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# Frontiers in Drug Design and Discovery



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Co-Editors:

**Atta-ur-Rahman**

**M. Iqbal Choudhary**

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# **Frontiers in Drug Design & Discovery**

*(Volume 8)*

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Editors: Atta-ur-Rahman, *FRS* & Mohammad Iqbal Choudhary

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## PREFACE

Drug discovery and development against prevailing and emerging diseases is one of the most important areas of modern health care research. This interdisciplinary area requires consistent well coordinated efforts of scientists with diverse expertise. It starts from target identification that underlies a particular disease process. It often takes years of study in order to characterize the targets for a potential drug. Once a receptor target has been characterized and validated, the most challenging task of identifying appropriate ligands from natural or synthetic sources begins. The study of the biochemical mechanism of the receptor-ligand interaction is the next step in this process. Often the ligands need to be modified to achieve greater specificity and affinity, requiring skills of medicinal chemists. This is followed by pre-clinical and clinical studies for safety, efficacy and specificity, often leading to frustrating failures, and re-initiation of the whole process. Finally, there are other considerations in the development of new drugs, termed ADMET (absorption, desorption, metabolism, excretion, and toxicity). Despite the challenges associated with the drug discovery and development, it is a fascinating and much needed scientific research which continues unabated.

The 8<sup>th</sup> volume of the ebook series entitled, “*Frontiers in Drug Design and Discovery*”, is a compilation of five exhaustively written reviews focussing on various aspects of drug discovery and development in key therapeutic areas. These reviews provide a wealth of information about topics of great interest in this field.

Parmer *et al.*, have contributed a comprehensive review on the development of new chemotherapeutic agents against haematological cancers. Hematological malignancies are among the most common cancer types. They affect the blood and lymph systems and include chronic and acute leukaemia, non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma. There has been a major gap between the needs of treatment for haematological cancers and the current pace of drug development in this field. The authors have skilfully dealt with the subject by highlighting major developments in this important area along with pharmacology, pharmacokinetics, and clinical studies on various classes of drugs, including targeted therapies.

In chapter 2, Rowe *et al.* review the recent literature on the current developments in the management of esophageal carcinoma. The review begins with the description of two major types of esophageal carcinoma i.e. squamous cell carcinoma and adenocarcinoma. Different therapeutic interventions at various stages of esophageal carcinoma, as well as the health status and age of patients are described. This review presents treatment options for squamous cell cancer such as chemotherapy and radiation therapy as the first lines of treatment followed by surgery. Studies showing that chemoradiotherapy before surgery is better than surgery alone are presented. For adenocarcinoma, the most common treatment is chemotherapy and radiation therapy, followed by surgery. For advanced stage esophageal cancer, chemotherapy and radiation therapy remain the only options. Most importantly, the review describes advances in endoscopic treatments of early stage esophageal cancers such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) as well as endoscopic ablation procedures, including photodynamic therapy (PDT) and radio frequency ablation (RFA). These advances have proven to be safe and effective for the treatment of esophageal dysplasia and early stage neoplasia.

Androgen hormones stimulate prostate cancer cells to grow faster. The most important among them are testosterone and dihydrotestosterone (DHT). Lowering androgen levels or stopping them from getting into prostate cancer cells have been used to slow down the growth of

*ik*

prostate cancers. This is called androgen deprivation therapy (ADT). However, there are a lot of controversies associated with ADT. Tai *et al* in chapter 3 have reviewed past uses, and recent scientific evidences concerning the ADT in the treatment of prostate cancer. Current trends of the use of ADT in combination with radiotherapy to avoid recurrence of cancer are discussed.

Secondary metabolites from natural sources such as plants, microorganisms, and marine organisms have played an important role in world's healthcare systems from ancient times till to date. Many cancer chemotherapeutic drugs have been obtained from nature and modified for optimal activity and safety. As cancers continue to take heavy toll of human life, the search for natural products with anti-neoplastic activities has continued in recent years with large scale screenings of marine fauna and flora, terrestrial microorganisms and plants in many laboratories of the world. Several new classes of natural products and their derivatives have been developed with the potential to be used as cancer chemotherapeutic agents. Lakshmi *et al.* comprehensively review the most notable discoveries of anti-cancer natural products in the last 5 decades in chapter 4. Most importantly, they describe the mechanism of action of key classes of natural anti-cancer agents at molecular levels, such as inhibition of enzymes and signalling pathways. The structure-activity relationships and results of pre-clinical studies add further value to this chapter.

Finally, chapter 5 by Kurcok *et al* is focussed on the tremendous new and well known biomedical and pharmaceutical applications of natural biopolymers, polyhydroxyalkanoates (PHAs). These natural linear polyesters are produced intercellularly by various species of bacteria through the fermentation of sugars or lipids. Many PHAs have also been prepared by chemical synthesis. PHAs are generally biocompatible and biodegradable in nature, and are used in the production of bioplastics. PHAs and their copolymers have found extensive applications in biomedical systems, including tissue engineering, orthopaedic materials, drug-loaded implants, drug carriers, transdermal administration drugs and cosmetics, *etc.* Recent research studies on the conjugation of drugs with low molecular weight PHAs have shown to improve the bioavailability and safety profiles of drugs.

The above chapters are contributed by leading researchers and experts in the fields making volume 8 of the *Frontiers in Drug Design and Discovery* an interesting and useful reading for both young and established scientists, as well as students of biomedical and health sciences, and medicinal and pharmaceutical chemistry. We wish to express our gratitude to them for their excellent scholarly contributions for this reputed ebook series. We also greatly appreciate the efforts of the entire team of Bentham Science Publishers for efficient and timely processing of the publication. The skills, efforts and commitment of Mr. Omer Shafi (Assistant Manager Publications), Mr. Shehzad Naqvi (Manager Publications) and leadership of Mr. Mahmood Alam (Director Publications) are especially praiseworthy. We also hope that like the previous volumes of this internationally recognized book series, volume 8 will also receive wide readership, and appreciation.

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# Cancer Chemotherapy: Recent Developments in Hematology Oncology

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**Abstract:** Research specialized in the field of hematology oncology over relatively recent years has revolutionized patient care and led to an array of chemotherapeutic agents approved by the Food and Drug Administration. Both oral and intravenous drug formulations have been marketed, including targeted therapies, for several hematologic disorders including acute and chronic leukemias, Hodgkin and non-Hodgkin's lymphomas, multiple myeloma, and myelofibrosis. The primary focus of this chapter will include latest chemotherapy developments in hematology covering critical topics of pharmacology, pharmacokinetics/pharmacodynamics, and pivotal clinical studies addressing both labeled and off-labeled indications. Lastly, future directions will be addressed, where applicable, in this continuously evolving clinical field.

**Keywords:** Acute lymphoblastic leukemia, Anaplastic large cell lymphoma, Bone marrow transplant, Cancer, Chemotherapy, Chronic lymphocytic leukemia, Chronic myeloid leukemia, Hematology, Hodgkin lymphoma, Mantle cell lymphoma, Multiple myeloma, Myelofibrosis, Non-Hodgkin's lymphoma, Oncology, T-cell lymphoma.

## INTRODUCTION

Substantial strides have been made in recent years in the diagnosis, prevention, and treatment of hematological malignancies due to ongoing specialized research. A multitude of chemotherapeutic agents have been made available in the United States, revolutionizing patient care and resulting in improved response rates and median survival. Both oral and intravenous drug formulations have been marketed, including targeted therapies, for several hematologic disorders including acute and chronic leukemias, Hodgkin and non-Hodgkin's lymphomas, multiple myeloma, and . The chapter will focus on state-of-the-art drug developments in malignant hematology, covering crucial topics of pharmacology,

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pharmacokinetics/pharmacodynamics, and pivotal clinical trials addressing both labeled and off-labeled purposes. Finally, advances and possible future directions in the treatment of chosen hematological malignancies will be presented.

## **CHRONIC LEUKEMIAS**

### **Background**

The chronic leukemias are a group of malignancies involving the hematopoietic system. They can be broadly classified into two types: chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL). CML is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate [1]. The median age at diagnosis is 67 years and it accounts for approximately 15% of all leukemias in adults. CML is rarely seen in the pediatric population. The estimated number of new cases in both males and females for the year 2015 is projected to be 6,660, with 1,140 predicted deaths [2]. CML was the first neoplastic process where a single chromosomal abnormality, the Philadelphia chromosome, was demonstrated as fundamental to the etiology of the disease. The Philadelphia chromosome results from a reciprocal chromosomal translocation consisting of juxtaposition of the ABL (Abelson Murine Leukemia) gene from chromosome 9 and the BCR (Breakpoint Cluster Region) gene from chromosome 22, consequently leading to unusual tyrosine kinase activity (see Fig. 1). CML occurs in three distinct phases (chronic, accelerated, and blast phase); nearly 90% of patients are diagnosed in the chronic phase. Patients in the chronic phase of disease often have splenomegaly and thrombocytosis with elevated white cell counts and circulating immature precursors. Typical symptoms at presentation include fatigue, night sweats, abdominal fullness, anorexia, and weight loss; however, up to 50% of patients are asymptomatic due to the initial indolent phase of the disease. Untreated CML inescapably progresses to the more aggressive accelerated and blast phases. The median survival of patients in blast phase is less than 6 months, with the most common causes of death being infection and hemorrhage [3]. Until the 1980s, CML was regarded as incurable and inevitably fatal [4]. Management of this disease has undergone a radical change in a very short period of time. The introduction of the tyrosine kinase inhibitors revolutionized the treatment of CML subsequently improving the ten year overall survival (OS) from 20% up to 90% [5]. Imatinib (Gleevec®) was the first tyrosine kinase inhibitor introduced for patients with CML, initially marketed in the United States in 2001. Since then, multiple options have emerged for this patient population. This review will focus on the latest therapies approved for the management of this disease [4].

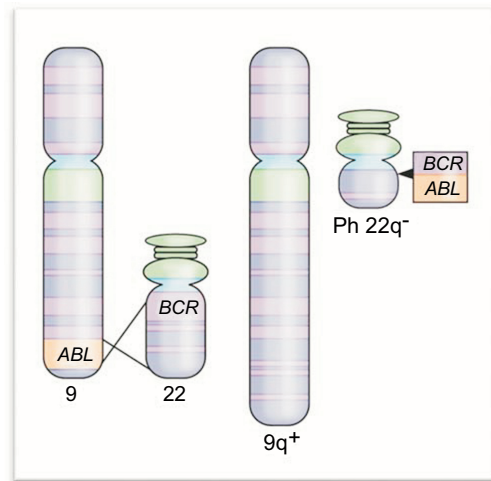


Fig. (1). Philadelphia chromosome shown.

Unlike the rarity of CML, chronic lymphocytic leukemia remains the most prevalent adult leukemia in Western countries [6]. In the United States alone, an estimated 14,620 new cases of CLL and 4,650 deaths will occur in 2015 [2]. CLL is a neoplasm characterized by proliferation and accumulation of small lymphocytes in the peripheral blood, lymph nodes, spleen, and bone marrow [7]. It is important to note that both CLL and small lymphocytic lymphoma (SLL) are essentially the same disease of B-cell lymphomas, with the only difference being where the malignancy predominantly occurs. In the simplest sense, in patients with CLL, majority of the malignant cells are located in the bloodstream and bone marrow; however, lymph nodes and spleen are also frequently involved. In SLL, malignant cells are merely isolated to the lymph nodes [8]. CLL is most common in the elderly, with a median age at diagnosis of 72 years. The disease is twice as common in males as females and occurs more frequently in Caucasians compared with African-Americans. CLL is considered an indolent disease however, it can be extremely heterogeneous in its clinical course. Some patients survive for decades without treatment, whereas others may suffer a rapidly progressive course despite aggressive therapy, eventually leading to fatality. In such cases, patient experience deteriorating blood counts (*e.g.*, anemia and thrombocytopenia) and organomegaly. Typical “B” symptoms of lymphoma may be present (*e.g.*, unintentional weight loss, fever, drenching night sweats, and significant fatigue). Recurrent infections and hypogammaglobulinemia are typical due to inherent impairment in cellular and humoral immunity [6]. Outside of the context of a clinical trial, in general practice, newly diagnosed patients with asymptomatic, low risk, early stage disease should be monitored without therapy unless they have evidence of disease progression. Those with advanced stage or high risk

## Current Innovations in Management of Esophageal Carcinoma

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**Abstract:** Esophageal cancer (EC) is the 8<sup>th</sup> most common cause of cancer worldwide and is endemic in certain parts of the world, especially in developing countries. The etiology of EC is multifactorial and includes tobacco and alcohol abuse, obesity, chronic gastroesophageal reflux disease (GERD), and Barrett's esophagus. In addition, there are hereditary cancer syndromes associated with an increased risk of ECs. Histologically, EC is classified as either squamous cell carcinoma (ESCC) or adenocarcinoma (EAC). The western hemisphere has seen a shift in decreasing incidence of ESCC *versus* increasing incidence of EAC. Human epidermal growth factor receptor 2 (Her2) gene and Her2 protein expression have been implicated in the pathogenesis of esophageal cancer. A multidisciplinary approach to EC is essential for workup, management, and treatment. Current therapeutic modalities include endoscopic treatments, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and ablation of early stage disease for both ESCC and EAC. For locally advanced disease, neoadjuvant chemotherapy and radiation followed by surgical resection are often used. However, the performance status of the patient as being “medically fit” *versus* “unfit” also plays an instrumental role in determining treatment. For metastatic EC, palliative chemotherapy remains the sole treatment. Most recently, there has been interest in moving beyond standard cytotoxic chemotherapy and to explore novel agents including immunotherapy, which could result in more promising outcomes in this malignancy.

**Keywords:** Endoscopy, Esophageal adenocarcinoma, Esophageal cancer, Immunotherapy, Squamous cell carcinoma, Targeted therapy.

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## EPIDEMIOLOGY

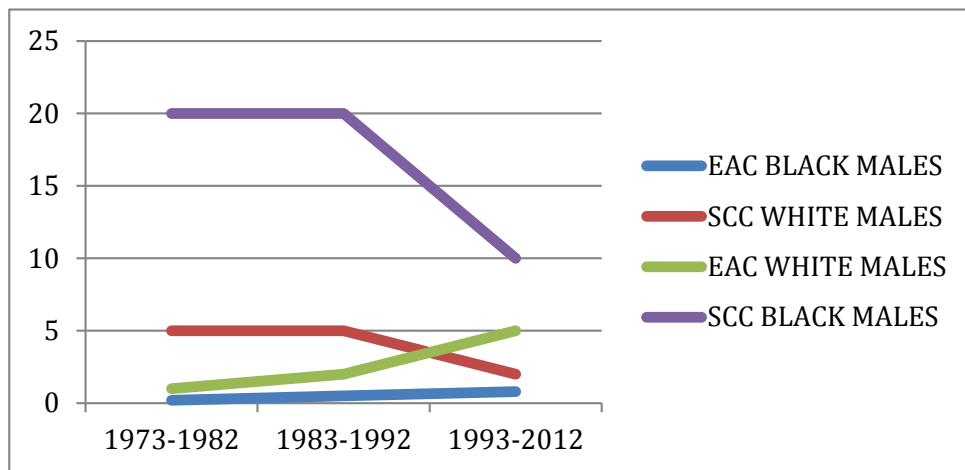
Esophageal cancer (EC) is the 8<sup>th</sup> most common cause of cancer worldwide and the 6<sup>th</sup> most common cause of cancer-related deaths. The incidence rates of EC vary regionally throughout the world with the highest rates seen in Southern and Eastern Africa and China [1]. In 2005, there were 497,700 new cases of EC, and the prevalence is expected to increase by approximately 140% by 2025 [2].

Worldwide, esophageal squamous cell carcinoma (ESCC) is the most common histological type of EC and predominates in Asian countries including China and Middle East and extends to southeastern Africa, often referred to as the “esophageal cancer belt” [3, 4]. However, focal areas in industrialized countries including northwestern France, Iceland, Scotland, Finland and eastern regions in the United States (US) including South Carolina and Washington D.C./Baltimore also have high rates of ESCC.

In the US and many Western countries, there has been a paradigm shift with increasing incidence of esophageal adenocarcinoma (EAC) and decreasing incidence of ESCC [1]; in which EAC has become the most prevalent form of EC. The annual incidence of EAC in the US increased sevenfold between 1974 (3.6 cases per million) and 2006 (25.6 per million) [4]. This epidemiological shift has been attributed to the rising incidence of gastroesophageal reflux disease (GERD) and obesity.

### Age, Gender, and Race

Independent of histology, the incidence of EC increases with age and peaks in the seventh decade of life [5]. In the US and worldwide, the incidence of EC is higher in males than females. ESCC is higher in black males than white males; conversely, EAC occurs predominantly in white males. Interestingly, the rates of ESCC have steadily decreased in the US over the past 40 years, though ESCC is the most common histology among black men (refer to Fig. 1) [4]. The incidence of EAC has increased dramatically within the last 3 decades and has become the major histologic type of EC in the US. The steep increase in incidence was largely seen in white males [6]. Based on a Surveillance, Epidemiology, and End Results (SEER) review, the incidence of EC is rising among white males and females and Hispanic males in the US. There is a steady decline in ESCC, most dramatically in black males but also seen in white males and females and black females [7]. Despite the rise of EAC in the western countries, ESCC is the most common histology worldwide with the peak incidence in regions of eastern Asia, eastern and southern Africa [8].



**Fig. (1).** Incidence of esophageal cancer in US males from 1973-2012. Data adapted from Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. In: *Seminars in radiation oncology* 2007 Jan 31 (Vol. 17, No. 1, pp. 2-9). WB Saunders [6].

### Risk Factors

Tobacco and alcohol are the 2 major independent risk factors and are synergistic in the pathogenesis of ESCC. Depending on the amount of tobacco use, smokers have a 5 to 10-fold increased risk of development of ESCC. The polynuclear aromatic hydrocarbons and nitrosamines contained in the tar fraction of tobacco are the propagators that initiate carcinogenesis [4, 9]. The duration of smoking history and the number of cigarettes inhaled per day have been directly correlated to the risk of EC. Other factors that cause chronic irritation and inflammation when combined with tobacco are synergistic in development of ESCC [5]. Similarly, the amount of alcohol consumed per week increases the relative risk of ESCC. The intensity and duration of alcohol used and type of alcoholic beverage have been implicated to affect the risks of ESCC. The pathogenesis of ESCC involving alcohol is less established but is thought to be attributed to local irritation of the esophageal mucosa from alcohol exposure, which can lead to increased susceptibility to carcinogenesis.

Several dietary factors have also been associated as a risk factor for ESCC. Consumption of large amounts of hot beverages and foods has been implicated to increase the risk of ESCC by causing thermal injury to the esophageal mucosa. Studies have shown an increased risk of ESCC with higher drinking temperature such as hot tea consumption as seen in northern Iran [4, 9]. Also, consumption of foods containing N-nitroso compounds increase the risk of ESCC as these compounds form potent electrophilic alkylating agents which subsequently reacts with DNA of target tissues to form altered bases, initiating carcinogenesis [10].

## Androgen Deprivation Therapy for Prostate Cancer

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**Abstract:** In the past, androgen deprivation therapy (ADT) was used for the conservative treatment of prostatic cancer, but now also used in the setting of neoadjuvant and adjuvant treatment in combination with radiotherapy. Another use is for loco-regional or distant recurrence after primary treatment of surgery or radiotherapy. ADT is an alternative for local failure after radical treatment and it compares favorably with cryotherapy or high-intensity focused ultrasound therapy. Traditionally gonadotropin releasing hormone (GnRH) agonists are used. A new class of agent in clinical use is the gonadotrophin antagonist degarelix. Newer choices for castrate resistant prostate cancer include abiraterone and enzalutamide. The emphasis of this review is on drug discovery, design and clinical trials. The indication and rationale for choosing the appropriate first and second line drugs will be discussed for easy access at point of care. This chapter summarizes the recent developments and the controversies to be explored in the future which will be of interest to all health care professionals, colleagues in the pharmaceutical industry, family physicians, urologists, radiation and medical oncologists. We also add our clinical experience of use of different ADT throughout this review to make it practical for bedside management. Common questions from physicians and patients are answered in this review.

**Keywords:** Androgen deprivation therapy, Anti-androgens, Agonist, Antagonist, Adjuvant, Biochemical failure, Clinical trials, Degarelix, Gonadotropin-releasing hormone, Metastasis, Prostate cancer, Prostate-specific antigen, Primary treatment.

### INTRODUCTION

Adenocarcinoma of the prostate is a hormone-sensitive tumor. In 1941, Higgins published the first observational study of effectiveness of orchiectomy (removal

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of testes) or estrogen on patients with metastatic prostate cancer [1]. Recent research found the biological basis that explains the phenomenon. There are androgen receptors on the tumors cells and the genes involved are also elucidated [2]. Almost all prostate cancer cells express receptors for male hormones (androgen) and androgen stimulates the growth of prostate cancer cells.

The emphasis of this review is on drug discovery, research findings and design of clinical trials. The rationale for choosing the appropriate drugs will be discussed in this chapter for easy access at point of care. This chapter summarizes the recent developments and the issues to be explored in the future which will be of interest to family physicians, urologists, radiation and medical oncologists.

## **WHAT ARE THE INDICATIONS OF ADT?**

### **Chemoprevention**

5-alpha-reductase inhibitors such as finasteride have been shown to decrease androgenic stimulation of the prostate, often used in benign prostatic hyperplasia. In clinical studies, 5-alpha-reductase inhibitors suppress serum and intra-prostatic levels of dihydrotestosterone, an important promoter of prostate cancer, leading to reduction in prostate size and suppression of glandular cell activity as measured by prostate specific antigen (PSA) secretion [3]. In addition, 5-alpha-reductase inhibitors have demonstrated an excellent safety profile and tolerance in controlled clinical trials. No significant metabolic effects have been observed in gonadotropin secretion, spermatogenesis, serum lipids or glucose tolerance. The efficacy and safety of 5-alpha-reductase inhibitors in published studies strongly supports investigating their use for chemoprevention of prostate cancer.

The Southwest Oncology Group (SWOG) S9207 study assessed the hypothesis that finasteride can reduce the prevalence of prostate cancer. It randomized over 18,000 healthy men, aged 55 and older, to either finasteride (5 mg/day) or placebo to be taken for seven years [4]. Low and intermediate-risk prostate cancers were less frequent among those who took finasteride than the placebo group [5, 6], with no difference in overall survival after 18 years of follow-up [7].

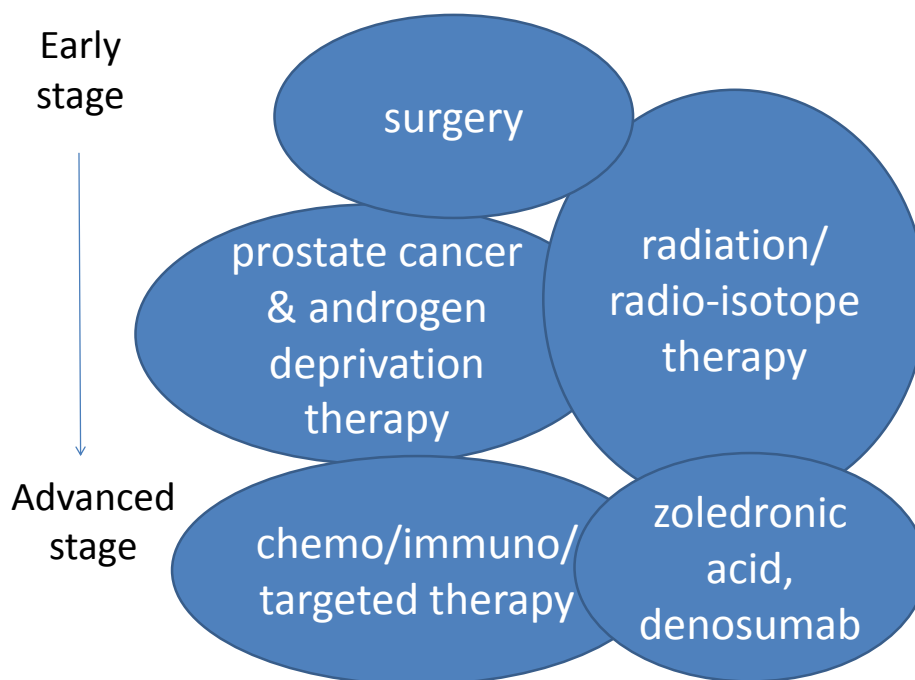
Similarly, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial also demonstrated overall decrease in prostate cancer incidence [8, 9]. For those with low-risk prostate cancers, the Reduction by Dutasteride of clinical progression Events in Expectant Management (REDEEM) trial showed that rates for either pathological progression or treatment intervention were lowered to 38% for dutasteride as compared to 48% for placebo [10].



These drugs can affect the quality of life with effects of sexual activity. Post-finasteride syndrome has been noted recently with effect on cognitive function [11].

### Treatment of Prostate Cancer (Fig. 1)

Hormonal therapy nowadays is based on ADT and no longer on estrogen. The clinical scenario for its use was in the conservative treatment of prostatic cancer as primary treatment when patients are unwilling or unfit to undergo radical, definitive treatments of either surgery or radiotherapy due to co-morbidities or life-expectancy of less than 10 years. Radiotherapy (RT) is only available in specialized tertiary centers which are concentrated in large cities. Patients in rural areas may be unwilling or unable to afford to travel for radiotherapy.



**Fig. (1).** Indications of androgen deprivation therapy in combination with other modalities.

In the past few decades, ADT is also given in the setting of neoadjuvant and adjuvant treatment in combination with radiotherapy. Patients with advanced prostate cancers are treated with ADT with or without radiotherapy. Bolla *et al.* of the European Organization for Research and Treatment of Cancer (EORTC) published the first study to show a survival benefit of 3 years from goserelin combined with radiotherapy [12].

## Cancer and its Treatment: Development of Anticancer Chemotherapeutic Agents from Natural Products

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**Abstract:** Over the last 5 decades, biologically active compounds derived from natural resources have provided a number of useful cancer chemotherapeutic drugs. The search for natural product based drug candidates is growing rapidly with the advancements in drug discovery and development techniques in recent years, with the active fractions and isolates of marine organisms along with terrestrial plants. Microorganisms are also being explored for their anti-cancer activities. The present review highlights the information about occurrence, types, clinical features pathophysiology and etiology of cancer as well as conventional and recent advancements in anticancer drug development along with description of selected medicinal plants and compounds derived from natural sources or their derivatives with potential use as cancer chemotherapeutic agents. It is expected that such promising leads from natural origin tend to create extensive interest among researchers including medicinal chemists and pharmacologists working in anticancer drug research and therefore the availability of a given brief information about cancer and anticancer drug development focused on natural product may be proved useful to develop preliminary ideas of biochemical pathways and key enzymes regulating these pathways as well as new targets involved in different stages of the disease along with chemotherapeutic agents which selectively target a specific signaling pathway through structure-activity relationships and preclinical trials.

**Keywords:** Anticancer, Chemotherapy, Drug development, Grafts, Medicinal plants, Natural products.

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## **INTRODUCTION**

Cancer is responsible for about 25% deaths caused due to diseases in the developed countries and is a major public health burden and challenge for world health organization and research organizations [1 - 3]. It is considered as an adversary of industrial revolution followed by advanced pattern of socio-cultural life dominated by excessive intake of exogenous chemicals and less physical activities. The number of incidences of different types of cancers is also increasing in developing countries, as the extensive technical advancements in the field of drug development and other areas allowed their populations live longer and make negative lifestyle changes leading to increased risk of cancer. Cancer is a broad group of diseases characterized primarily by uncontrolled cell division leading to increase in the number of malignant cells in a tissue, invasion of adjacent tissues by malignant cells, or spread of malignant cells through lymphatic or circulatory system to regional lymph nodes and distant tissues (metastasis). It develops through multi-step process that initiates with small preneoplastic changes, which may subsequently progress to neoplasia [4, 5]. Under certain conditions, neoplastic cells escape the host's immune surveillance that helps to develop the capacity of growth, invasion and metastasis. Cancer cells behave as independent cells and proliferate continuously without growth regulation, leading to tumor development through multistep process. An ideal anticancer drug would restore normal growth regulation and cell cycle control to cancer cells through restoring aberrant molecular signaling pathways and inducing apoptosis in these cells. It should selectively target different components of physiological and biochemical pathways related to different stages of cancer development without affecting the normal cells. The discovery of new compounds with novel mechanisms of action, contribute to improved and highly effective methods for cancer treatment.

A newer dimension in the anticancer drug research is the increasing awareness about natural product based chemotherapy. Several studies have demonstrated that different plant-based foods such as onion, grapes, garlic, ginger, soybean, turmeric, cabbage, cauliflower, broccoli and tomato can offer significant anticancer potential. Natural products have provided four important categories of antitumor agents: taxanes, camptothecins, bisindole alkaloids also known as vinca alkaloid and epipodophyllotoxins. Microorganisms have also provided several potent anticancer drugs in form of anticancer antibiotics such as doxorubicin, actinomycin and mitomycin C.

A natural product is a chemical compound or substance produced by a plant, animal or microorganism and usually has a pharmacological or biological activity which can be utilized in pharmaceutical drug discovery and drug design.

Chemically natural products are secondary metabolites, specifically produced by a particular group of organisms and have been postulated to play an important role in self defense against predators as well as in interspecies interactions. Their role is exceptionally pronounced in the field of anticancer drug research. Roughly 50% of the new chemical entities introduced during last three decades were either natural products or derived from natural products through structural modifications. Due to enormous advancement in the field of medicinal chemistry, design of natural product or natural product-mimetic scaffolds can be achieved readily in one-step with the help of multicomponent reactions. Usually, natural products are isolated only in minute amounts and thus subsequent techniques are required to scale-up of the biologically active molecules.

With reference to above facts, the review has been designed to cover the history of drug development from natural resources, anticancer compounds isolated from different natural resources along with brief view of occurrence, etiology, pathophysiology of cancer and mechanism of action of currently used anticancer agents.

## **CANCER**

Cancer is recognized as the second most dangerous diseases of modern era and spreading continuously with increasing incidences [1 - 3]. It is caused due to series of intracellular molecular events leading to alteration of the fundamental properties of the cell including regulation of growth and cell cycle progression. These transformed cells develop new morphological and biochemical features and can grow and proliferate in absence of growth signals. These morphological and biochemical changes also promote angiogenesis and metastasis of tumors. It is well established that breast cancer, prostate cancer, lung cancer and colorectal cancer account for approximately 50% of all cancers. In the same way nearly half of the cancer mortality occurs due to these four types of cancers with lung cancer exceeding breast/prostate cancer as the main cause. Prostate cancer is the most commonly occurring cancer in males (about one fourth of new cases) while breast cancer is the most predominant cancer in females (also about one fourth). Other high incident types of cancer include lung, bronchial, colon and rectal cancers which occur equally in men and women. Consequently, the anticancer drug development is the major concern for the research organizations and pharmaceutical industries all over the world. Cancers are classified primarily on the basis of morphological appearance of the tumor, although it has serious limitations. For example tumors with similar histopathological appearance show significantly different clinical outcomes as well as show different responses to therapeutic agents because of significant different in nuclear morphology and molecular markers. Currently the classification of cancer is based on morpho-

## Polyhydroxyalkanoates as Promising Materials in Biomedical Systems

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**Abstract:** Polyhydroxyalkanoates (PHAs) are the natural polymers that have been a subject of a significant research interest in the past few decades. The PHAs (natural as well as their synthetic analogs) as biodegradable and biocompatible polymers were studied intensively for biomedical applications, that is, scaffolds for tissue engineering. Drug-loaded implants or scaffolds based on these polyesters were also used in the drug release systems. Drug delivery systems should provide an optimal release profile of an active compound that allows to increase therapeutic effect, decrease side effects, and improve patient convenience and compliance. Therefore, recently, the increasing interest is focused on the use of PHA as drug carriers because of significant improvement in the bioavailability of bioactive substances. Recent developments introduced such strategies as conjugation of the drug with low-molecular-weight poly(3-hydroxybutyrate) or preparation of PHA particles loaded with the drug. On the contrary, there is a growing interest in functionalized PHA technology. The advancement of these strategies allows to obtain the targeting systems based on the chemical modification, for example, by folic acid attachment or biosynthesis of targeting proteins on the PHA particle surface. In addition, the PHAs were presented as materials that could be used in transdermal administration of bioactive substances for medical or cosmetic purposes. The development of novel functionalized PHAs has opened new possibilities to combine good biocompatibility of PHA-based drug delivery systems with improved drug loading and release properties, targeting, or imaging possibilities. Further progress in PHA-based drug delivery systems is expected because of the combination of excellent biocompatibility of these biopolymers and strong beneficial effect on drug administration.

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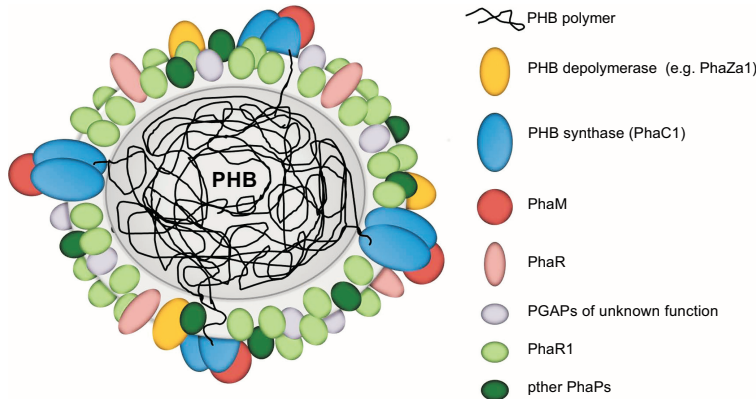
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**Keywords:** Polyhydroxyalkanoates, Poly(3-hydroxybutyrate), Drug delivery systems, Implants, Polymeric nanoparticles, Conjugate.

## INTRODUCTION

A large number of biodegradable polymers have been explored to be used as drug delivery systems such as scaffolds and implants releasing drugs or micro- and nanoparticles. The most commonly used synthetic polymers include (co)polymers of lactic acid, poly( $\epsilon$ -caprolactone), poly(anhydrides), and so on. However, natural polymers have also been utilized for the formulation of drug delivery systems. Among many natural polymers such as chitosan, hyaluronic acid, dextran, starch, collagen, and others, polyhydroxyalkanoates are an interesting and versatile option.

Polyhydroxyalkanoates (PHAs) are a family of biopolyesters, homo- or copolymers, mainly consisting of 3-hydroxyalkanoate units; however, sometimes copolymers also contain 4-hydroxybutyrate (4HB) or other hydroxyalkanoate units. PHAs with high molar mass are produced by many bacteria under nutrient-limited conditions as a carbon and energy storage source in the form of granules within the microorganisms [1, 2]. For example the simplest PHA homolog poly(3-hydroxybutyrate) (P(3HB)) is presented in Fig. (1) [3, 4].



**Fig. (1).** Model of an *in vivo* PHB granule in *Ralstonia eutropha* H16. The surface layer is free of phospholipids and consists of only proteins. The presently known PHB granule-associated proteins (PGAPs) are symbolized by differentially colored globules (PhaP, PhaM, PhaR – phasin proteins; phasins are PHB granule-associated proteins with putative structural function). Reprinted with permission from Bresan *et al.* [4].

Low molar mass P(3HB), the so-called complexed P(3HB) (cPHB), includes polyesters of chain lengths in the range from several to 100 repeating units. Such cPHB, associated with other biological polymers including proteins and pol-

yphosphates [5, 6], has been found in all living organisms, suggesting that it may have an important biological role [7 - 10].

Based on the monomeric unit chain length, the high molar mass PHAs are divided into two groups. The first group consists of short chain length 3-hydroxyalkanoate constitution units (scl-PHAs), composed of units with 3–5 carbon atoms, and the second group consists of medium chain length PHAs (mcl-PHAs), with 6–14 carbon atoms in the repeating unit [11].

In 1926, Lemoigne [12] identified poly(3-hydroxybutyrate) (P(3HB)); however, the biosynthetic pathway for its production from sugar was proposed many years later. It involves three enzymatic reactions catalyzed by three different enzymes, respectively. Biosynthetic pathways from fatty acids as a carbon sources were also proposed Fig. (2) [2, 13, 14].

Chemical composition and molar mass of these biopolyesters highly depend on the bacterial strain as well as the carbon source [15, 16] including renewable resources [17 - 19]. Broad range of PHAs with various compositions and properties were described in the literature [2, 13, 20, 21]. What is important is that PHAs are biodegradable and usually biocompatible and also the products of their degradation are not harmful for natural environment [22 - 24]. Moreover, depending on the composition, PHAs may exhibit different properties including tunable mechanical properties [14, 25, 26]. This feature is driven by the molar mass and crystallinity of the polymer. For instance, bacterial P3HB is a highly crystalline material, and its degree of crystallinity reaches 80%, contrary to a polymer containing 4HB units in the main chain, which possesses relatively low crystallinity [23, 27]. Therefore, properties of the materials can be tailored by the application of respective carbon source and selection of bacterial strain. The possibility of tailoring the properties of PHAs makes PHAs very good candidates for use in many fields [21]. They can be applied as packaging materials; however, one may also use them in regenerative medicine as well as in pharmaceutical applications for instance in drug delivery systems [25, 28 - 30].

Recently, several scientific groups have elaborated catalysts for the synthesis of various  $\beta$ -lactone monomers from carbon oxide, derived from synthesis gas, and respective oxiranes [31 - 33]. Therefore, significant improvement in access to various  $\beta$ -lactones is expected. PHAs can be chemically synthesized through ring-opening polymerization (ROP) of  $\beta$ -lactone monomers, which is a convenient way to obtain PHAs [34 - 37]. By applying coordination or anionic catalytic systems for such processes and depending on the monomers used, respective materials such as homopolymers and/or copolymers with blocky or random microstructures can be obtained [21, 38 - 41]. Moreover, in contrast to natural PHAs containing

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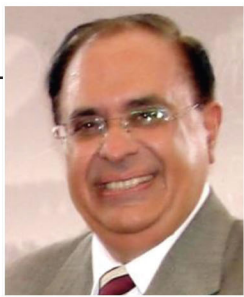
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