiviral drugs inhibit the growth of the viral pathogen, unlike the action of most antibiotics drugs which kill the targeted pathogens. Therefore, it is very difficult to search such drug targets that would only interfere with the virus without affecting the host's cell. Furthermore, due to continuous changing in the viral strains, the development of effective antiviral drugs and vaccines is a very complicated task [2].

The discovery and approval of idoxuridine in June 1963 as an effective antiviral agent opened a new area of discovery of antiviral drugs. Since then, a large number of antiviral drugs have been discovered for treating the virus disease in humans, and many others are also in clinical trials [3].

The process of discovery and development of an antiviral drug is very tedious and consists of a number of stages which include identification of the target, biological screening, generation of lead molecules and lead optimization, studies at the clinical level, registration of the drug, *etc* [4]. Continuous research on the discovery of potential antiviral agents is an urgent need in order to control the millions of human fatalities due to viral infections worldwide over the course of human civilization.

1.1. DNA Virus

The herpes viruses, papilloma viruses, poxviruses and adenoviruses and other DNA viruses generally have double standard DNA, leaving single-digit DNA that enters the cell centre and develops new viruses.

1.2. RNA Virus

The measles, influenza, colds, mumps, polio, meningitis, retroviruses (T-cell leukaemia, AIDS), arenaviruses and other RNA viruses are single descriptors.

RNA does not enter the cell centre. DNA copy of the viral RNA is formed by using the viral RNA, this process is organized by the host genome followed by retroviruses.

1.3. Steps of Viral Infections

The initial stage of viral infection is the entry of the viral DNA in the host cell and then releasing of new viruses after the replication (which includes a viral attachment, invasion, uncoating, replication, assembly and release) of that DNA. Hence, the first stage of viral infection is the attachment and penetration in which the virus attaches to a host cell, followed by injecting its genetic material into the host cell. Then incorporation of the viral genetic material (RNA or DNA) itself into the genetic material of the host cell and inducing it to replicate the viral genome, this step comprises uncoating, replication, assembly and release. Thus newly created viruses are released from the host cell either by breaking the cell, budding off through the cell membrane or by waiting for cell death [5, 6].

1.4. Inhibitory Action of Antiviral Agents

Two modes of inhibitory action due to antiviral drugs include targeting viral function and targeting cellular function that the virus needs. Generally, nucleic acid polymerases are divided into three categories *viz.* DNA dependent DNA polymerase, RNA dependent RNA polymerase and DNA dependent RNA polymerase. Due to the high mutability of the viruses and newly developed drug resistant viruses, the developments of vaccines and synthetic effective chemotherapy agents against influenza virus (flu) are of limited use [7, 8]. Designing and synthesis of potential antiflu drugs are based on the use of several potential molecular targets, *viz.* M2 proteins [9], endonuclease [10], hemagglutin [11] and neuraminidase [12], as revealed by various viral replicative cycles. A few drugs, namely rimantadine and amantadine, are only currently available for the treatment of Influenza, which provide limited protection as they have activity limitations and work as M2 inhibitors against influenza A by blocking the ion channel of the M2 protein [13]. Zanamivir and oseltamivir are potential neuraminidase (NA) inhibitors that displayed significant antiviral activity when taken intranasally, but poor NA if given systematically. However, the poor bioavailability of these drugs is a major concern as it is rapidly eliminated through renal excretion [14]. The orally active antiviral drug, namely oseltamivir, has side effects of nausea and vomiting. However, a recent report revealed that drug resistant strain of influenza A was developed in 20% of children when treated with oseltamivir [15, 16] and partially drug-resistant H5N1 strain 1 to oseltamivir was also recently reported [17, 18]. Thus the emergence of drug resistant strain of influenza needs to search for new and effective drugs against this mutant viral

CHAPTER 4

Drugs and Phytochemicals Targeting Cancer

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Abstract: Cancer which is basically uncontrolled cell division and, thereby, the formation of tumors, has been a prominent cause of death across the world. More than 10 million people have lost their lives due to different types of cancer such as breast, lung, prostate, gastrointestinal, *etc.* Several pathways, including metabolic, signalling, *etc.*, get altered to support uncontrolled cell division and their growth in case of cancer. Despite an increasing understanding of this disease over the period of time, still, specific causes could not be held responsible for the occurrence. Therefore, various different strategies mainly focused on preventing and killing cancerous cells have been explored. This chapter will primarily focus on the different drugs, including different types of chemotherapeutic agents such as DNA-alkylating agents like nitrogen mustard, cyclophosphamide, drug-peptide, drug-steroid conjugates, antimetabolites, antibiotics, *etc.* In addition to that, phytochemicals, which have also been investigated for their anti-cancerous activities and are under clinical trial, have also been discussed.

Keywords: Alkylators, Antimetabolite, Berberine, Cancer, Chemotherapeutic agent, Curcumin, Isothiocyanate, Phytochemicals, Quercetin, Resveratrol.

1. INTRODUCTION

Owing to mutation, some of the cells start proliferating uncontrollably, lose the ability to differentiate and may lead to the formation of tumors which could be *cancerous* or *benign*. Although the evidence suggests that the existence of cancer was there even before the existence of humans on the earth but in humans, it is as old as 3000 B.C., as some evidence has been found related to breast cancer [1]. Earlier supernatural powers and events were considered to be the real cause of cancer. But in 400 B.C., Hippocrates revealed that it occurs due to biological reasons and mainly due to the excess production of *black bile* in the body [2, 3].

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According to the American Cancer Society (ACS), cancer could be defined as *a group of diseases characterized by uncontrolled growth and spread of abnormal cells.* Abnormal function, uncontrolled rate of proliferation and tendency to invade nearby tissues are some of the important characteristics of the cancerous cells. In general, such an abnormally higher rate of proliferation leads to the formation of *tumors* that could be *benign* in nature and may remain confined to the area where it originates and does not spread to other tissues, whereas *cancerous or malignant tumors* may also invade other nearby tissues and could also spread to the other parts of the body through a process known as *metastasis* [4]. Although the term *cancer* is used to refer to a group of diseases having similar characteristics, such as uncontrolled cell division, growth and invasion of other tissues, it gets its name depending on the area of origin and the name of the organ. Importantly each type of cancer has its own characteristic features, and therefore, they vary in their behavior and responses to the treatment. Even after metastasis, it continues to maintain its properties [5].

Table 1. The most common types of cancer and estimated new cancer cases and death as projected for the year 2022 in the United States [6].

Type	Estimated New Cases	Estimated Death (Approx.)
All sites	1918030	609360
Breast	290560	43780
Prostate	268490	34500
Lung and Bronchus	236740	130180
Colorectal	151030	52580
Lymphoma	89010	21170
Skin Melanoma	108480	11990
Urinary Bladder	81180	17100
Leukemia	60650	24000

Carcinoma *(Skin or epithelial tissues),* Sarcoma *(supportive and connective tissue),* Myeloma *(Plasma Cell of bone marrow),* Leukemia *(Blood Cancer),* Lymphoma *(gland and lymph nodes)* are a few major categories of cancer. 80-90% of the total cases fall in the category of *carcinoma*. More than 19 million new cases and over 10 million deaths have been reported worldwide in 2020. As per the data produced in *CA: A Cancer Journal for Clinicians,* a journal published by the *American Cancer Society,* 609 360 million deaths and more than 19 million new cases have been estimated to be registered only in the United States in 2022 (Table **1**) [7]. Among the different types of cancer, lung and bronchus cancer is one of the leading types of cancer, which itself accounts for more than one lakh

death each year and as per the data, it is almost equally common in both males and females. In males, lung, along with prostrate and colorectal cancer, accounts for almost 42% of all types of cancer, whereas in females, breast cancer (~26%) remained the most diagnosed type of cancer in 2020. Lung, colorectal and cervical cancer remained another prominently diagnosed cancer type in females [6].

2. CAUSE AND RISK FACTORS LEADING TO CANCER

Unlike various other diseases, especially pathogen caused ailments where the causative agent is known, in the case of cancer, there is no such single reason or therapeutic target which could be held responsible for the occurrence of cancer. In fact, it is the result of a diverse range of factors, including environmental, hormonal, occupational, pharmaceutical, dietary, *etc.*, which could contribute to this disease [8]. Although smoking and the use of tobacco-based products are a well-established reason that contributes to a wide range of cancers almost at all sites of the body, various other lesser known facts are there which may contribute to cancer [9, 10]. Any agents which are capable of causing cancer are termed *carcinogens* and these could be chemical, physical or biological in nature. Exposure time, amount of exposure and genetic background of a person are some of the key factors which determine the occurrence of cancer. Some of the examples have been discussed below.

2.1. Chemical Carcinogens

Several chemicals which could be of natural origin or could be synthesized have been found to exhibit carcinogenic effects. For example, Aflatoxin B_1 (Fig. **1**), which is an example of aflatoxin produced by fungi *such as Aspergillus flavus*, has been found to be carcinogenic in nature and may cause liver cancer [11, 12]. Similarly, other polyaromatic hydrocarbons (PAH), such as benzo[α] pyrene, benzo [α] anthracene, *etc.*, are well-known examples of carcinogens. Similarly, other organic compounds, such as 4-(4-aminophenyl) aniline and *N*-nitrosodimethylamine (NDMA), also exhibit carcinogenicity. In addition to that, several organic solvents, such as benzene, toluene, carbon tetrachloride, *etc.*, also display a carcinogenic effect [13]. Apart from the well-documented organic compounds, various inorganic compounds, such as $Ni(CO)_4$, and heavy metals, such as arsenic (As) and cadmium (Cd), are a few important examples of inorganic carcinogens [14]. In particular, Arsenic contamination in drinking water has been considered a major cause of cancer in the Indo – Gangetic region of Bihar in India.

CHAPTER 5

Harnessing the Neurological Properties of Indian Brain Health Booster Brahmi

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Abstract: Brahmi (*Bacopa monnieri* Linn.) is a well-known therapeutic herb used in a broad spectrum of conventional medicines to alleviate various ailments, prominently those involving intellect, anxiety and mental health. In Ayurveda, it is classified as Medhya rasayanas (meaning intellect rejuvenator) and claimed to be a cognitive nutrient and memory enhancer. Although the plant possesses a plethora of compounds, its neurological activity is mainly attributed to its major phytochemical constituents, *i.e.*, bacoside saponins. Majorly isolated compounds are dammarane triterpenoids glycone and aglycones. There are several reports published with neurological activities on *Bacopa monnieri* to validate traditional claims through scientific findings. Some therapeutic formulations containing standardized extracts of *Bacopa monnieri* have also been developed for the betterment of mental health. Besides, being neuroprotective, the plant is reported to possess anti-inflammatory, analgesic, and antipyretic properties and systemic disorders like cardiovascular, hepatic, gastrointestinal, myocardial ischemia, respiratory problems, opioid-related nephrotoxicity and hepatotoxicity. The present chapter described the phytochemical profiling, extraction and isolation, neurological properties, as well as toxicological and clinical studies of the plant.

Keywords: *Bacopa monnieri*, Bacoside, Brahmi, Dammarane triterpenes, Neurological disorders, Neurodegenerative disease.

1. INTRODUCTION

The Indian nootropic creeper *Bacopa monnieri*(L.) Wettst (Family: Scrophulariaceae), commonly known as Brahmi, is the most important medicinal herb of Ayurveda. The genus bacopa comprises more than 100 species. It is a

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creeper with succulent, oblong, and 4–6 mm (0.16–0.24 inch) thick leaves. The leaves are oblanceolate and arranged oppositely on the stem.

The flowers of *Bacopa monnieri* (BM) are small, actinomorphic and white, with four to five petals. It is grown in wet and muddy land and distributed throughout the southern and eastern parts of the Indian subcontinent. In the traditional medicinal system, Brahmi is used as a nerve tonic, diuretic, cardiotonic and as therapeutic against insomnia, epilepsy, asthma and rheumatism. Numerous studies on its neuroprotective, anxiolytic and anti-depression properties craftafirm staging to its traditional medicinal usage.

Bacopa has been used as traditional medicine for the management of anxiety, poor cognition, and lack of concentration and other neurodisorders [1]. It has been mentioned in Charaka Samhita (2500 B.C.) and Sushruta Samhita (2300 B.C.) as a medhyarasayana (brain tonic) to sharpen intellect and attenuate mental deficits [2, 3]. Several therapeutic formulations have been prepared to target CNS disorders and manage conditions such as memory impairments, lack of concentration, and anxiety [4]. Besides boosting CNS, it has been reported to treat numerous inflammatory conditions like asthma, bronchitis, dropsy, rheumatism, cardio tonic, nervine, diuretic, *etc.* [5]. Several studies have been published describing the nootropic functions of *Bacopa monnieri* [6, 7].

This renowned ayurvedic medicinal herb contains a vast variety of specialized secondary metabolites, including dammarane triterpenoid glycosides or bacosides, steroids, phenylethanoids, cucurbitacins and alkaloids. However, the pharmacological studies revealed that the neuroprotective effects of BM may be attributed to its most abundant constituents, *i.e.*, dammarane triterpenoids saponins called bacosides. These triterpenoids saponins are further classified as mono-andbi-desmosides on the basis of the linkage of sugar units to attach with aglycones, *i.e.*, at C-3 and C-20 [8].

In the present chapter, we focus on the phytochemical investigation, extraction methods and neurological properties of *B. monnieri*.

2. PHYTOCHEMICAL EVALUATION

The brain tonic herb BM contains a wide range of secondary metabolites such as triterpenoids, alkaloids, and aliphatic compounds. Damarane triterpene glycosides (bacosides) (Fig. **1**) are the majorly occurring and responsible compounds for the neurological activity of BM. The isolated and characterized dammarane triterpenoid glycosides possess atetracyclic ring with *β*–orientated methyl group at C-8. The most commonly occurring sugar units in dammarane triterpenoid saponins are *β*-D-glucopyranosyl, *α*-L-arabinofuranosyl and *α*-L-arabinopyranosyl. Despite the presence of these sugars, three dammarane

triterpenoid glycosides are reported to have 6-*O*-sulphonyl-*β*-D-glucopyranosyl sugar moiety [9] Chakravarty *et al.*, 2001a, [10] Zhou *et al.*, 2007b). The aglycon moieties of the dammarane triterpenoids are jujubogenin or psuedojujubogenin. The distinctive feature of jujubogenin (**1**) and psuedo jujubogenin(**2**) is the isobutylene linkage to the 23 or 22 positions of the triterpene skeleton, respectively. Different dammarane triterpenoids, alkaloids, steroids, cucurbitacins, and flavonoids have been isolated and characterized from BM and explored for their pharmacological importance.

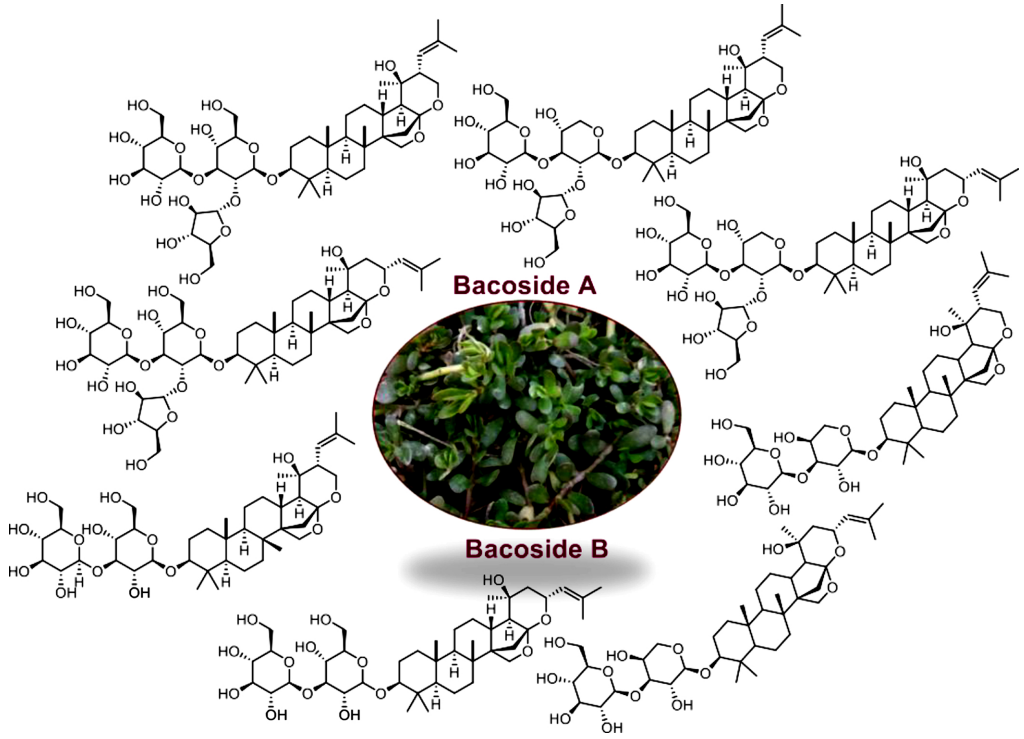

Fig. (1). Major dammarane triterpenes of the *B. monnieri*.

In view of the stature of BM in the traditional medicinal system, several research groups have explored this plant for phytochemical characterization and pharmacological evaluations. In 1963, Dutta & Basu isolated a triterpene saponin, monnierin (**3**) [11]. The compound showed a close resemblance of IR spectra with betulinic acid (**4**), no UV absorption and gave a red color with the Libermann-Burchard reagent. The molecular formula of the triterpenoid tetrosidecontains three sugar units, *i.e.*, two arabinoses and one glucose. The physical constants of the compound were in agreement with isolated sapogenin bacogenin A. The

CHAPTER 6

Carcinogenicity of Hexavalent Chromium and Its Effects

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Abstract: Hexavalent chromium has been a potential threat to human beings due to its toxicity and carcinogenesis. The pathway of entry of hexavalent chromium in an aqueous medium is both anthropogenic and natural through ores of chromium. Prolonged exposure to hexavalent chromium may cause DNA mismatch and gene mutation, resulting in cancer. Cr(VI)- induced malignant cell and its study has become very important towards the possible mechanism of Cr(VI) binding. When a cell of the human lungs adsorbs hexavalent chromium due to prolonged ingestion of Cr(VI) contaminated water or inhalation, oxidative DNA damage is caused in the specific gene. This causes mutations in adenine and guanine bases of DNA in cases of lung cancer.

Keywords: Cr(VI), Carcinogenicity, DNA, Mutation.

1. BACKGROUND

People working in industrial processes of chromium suffer from lung and nasal cancers. The saliva, gastric juice and liver have been associated with the elimination of Cr(VI) from the body. First time people of Hinkley faced cancer of liver, heart, brain, kidney, uterus and gastrointestinal system. A suit against Pacific gas and Electric Company has also been filed for claim. Since then the use of Cr(VI) in the industry was curbed. A few groundwater samples of Naugachia, Koshi region in Bhagalpur district of Bihar, India, have also been found to be contaminated with hexavalent chromium, resulting in cases of liver cancer.

2. INTRODUCTION

The aquatic kingdom is very susceptible to the adverse health effects of Cr(VI). Chromium has three oxidation states 0, 3+ and 6+, out of which Cr(VI) is very toxic and carcinogenic [1 - 4]. Hexavalent chromium migrates in an aqueous med-

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ium and is reduced to trivalent chromium, which gets precipitated or adsorbed. Cr(VI) is obtained by extraction of chromite ore and finds its way into water bodies through geological and anthropogenic activities, *i.e.,* leather tanning, anticorrosive agent, paints and other industrial activities [5, 6].

Chromium is a d block of 3d series having atomic number 24. Extraction of chromium is done from chromite mineral which is found in large amounts in South Africa, out of a total reserve of 11 billion tons. The use of chromium in stainless steel is very common as an anticorrosive agent. India is also one of the important countries producing Cr from the ore deposit. The processes of mining, grinding, smelting, and refining add chromium concentration to the water. In addition to this, geological factors also increase the concentration of Chromium (III) and Chromium (VI) in groundwater [7, 8]. In the Ferro alloy industry, chromites are also used, thus increasing hexavalent chromium. A comparison of the toxicity of chromium (III) and (VI) shows that chromium (III) is the more common but inert.

The cases of acute chromium carcinogenicity first came to light in 1987 and were published as ―Hexavalent chromium – one Town's Story on 7 December 1987. Hexavalent chromium has been detected at a level of 580 micrograms per liter. Pacific gas and Electric company used Cr(VI) as an anticorrosive agent in the cooling towers of the compressor station in the Mojave Desert town of Hinkley. Until 1972, PG and E had knowingly released 370 million gallons of wastewater contaminated with Cr(VI) into the water bodies, which finally polluted the groundwater. Hinkley plaintiffs filed suit for compensation of settlement, and finally, a compensation of 333 million was settled, followed by restrictions on the use of Cr(VI) and cleaning up the contamination. People of Hinkley town have been facing liver, heart, respiratory, cancer of the brain and uterus-related health problems for a long time due to the use of Cr(VI) by PG and E company.

Project on case studies regarding Cr(VI) contamination and the latest remediation techniques have been started in my laboratory since 2008 which is still ongoing. Some liver cancer cases have been detected in place where people use Cr(VI) contaminated water in a particular region.

Almost all compounds having oxidation state of +6 are carcinogenic [9, 10]. Lung cancer has been detected in workers due to prolonged inhaling of Cr(VI) [11]. Prolonged use of Cr(VI) contaminated drinking water causes liver cancer and nasal epithelia [12, 13]. It has been observed that the effect of hexavalent chromium on the stress response plays an important role in carcinogenesis [14, 15]. This may be one of the probable mechanisms. Lung tissues and biopsies of patients having prolonged exposure to Cr(VI) in industries revealed particulate

deposits at the bronchial bifurcations [16]. Prolonged exposure of lung epithetical cells to chromate causes an increased risk of lung cancer. The inhalation of particulate Cr(VI) in the air is a potential source of cancer. This is why industries related to chrome plating, leather tanning and extraction of chromium from its ores have become a potential threat to the workers engaged in such industries. A large portion of Cr(VI) gets converted to Cr(III) in the stomach. Chromium may be measured in the urine, serum red blood cells and whole blood. Secondary uses of chemicals having chromium refractory brick industry, steel grinding and welding also increase the contamination of chromium in water, and air workers of these industries have exposure to chromium and face an increased risk of lung cancer, liver cancer and genetic disorders. In many countries, workers in chromate industries have been found to be associated with respiratory tract and gastrointestinal tract problems [17, 18].

The physico-chemical properties of chromium decide the toxicity. Hexavalent chromium generally occurs as $HCrO_4^-$, CrO_4^{2-} and $Cr_2O_7^{2-}$.

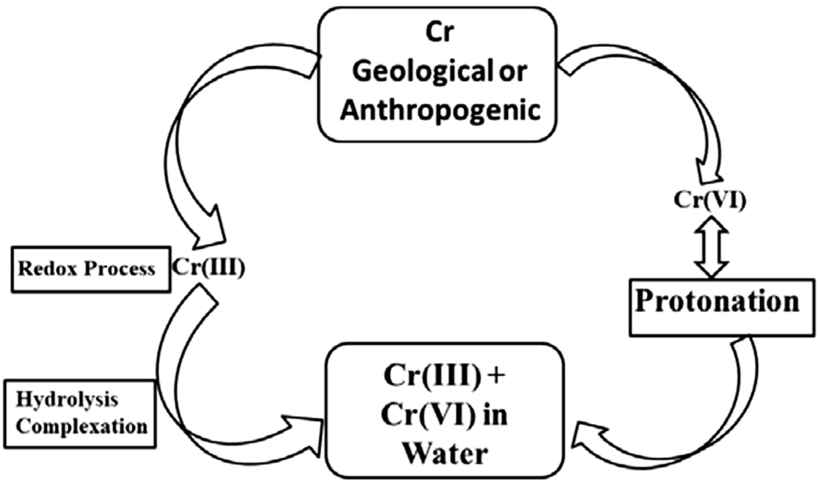

Fig. (1). Geochemistry of Cr.

Hexavalent chromium is reduced to trivalent chromium and thus precipitated. If the aqueous medium has a greater content of ferrous ion, the reduction of Cr(VI) to Cr(III) is facilitated.

But CrO_4^{2-} anion is isostructural with sulphate and phosphate ions. Due to structural similarity, they easily move through the cellular membrane, whereas large-sized Cr(III) do not enter the cellular membrane, and consequently, Cr(III) remains inert [19, 20]. If there is an organic matter or ferrous ion, the reduction of hexavalent

CHAPTER 7

Medicinal Plants: A Future of Modern Medical System

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Abstract: Humans, since their evolution, have always been in close contact with mother nature. Early life has been dependent solely on environmental resources for their livelihood. The trial-and-error approach in utilizing different resources came up with incorporating plants as a whole or their parts for food and survival. Gradually, the knowledge of medicinal plants was gained by our ancestors, and there started the Indian medical history of Ayurveda. In the current scenario, a huge number of medicinal herbs are being consumed in day-to-day life, which imparts tremendous benefits to human health. Our interest in gaining knowledge of medicinal components present in these herbs has led to many important discoveries in the area of drug development. Nowadays, numerous plants derived compounds are being used in modern medicines. In view of utilizing these natural resources efficiently, we need to understand their components in a better way. This chapter is towards gaining a deeper knowledge about medicinal plants, their role in different diseases, and insights into drug discovery.

Keywords: Bioactive compound, Medicinal plants.

1. INTRODUCTION

The co-existence of humans and plants has established ages ago, and plants have always played a pivotal role in human life. From consuming plants as a food source to utilizing them in curing several diseases, we have evolved our knowledge at an accelerating pace. Primitive man, in search of sustenance and to alleviate human misery, began to identify plants that were suitable for medicinal purposes, having some pharmacological qualities. This relationship between humans and plants bloomed, and a plethora of medicinal plants came into use. In

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terms of therapeutic herbs, Mother Nature has blessed our land abundantly. In the Eastern Himalayan areas, the Western Ghats, and the Andaman and Nicobar Islands, India has a concentrated hotspot of medicinal plants [1]. This is the reason why India is often regarded as a hub for medicinal plants. The clinical use of a huge number of medicinal plants has been reported in Indian Vedas and was used by our ancestors in treating diseases. Several herbs and plants, including species, are consumed by us regularly to enhance our immunity. Scientists are keenly interested in understanding the pharmacology of the biologically active compounds of these herbs. In the 21st century, we have many herbal-compound-based medicines in treating a large spectrum of diseases, and the discoveries are still on. From treating most common disorders like diabetes to treating deadly diseases like cancer, medicinal plants are contributing a major portion all over the world. With evolving knowledge of science and technology, researchers are trying to set a benchmark for the use of medicinal plants and their bioactive compounds. Concepts like herbal drug designing and chemo-informatics have become more common in the field of drug discovery.

2. TRADITIONAL MEDICAL SYSTEM

Ayurveda, or "Science of Life," is an ancient Indian medical system that dates back around 5000 years. Ayurveda was practiced in India's medical system during the Vedic period. During the first millennium BC, the CharakaSamhita and SushrutaSamhita list roughly 700 plant species. This medicinal system is widely used as a supplemental medicine in many parts of the world. India's Ayurveda attempts to preserve, promote and sustain human health and wellbeing. Studies report the use of over 7500 different plant species as medicine in tribal and rural areas of India [2]. Herbal products account for nearly half of all medications that are in clinical use in the 21st century, either directly or as purified components. Through its global network, India's ancient medical system AYUSH (Ayurveda, Yoga, Unani, Siddha, and Homeopathy) is moving forward to revolutionize the healthcare sector [1].

3. WHAT ARE MEDICINAL PLANTS?

Medicinal plants are plants containing chemicals in different organs which can be utilized for therapeutic reasons or are precursors to manufacture valuable pharmaceuticals. Information about their constituents makes it simpler to distinguish between medicinal plants whose therapeutic and chemical functions have been scientifically established and those that are considered medicinal but have not been exposed to scientific study. Numerous plants have been used in traditional medicines, some of them are effective against diseases but do not have any scientific reporting [3]. These plant or their extract need to qualify as medical

plants. According to Sofowora & Evans (2008), for categorizing plants as medicinal ones, they should fall under the following categories:

• Microscopic plants, like fungi, actinomycetes, *etc.,* used in drug formulations, mostly antibiotics. For example, *Streptomyces griseus* and ergot.

• Plants or their extracts that have direct medicinal use or their Hemi- synthetic formulations as medicinal compounds. For example, diosgenin, used for the hemi synthesis of sex hormones.

• Spices, food, and perfumery plants used for medical purposes like ginger.

4. ENVIRONMENTAL FACTORS AND SECONDARY METABOLITE PRODUCTION

Plants are thought to be a living chemical factory that creates a wide range of secondary metabolites (SMs), which are the foundation for many commercial pharmaceutical medications and herbal therapies derived from medicinal plants. Various compounds found in these plants have biological activities that benefit human health. Metabolites like alkaloids, terpenes, polyphenols, *etc.,* are some of the vital chemicals that are considered well for drug development [4]. Before going deep into how plants regulate secondary metabolite production, we need to get a brief of some terms used in advanced science these days. The first is the metabolome, which is used to define all of a cell's tiny components and is the fourth most important term in the "systems" approach to biology. Genomic (DNA), transcriptomics (RNA), and proteomics (protein) are the other three. In this context, secondary metabolites are a subgroup of the metabolome produced by plants, distinct from primary metabolites such as glycolysis intermediates and TCA cycle intermediates, which are vital in development and growth. A technique called mass spectroscopy has emerged to be the workhouse of recent studies that aim to identify and quantify metabolome [5].

Thousands of SMs exist in the plant kingdom; however, they are confined to specific taxonomic levels. SM synthesis is usually tightly controlled and restricted to specific tissues, organs, or developmental phases. The production of SMEs, which are important for adaptive responses, mediates the chemical interaction between the environment and plants. Abiotic and biotic stresses influence how plants interact with their environment to survive, which leads to the production of a variety of SMs. These stresses redirect the plant‘s primary metabolism and help in increased enzymatic activity and SMs production (Fig. **1**).

CHAPTER 8

Shikonin, a Naphthaquinone of Commercial Importance: its Biosynthesis and Prospect for Use as Drugs

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Abstract: Shikonin is a red naphthaquinone pigment present in the roots of plants of the Boraginaceae family. This pigment is an as active ingredient in several pharmaceutical and cosmetics preparations, and as a dye for fabrics and food items. It shows many bioactivities such as stimulation of peroxidase, protection against UV-radiation, inhibition of microsomal monooxygenase and induction and secretion of nerve growth factor. In this book chapter, we have provided detailed information on its biosynthesis and prospects for pharmaceutical use.

Keywords: Biosynthesis, Naphthaquinone, Secondary metabolites, Shikonin.

1. INTRODUCTION

Shikonin is a monoterpenoid with IUPAC name 5, 8-dihydroxy-2-[(1R)-1-hydroxy-4-methylpent-3-enyl] naphthalene-1,4-dione (Fig. **1**; redrawn [1]). Various derivatives of shikonin are formed by variation in the "–R" group attached to the naphthazarin (5,8-dihydroxy-1,4-naphthoquinone). The history of the importance of shikonins to mankind, notably as medicines and dyestuff for silk and food products, was known since ancient times [1, 2]. The use of shikonins in traditional Chinese medicine might have originated with the great surgeon Hua To (born ca. 136 ± 141 AD). Records of the use of shikonin in Chinese medicine can be found in Pen Ts'ao Kang Mu, the classic compilation of traditional Chinese medicine, which was written in 1596 AD 1[]. This molecule

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was the major constituent of the red pigment extract of the roots of *Lithospermum erythrorhizon* Sieb. et Zucc., and is known in Chinese by name as tzu tsao, tzu-ken, and hung-tzu ken and other boraginacae plants, including *Arnebia euchroma* (Royle) Johnston.

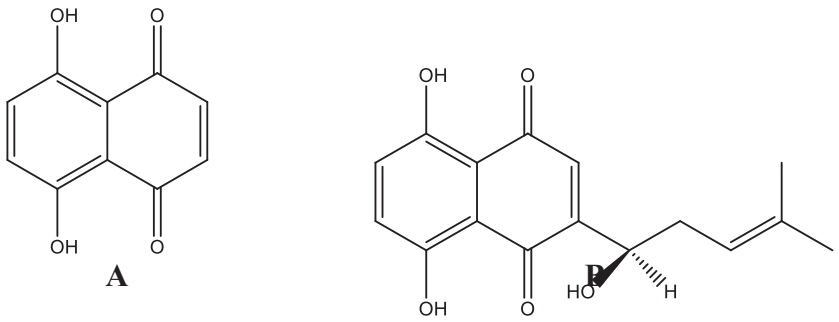

Fig. (1). All shikonin and its derivatives are derived from the basic structure of naphthazarin **(A),** wherein the variation in "–R" group attached to the naphthazarin moiety determines the structures of shikonin and its derivative **(B).**

Shikonins have wider uses in phytoceuticals, andcosmetics products, and are also used as a colorant for fabrics and food products [1 - 3]. Other bioactivities of shikonins include stimulation of peroxidase, antimicrobial properties, protection against UV-radiation, inhibition of microsomal monooxygenase and induction and secretion of nerve growth factor [4]. Shikonins are also present in *Onosma paniculatum, Arnebia hispidissima, Arnebia guttata, Arnebia tibetiana, Cynoglossum officinale*, and *Echium lycopsis*.

2. BIOSYNTHESIS OF SHIKONIN

2.1. Routes for The Biosynthesis of Secondary Metabolites

Most of the secondary metabolites are derived from three basic biosynthetic pathways, the shikimate pathway, the isoprenoid/terpenoid pathway, and the polyketide pathway. After the synthesis of the major basic skeletons, further modification by hydroxyl, methoxy, aldehyde, carboxyl groups, and carbon atoms creates a large variety of compounds [5]. Analysis of *Arabidopsis thaliana* and other plant genomes suggested that nearly 15-25% of the genes encode for enzymes involved in secondary metabolism [6]. Since the majority of secondary metabolites are plant or species specific, and the biosynthetic enzymes are substrate-exclusive, it is likely that thousands of enzymes and hence are genes involved in secondary metabolite biosynthesis, and most of these remain to be elucidated [7].

The biosynthesis of secondary metabolites and their accumulation, storage and release occurs in specialized organs or tissues. Flowers, fruits and seeds are usually rich in secondary metabolites, especially in annual plants. While in perennial species, a high amount of secondary metabolites is found in bulbs, roots and stems [7]. In many cases, the site of biosynthesis, processing and accumulation are different [8]. The corresponding product could be detected in several other tissues *via* transport routes, such as the xylem or phloem for the translocation of secondary metabolites [9]. For example, nicotine synthesized in the roots of tobacco is transported upwards *via* the xylem to the leaves, where it is accumulated as well as transformed into a wide array of products. Vacuoles occupy the most part of the inner volume of plant cells (40-90%) and play a critical role in the accumulation of secondary metabolites [10]. Water soluble compounds are usually stored in the vacuole [7, 11], whereas lipophilic substances are sequestered in resin ducts, lactifers, glandular hairs, trichomes, thylakoid membranes or the cuticle [12]. Two major mechanisms were proposed for the vacuolar transport of secondary metabolites: H^+-gradient-dependent secondary transport *via* H^+-antiport and directly energized primary transport by ABC transporters [13].

2.2. IPP Biosynthesis Pathways

IPP is the central intermediate in the biosynthesis of isoprenoids. Two routes of IPP biosynthesis have been established in cells [14]: the mevalonate (MVA) pathway and the methylerythritol 4-phosphate (MEP) pathway [15, 16]. The evolutionary history of the enzymes of these pathways and the phylogenetic distribution of their genes suggested an archaebacterial link to the MVA pathway and an eubacterial link to the MEP pathway [17]. This implies the prokaryotic origin of IPP biosynthesis and eukaryotes have inherited genes of these pathways.

2.2.1. MVA Pathway

In the MVA pathway (Fig. **2**), HMG-CoA results from the coupling of three molecules of acetyl-CoA, which is reduced by the enzyme HMGR to yield MVA. In the next two steps, MVK and PMVK catalyse conversion of MVA to form MVD, which in turn is decarboxylated to yield IPP. IPP is converted into GPP using the enzyme GDPS. The MVA pathway provides IPP for the synthesis of various isoprenoids/metabolites, for example, natural rubber, linalool, dolichol, and ubiquinone [16, 18, 19, 20]. This pathway (Fig. **2**) was first discovered in yeasts and animals in the 1950s [21, 22]. HMGR is a major enzyme of the pathway that has been studied extensively. It is considered to be the major point of regulation of substrate flux through the pathway [23, 24]. MVA pathway

CHAPTER 9

Fast Foods: Chemical Composition and Implications for Health

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Abstract: With changing the scenarios of living style, professional work culture, and daily hectic routine, liberal and global thoughts are impacting our dietary patterns and normal food consumption. So the preference for foods is changing, and foods that can be ready in a shorter time, like "fast foods", are gaining popularity among the masses, especially young generations. The fast food business has become one of the fastest-growing industries across the globe. This growing trend of fast food consumption has also brought several health-associated issues, like obesity and heart-related problems. Therefore, health-conscious people do like to know the chemical ingredients embedded in fast foods as well as their packaging and storage. For this purpose, the chemistry relating to quality aspects of fast foods, including nutritional, physiological, sensory, flavor, microbiological and packaging, is very important for healthy consumption of fast food for a healthy life. In this book chapter, we have made efforts to bring updated information related to fast food, its chemical composition and implications for human health.

Keywords: Chemical composition, Calorie, Fast food, Indian fast food, Western fast food.

1. INTRODUCTION

With changing the scenarios of living style, professional work culture, and daily hectic routine, liberal and global thoughts are impacting our dietary patterns and normal food consumption. So the preference for food is changing, and foods that can be ready in a shorter time, like "fast foods", are gaining popularity among the masses, especially young generations. The fast food business has become one of the fastest-growing industries across the globe. The National Institute of Health

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(NIH, USA) defines fast food as quick and cheap alternatives to home meals. These foods are rich in saturated fat, sugar, salt and calories. As per the definition quoted at Wikipedia, fast food is food that is sold in a restaurant or store with pre-heated or pre-cooked ingredients and served to the customer in a package form for take-out/take-away. Bender and Bender's [1] definition of fast food is a universal term used for foods that can be produced in large quantities or mass production. Banerjee *et al.* [2] stated that fast food is a byproduct of technological advances in food processing, newly invented food additives and techniques for preservation. Though fast food saves time, it does not save us from consuming fats, sodium and preservatives.

Eating out in India has evolved from an occasion-driven activity to an everyday activity, and fast food has become a significant symbol of modern culture as it tends to satisfy customers in a relatively short time [3]. The emergence of the fast food industry has transformed global food culture in general, and particularly its effect can be seen in urban areas of India. In India, fast food culture emerged after independence and decades later due to the growth in the number of nuclear families as well as working parents, increasing per capita income as well as globalization. This culture further rose to prominence with the liberalization of the Indian economy after 1990. Reputed multi-national companies (MNCs) started their business in India, and the Indian market flooded with their outlets especially in the metro, even the presence can be seen in small cities, with some outlets functioning in shopping malls and other public areas. MNCs like Burger King, Pizza Hut, Domino's Pizza, McDonald's and KFC (Kentucky Fried Chicken) are serving several Western fast foods, including Burger, French fries, Pizza, Hamburgers, *etc.,* to satisfy the Indian consumer's taste buds [4].

India also has a long tradition of delicious foods with a variety of recipes that exist in every part of the country. Indian food included in the list of fast food are Alloo-tikki, Bhelpuri, Panipuri, Paav-bhaji, Chat, Pakora, Samosa, Kachaudi, Chole-Bhature, Idli, Dosa, Uttapam, *etc.*(Kumari 2020). Indian fast food depends on the cooking method. Indian fast foods are traditionally prepared by deep frying in fat [5]. There are enough data that suggest that fast foods have become an integral component of the diet in all sections of society. It was also found that youngsters often visit fast food channels just for the sake of fun and some change from daily routine eating [6]. Today, the fast food industry is adapted to Indian food requirements and is growing rapidly. As fast food is generally considered rich in calories, fat, sugar, and salt and poor in other nutrients, it has contributed to the rise of many non-communicable diseases and metabolic diseases such as obesity and overweight, type 2 diabetes mellitus, hypertension and heart-related issues, *etc.* In contrast to the classical way of qualitative and quantitative chemical analysis of foods, new ways and approaches are also being adopted that study the

food and nutrition aspects on the line of other " omics" technologies such as metabolomics, genomics, transcriptomics, proteomics to enrich human health and knowledge. These "omics" approaches are helpful in understanding humans, food, microbe and the environment under the aegis of "Foodomics", a new multidisciplinary approach. It involves a range of aspects, from analysing the composition, quality, processing, safety and storage of foods to microbial interaction with pathogens and probiotics, to environmental safety and contamination, and to human clinical and nutrition aspects [7]. Foodomics unravels food-responsive gene regulation by integrating the study of nutrition, gene and omics. Further, foodomics is basically the study of chemical compounds present in food and their influence on gene expression by the application and integration of advanced omics technologies.

2. CHEMICALS USED AS FOOD ADDITIVES AND HEALTH ISSUES

Fast foods served in restaurants or stores are quickly ready and packaged for takeaway. These foods are energy rich foods with many things in higher concentration than the normal human requirement and considered nutritionally low grade for health point of view, for example, high content of sugar, fat, salt, protein and lower health friendly fiber, vitamin and mineral. Some of the chemicals such as sodium nitrite, sodium benzoate, azo-dicarbonamide (as a preservative), dimethyl-polysiloxane (as an anti-foaming agent), calcium caseinate (as an emulsifier), monosodium glutamate (as a flavor enhancer) often used in fast food, making these foods unsafe and unhealthy. Food packaging materials like wrappers usually contain phthalates, perfluoroalkyl and polyfluoroalkyl (PFAs), are reported to leach out of the wrapper and contaminate fast foods raising health issues, as these compounds are linked to infertility, diabetes, obesity and cancer. The chemistry of fast food additives, contaminants, agro-chemicals, together with their metabolism and toxicology decides the fate of the end product we consume. Food additives used to prolong the shelf life of foods and making more attractive are also sometimes a health concern. It is evident that too much fatty foods and sweets increase the insulin levels in the human body. Excess consumption of trans-fats due to deep frying can send mixed signals to the brain about hunger. Foods high in sugar and fat suppress the activity of a brain peptide called brain-derived neurotrophic factor that helps with learning and memory formation. Excess intake of fast foods increases calories that can interfere with the healthy production and functioning of brain synapses governing the function of learning and memory. Further, some of the fatty acids like omega-6 and omega-3 are essential for normal brain functions. A lower daily dose of these two increases the risk of dementia and other brain-related problems. Also, too much fast food intake leads to the loss of essential amino acids like tryptophan

CHAPTER 10

Implications of DNA-acting Agents as Anticarcinogenic Potential in Breast Cancer Therapeutics

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Abstract: Breast cancer is the most prevalent neoplasm diagnosed in women worldwide. There are many factors responsible for breast cancer susceptibility. Mutation in tumor suppressor genes *BRCA1* and *BRCA2* predispose women to the early onset of breast cancer. The *BRCA* genes are involved in multiple cellular processes in response to DNA damage, including checkpoint activation, gene transcription, and DNA repair. Several DNA-acting agents act as effective anticancer used for treating cancer disease. Certain groups of chemicals are known to affect specific phases of cell division, such as, Cyclophosphamide is the most potent and successful anticancer agent that acts by alkylating the N-7position of guanine to cause crosslinking of DNA's double helix, resulting in DNA breaks that interfere with the DNA replication and RNA transcription. This chapter deals with the classification of DNA-acting agents according to their modes of action.

Keywords: Breast Cancer, Cyclophosphamide, DNA-acting agent, DNA damage.

1. BACKGROUND

Breast cancer continues to be a leading healthcare problem and the most common cause of cancer deaths among women worldwide in the current scenario [1]. In recent years, the incidence rates of breast cancer have been high in more developed countries, whereas rates in less developed countries are low but increasing. The three most common cancers—breast, lung, and colorectal—together represent one-half of all new diagnoses, with breast cancer alone accounting for 30% of all new cancer diagnoses in women. According to the

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Global Cancer Statistics 2020, the number of new deaths due to breast cancer has risen to 684,996 (6.9%), more than the number reported in earlier years [2]. In fact, India has seen a drastic increase in breast cancer, and the death rate is higher in rural areas despite lower incidences of breast cancer compared to urban cities, indicating variation in disease susceptibility and clinical outcomes [3].

Cancer is a multistep process that involves cumulative genetic and epigenetic alterations, including the activation of oncogenes and the dysfunction of tumor suppressor genes [4]. *BRCA1* and *BRCA2* are tumor suppressor genes that control cell growth and cell death and also show inherited mutations in women with breast cancer. The estimated lifetime risk for females who carry *BRCA1* and *BRCA2* gene mutations is about 65% of total breast cancer cases. Those who have already developed breast cancer are at an increased risk for secondary malignancy compared to non-carriers and their families of *BRCA1* & *BRCA2* mutations [5].

Genetic changes are involved in the origin of breast cancer, as well as in various other human cancers. Epigenetic changes in DNA may be caused by a number of mutagens to which the individual is exposed through lifestyle or environmental factors such as heavy metal contamination, but they also represent physical and chemical changes in the DNA. Numerous factors are attributed to causing breast cancer. These factors include chemical substances (such as tobacco, asbestos, industrial waste, groundwater arsenic contamination, and pesticides), diet (saturated fat, red meat, overweight), ionizing radiation, pathogens, etc. Both genetic and environmental factors affect breast cancer risks, but the molecular pathophysiology of gene-environment interactions is complex [6, 7].

Long-term exposure to environmental pollutants (*e.g.*, fossil fuel combustion products and cooking oils in the home, heavy metals, and occupational respiratory carcinogens) has a significant effect on influencing breast cancer incidence and mortality [8]. Carcinogenic residues of environmental pollutants halt the cell cycle events and cause DNA damage. The cell cycle is the progression of events that ensures the generation of two daughter cells from one parental cell. It is described in four major phases: the First gap phase (G1), DNA synthesis stage (S), the Second gap phase (G2), and the Mitosis phase (M), respectively. The time period that a cell remains in the G1 phase depends on the tissue type and whether it is a normal or tumor cell. If the cell is a proliferating cell, it will quickly move into the synthesis phase (S). During this phase, the DNA is replicated, and at the end of the S phase, two copies of DNA are present in the cell. The next phase is the G2 phase, where preparations are largely made for the final cell cycle phase, the M phase or the mitosis phase. There are two major control checkpoints in the cell cycle. One of these is at the G1/S stage when cells commit to replicate, while the second is at the G2/M stage, when cells commit to divide [9]. Of these two major

points in the cell cycle, the G1/S stage is of major importance in understanding cancer and chemotherapy.

2. DNA ACTING AGENTS

Chemicals specific for DNA synthesis inhibition and others that modify the structure are also known. It is understood that the mechanism could be different, but the ultimate results may be the same, for example, the inhibition of cell division or alteration of gene expressions in the growing cell population or differentiating cells [7]. These compounds act as anticancer or antineoplastic agents that are useful in the treatment of cancer.

These compounds can be broadly classified into a few groups:

a. Nucleic acid base analogues
b. Nucleoside antibiotics
c. Alkylating agents
d. Nitroso compounds

2.1. Nucleic Acid Base Analogues

Purines and pyrimidines are basic components of nucleic acids. In both normal and altered growth of living systems, these universal components are involved in cellular functions and multiplication. A base analogue should be sufficiently similar to one of the four normal bases of DNA or ribonucleic acid (RNA) so that it can be incorporated into DNA during replication or into RNA during transcription by competing with the endogenous ones. Such a substance should be able to alter base pairing in the template strand. However, if a base analogue has more than one mode of hydrogen bonding, it could be mutagenic. Most of the analogues can participate in many reactions of their normal counterparts and may act on multiple loci [10]. However, it has become increasingly clear that there are qualitative differences that can be utilized as a rational approach to cancer chemotherapy. Nucleic acid base analogues can be categorized into two classes:

2.1.1. Purine Analogues

These analogues are structurally and functionally similar to naturally occurring purines like adenine and guanine. Examples include 6-mercaptopurine, 6-azathiopurine, 6-methylthiopurine, 6-thioguanine, Allopurinol, *etc.* [10].

CHAPTER 11

Aloe Vera-A Medicinal Plant as Potential Therapeutic Agents for Liver Cancer

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Abstract: Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide. Research over the last two decades has revealed that medicinal plants have been used for the treatment of various neoplastic diseases. *Aloe vera* is a ubiquitously naturally occurring and drought-resisting herbal medicinal plant. Some reports suggest that Aloe vera possesses wound and burn healing activities and anti-inflammatory as well as immunomodulatory effects. There are no direct studies available on the role of the Aloe vera extract and its active ingredient like aloe-emodin that modulates antiaging and anticancer activities, particularly on immune cells as well as liver cancer cells. *Aloe vera* has many bioactive compounds and pharmacological properties that may show an important role in liver cancer prevention and treatment through the enhancement of regeneration, antiaging activity, antioxidant activity, anticancer activity and modulation of genetic pathways. Here, we discuss the study of the anticancer effect and modulation of expression of various genes in response to *Aloe vera* in liver cancer.

Keywords: Aloe-vera, Anti-cancer, Anti-aging, Liver cancer.

1. INTRODUCTION

1.1. Overview

Cancer is responsible for one in eight deaths and is a major public health problem worldwide [1-2]. According to estimates from World Health Organization (WHO) in 2015, cancer is the first or second leading cause of death before the age of 70 years in 91 of 172 countries, and third or fourth rank in an additional 22 countries. In 2019, 1,762,450 new cancer cases and 606, 880 cancer deaths are

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projected to occur in the United States [3]. Now a days, a higher mortality rate due to liver cancer or Hepatocellular carcinoma (HCC) worldwide may be attributed to aggressive cancer cell growth and increases global health challenges [6]. It may arise as a result of chemical or biological damage to normal cells in a multistep process that involves changes at the initiation level followed by promotion and progression, which lead to malignancy [4].

Globally, liver cancer ranks third in terms of cancer mortality. This malignancy occurs more often among men than women, with the highest incidence rates reported in East Asia [5]. It is predicted that liver cancer will rank sixth among the most frequently diagnosed diseases and fourth among the leading causes of cancer-related death worldwide in 2018. The two to three times rate of mortality and incidence are higher among men in most world regions. Liver cancer is the leading cause of cancer death among men in 20 countries, in part because of its high fatality rate [3]. Due to improved clinical practices in the developed world, there has been a constant increase in 5 years survival rates from 3% to 18% for liver and intrahepatic bile duct cancer from 1975 to 2011. For 2018, the estimated cases of liver and intrahepatic bile duct cancer were 42,220 (30,610 Males and 11,610 Females), and estimated deaths were 30,200 (20,540 Males and 9,660 Females) in the United States. This poses a socio economic toll, and there is a need to further enhance research efforts in finding new promising therapeutic entities against longer cancer cell survival and enormous growth [6]. Different methods like surgery, radiotherapy, chemotherapy, hormone therapy, photo-dynamic therapy, immunotherapy, monoclonal antibodies therapy, gene therapy, *etc.,* are used currently, single or in a combination of two or more, for the treatment of cancer. The most common mode of treatment for cancer includes radiotherapy, chemotherapy and surgery. But nowadays, current treatment modalities are failing because of serious side effects and merely extend the patient's lifespan by a few years only. Considering these drawbacks, efforts have focused on identifying new molecular targets that would allow limited cancer treatment side effects. Thus, there is a need to utilize alternative concepts or approaches to the prevention of human cancer. In this regard, we targeted the herbal products that have been implicated in cancer prevention and that promote human health without recognizable side effects.

Plants have been used for the treatment of various diseases of human beings and animals since time immemorial. Briefly, Aloe vera is a ubiquitously naturally occurring and drought-resisting herbal plant. Aloe vera has its many bioactive compound and pharmacological properties and it may show an important role in liver cancer prevention and treatment through the enhancement of regeneration, antiaging activity, antioxidant activity, anticancer activity and modulation of genetic pathways [7]. A natural constituent of Aloe vera leaves Aloe-emodin has

been reported to be nontoxic for normal cells but possesses specific toxicity for neuroectodermal tumor cells [7, 8, 9]. Aloe-emodin has been reported to induce apoptotic cell death in H460 cells. The expression of PKA, PKC, Bcl-2, caspase-3 and p38 was involved in aloe-emodin induced apoptosis of H460 cells. The signaling order in the aloe-emodin induced cell death pathway may be PKA, PKC, Bcl-2, caspase-3 and then p38. P38 clearly is an important determinant of apoptotic death induced by aloe-emodin [10]. Moreover, the reactive oxygen species (ROS) is one of the causes of cancer progression. The imbalance between the production and accumulation of ROS which further results failure of cells to maintain normal physiological redox-regulated functions. This, in turn, leads to DNA damage, unregulated cell signaling, change in cell motility, cytotoxicity, apoptosis, and cancer initiation [11]. Low molecular weight fraction (LMWF) obtained from Aloe vera extract induced disruption of intercellular junctions, and it inhibited the production of reactive oxygen species [12]. It has been reported that there is an increased generation of ROS and oxidative stress associated with cancerous cells in comparison to normal cells and results in stimulation of cellular proliferation, mutations, genetic instability and cell death. Aloe vera has several bioactive compounds including aloe-emodin that can reduce ROS and thus, it can be used for potential biomedicines in cancer treatment. The current study is focused to investigate the anticancer effect of aloe vera in liver cancer as a medicinal therapeutic agent. This review provides an update on the modulation of expression of various genes in response to Aloe vera in liver cancer.

2. LIVER CANCER

Hepatocellular carcinoma (HCC) or Liver Cancer is one of the most frequent cancers among humans, with 0.25–1 million newly diagnosed cases each year. It is developed due to various factors, including chronic hepatitis-B infection, chronic hepatitis-C infection, exposure to aflatoxin-beta, cirrhosis of the liver, oral contraceptives, cigarette smoking, *etc.* It is essential to understand how the liver works in order to understand liver cancer thoroughly. Physiological processes such as metabolism, secretion, and storage are regulated by the liver. Unfortunately, numerous toxicants attack it. Throughout tumor progression and its inhibition through chemotherapy, the host system's biological and histological parameters will reflect the numerous pathological changes, particularly pertaining to the liver, which is known to be the major organ affected in carcinogenesis [13]. The liver is the second largest organ and the largest gland in human beings. It is found in the upper belly, the internal form of the human being, its function is to absorb and remove waste from the blood. In the liver, there can be a mass of tissue called a tumor or growth in the presence of additional waste cells. Benign or malignant tumors may occur.

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