Frontiers in Clinical Drug Research

(Anti-Cancer Agents)

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Frontiers in Clinical Drug Research - Anti-Cancer Agents

(Volume 9)

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PREFACE

Frontiers in Clinical Drug Research - Anti-Cancer Agents presents recent developments in therapeutic approaches against various types of cancer. This volume is a valuable addition to the series, serving as an important resource for pharmaceutical scientists, postgraduate students, and researchers who seek updated and critical information for devising research plans in anti-cancer research.

The chapters in this volume are written by eminent authorities in the field. Chapter 1, authored by Kang and Li, discusses dietary strategies for cancer therapy, with a focus on amino acid restrictions in cancer interventions. Verma *et al*., in Chapter 2, elaborate on the role of noble metal nanoparticles (NPs) in creating an effective anti-cancer therapy paradigm, focusing on theranostics and drug delivery mechanisms.

In Chapter 3, Mohamed Gomaa explores the recent anticancer properties of algal polysaccharides from different algal groups and their modes of action. Chattipakorn *et al*., in the next chapter, summarize current mechanistic insights into the cardiotoxicity of doxorubicin and trastuzumab, addressing the pathophysiology of contractile dysfunction (cardiomyopathy) and electrical disturbances (arrhythmia). Gaps in knowledge and recommendations for future advances are also discussed to encourage further investigations in the field. Finally, in the last chapter of the book, Ahmad *et al*. comprehensively summarize the anti-proliferative and anti-carcinogenic properties of emodin.

I hope that the readers will find these reviews valuable and thought-provoking, triggering further research in the quest for new and novel therapies against cancers. I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (In-charge, Books Department), and Miss Asma Ahmed (Senior Manager, Publications) at Bentham Science Publishers.

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CHAPTER 1

Dietary Strategy for Cancer Therapy - Amino Acid Restrictions and beyond

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Abstract: According to the World Health Organization (WHO) report, cancer is one of the leading causes of death, particularly in developing countries. The malignant proliferation and survival of cancer cells rely on the biosyntheses of proteins, nucleotides, and fatty acids. Accumulating pieces of evidence demonstrate that amino acid restrictions are valuable for cancer interventions. Meanwhile, folk remedies using dietary strategies are abused and lack solid rationale. To clarify what, why, and how the potential strategy is, here, we update and recommend a dietary strategy for cancer therapy: the intermittent dietary lysine restriction with the normal maize (lysine deficiency) as an intermittent staple food for days, weeks, or even months, will be a feasible strategy for cancer intervention. In addition, dietary and immunomodulatory supplements, such as low protein starchy foods, vegetables, fruit, and mushrooms, may serve as supplements to satisfy the daily needs of micronutrients and the plethora of dishes.

Keywords: Amino acid restriction, Arginine, Cachexia, Cancer, Glutamine, Kwashiorkor, Lysine, Tryptophan.

INTRODUCTION

Cancer is a complex disease such that there are more than 100 distinct types of cancer sharing common metabolic characteristics, such as sustained proliferation and insensitivity to growth suppressors [1, 2]. The metabolisms of cancer cells are reprogrammed to maintain their proliferation and may even hijack normal cells to create a tumor microenvironment (TME) for survival and escaping the immune destruction [2]. For the sake of cancer cell growth and newly synthesized proteins as the actuators of cellular activities, protein biosynthesis consumes ~33% of total ATP consumption, which is the most energy-consumption process [3 - 5]. Intriguingly, recent pieces of evidence have demonstrated that amino acid restrictions

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play crucial roles in cancer intervention and therapy, including glycine restriction [6], serine starvation [7 - 9], leucine deprivation [10], glutamine blockade [11, 12], asparagine deficiency [13, 14], methionine limitation [15] and cysteine depletion [16]. We have recently recommended that a convenient dietary strategy for cancer intervention using the normal maize (lysine deficiency) as an intermittent staple food for days, weeks, or even months for lysine restriction, and low protein starchy foods, vegetables, and a fruit serving as complementary foods to meet daily micronutrient needs and for a rich diet [17]. Here, we update and summarize the dietary restriction of amino acids for cancer therapy in this e-book series 'Frontiers in Clinical Drug Research - Anti-Cancer Agents'.

THE HETEROGENEITY AND HOMOGENEITY OF CANCER CELLS

According to the latest global cancer statistics in 2020, the GLOBOCAN estimates for 185 countries and 36 cancers and shows that there are an estimated 19.3 million new cancer cases and 10 million cancer deaths worldwide [18]. The top five diagnosed cancers are female breast (~2.3 million, 11.7%), lung (11.4%), colorectal (10.0%), prostate (7.3%) and stomach (5.6%) cancers. The top five leading causes of cancer death are lung (~1.8 million, 18%), colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers [18]. These different types of tumors reflect the genetically/epigenetically diverse populations. The genetic and spatial heterogeneities of cell subpopulations are also apparent in the niche of TME. Importantly, the genetically temporal heterogeneity of cancer provides the fuel for resistance to drugs, such as tyrosine kinase inhibitors (TKIs) of EGFR [19]. The spontaneously resilient resistances in lung cancer under the pressure of TKIs strongly suggest that it is time to focus on an alternative strategy for cancer therapy beyond targeting cancer mutations.

In contrast to genetic heterogeneity, the metabolism of cancer is relatively homogenous. In the 1920s, Warburg made an important discovery (Warburg effect) that cancer cells preferred to metabolize glucose by glycolysis even in the presence of sufficient oxygen [20]. Compared to oxidative phosphorylation, glycolysis is a less efficient pathway to generate ATP with the concomitant production of lactic acid and the consequential acidification of the intracellular and extracellular microenvironment, which further leads to the deterioration of tumor [21 - 23]. Due to the requirement of growth of cancer cells for glucose, fluorodeoxyglucose positron emission tomography (FDG-PET) has been clinically exploited to diagnose tumors [22]. Consistently, the release and consumption patterns of NCI-60 cancer cell lines (Fig. **1**) have demonstrated that glycolysis and glucose consumption are common characteristics of cancer metabolism [6].

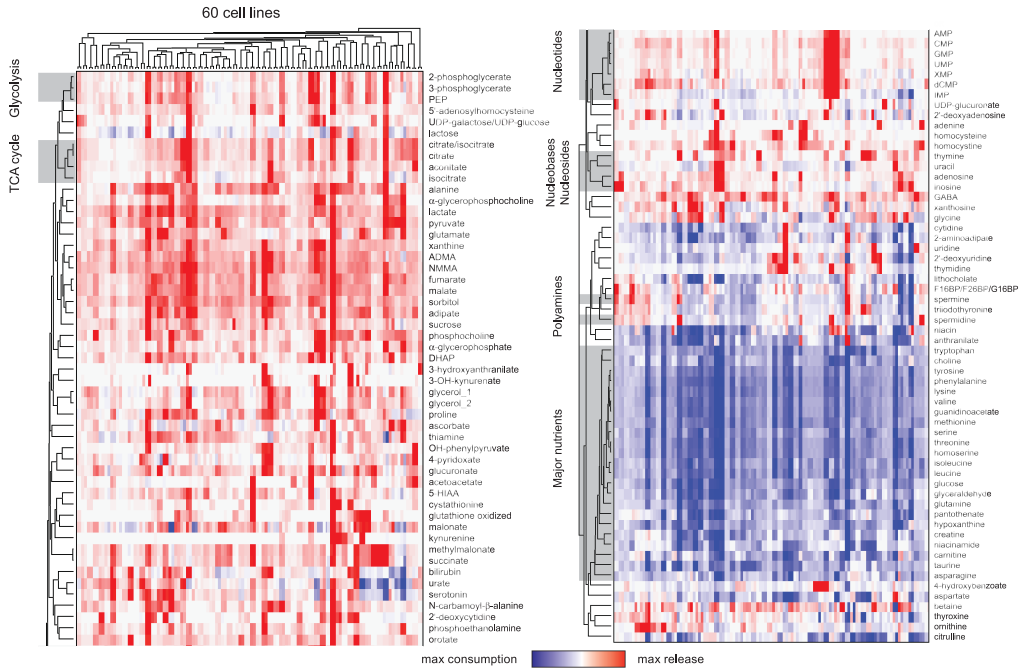

Fig. (1). The consumption and release profiles of 111 metabolites for the NCI-60 cancer cell lines [6] (reproduced with permission). Consumption is indicated by blue, while red color represents release.

Amino Acid Metabolism is the Leading Energy-consuming Process

The consumption and release (CORE) profiles of 111 metabolites (Fig. **1**) illustrated the anabolic and catabolic features of the NCI-60 cancer cell lines [6]. The CORE profiles of cancer cells demonstrated the homogeneous demands for energy metabolism and protein synthesis, as both essential for the malignant proliferation of cancer cells. The substrates largely consumed in cancer cells include glucose and amino acids, such as leucine (L), tryptophan (W), serine (S), lysine (K), glycine (G), arginine (R), glutamine (Q), methionine (M), cysteine (C), tyrosine (Y) [6]. Meanwhile, the CORE profiles of glycine, aspartate, cytidine, uridine, and polyamines showed heterogeneous patterns in the NCI-60 cancer cell lines (Fig. **1**) [6].

The CORE profiles also showed another common characteristic of the NCI-60 cancer cell lines, that is, the release of nucleotides and nucleobases [6]. Importantly, the CORE profiles suggested that cancer cells did not directly take the nucleobases and nucleotides as their substrates for RNA/DNA anabolism. The ATP consumption (approximately 25%) of RNA/DNA synthesis ranks second among the energy-consuming processes (Fig. **2B**) [3, 4]. Cells can use aspartate, glutamine, serine, and glycine, as carbon and nitrogen resources for the syntheses of nucleobases (Fig. **2A**) [24-26]. Hence, the amino acid metabolism for protein

CHAPTER 2

The Revolutionary Potential of Noble Metal Nanoparticles as Anti-Cancer Agents: State-Of-The-Art Applications and Future Perspectives

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Abstract: Cancer is perhaps one of the gravest challenges that humanity has been facing for centuries. According to the World Health Organization (WHO), cancer is the second leading cause of death worldwide. Nanotechnology has revolutionized cancer research by providing a targeted and selective alternative to conventional treatment modalities and drug delivery protocols with lesser side effects and negligible systemic toxicity. Nanoparticles (NP), particularly noble metal nanoparticles, are one such competent alternatives that have been extensively studied and applied to various aspects of cancer therapy with exemplary results. Nanoparticles of noble metals such as silver, gold, and platinum possess unique properties like small size, non-toxicity, high surface-to-volume ratio, tunable optical properties,and ease of functionalization with antibodies, nucleic acids, nucleotides, and peptides. These nanoparticles have an inherent advantage over traditional moieties regarding intracellular delivery due to their small size. This proved very helpful in the gene silencing method involving small-interfering RNA for the down-regulation of gene expressions in cancerous cells. In particular, gold nanoparticles (AuNP) are highly selective radiosensitizers, whereas silver nanoparticles (AgNP) have anti-proliferative and apoptosis-inducing effects on cancer cells. Platinum nanoparticles (PtNP) and AuNPs display exceptional thermoplasmonic properties and hence are being used effectively in cancer photo thermal therapy (PTT). PtNPs have the potential to amplify the efficacy and selectivity of the hadron therapy. This chapter will elaborate on all the above-mentioned roles of noble metal NPs in creating an effective anti-cancer therapy paradigm focusing on theranostics and drug delivery mechanisms.

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Keywords: AgNP, AuNP, Blood-brain barrier, Cancer, Chemotherapy, Cytotoxicity, Drug delivery, Genotoxicity, Green synthesis, Hadron therapy, Laser ablation, PtNP, Nanotechnology, Nanoparticle, Nanomedicine, Photo thermal therapy, Surface-to-volume ratio, Theranostics, Radiotherapy, Quantum dots.

INTRODUCTION

As per the standard definition, nanotechnology is 'the design, characterization, production, and application of structures, devices, and systems by controlling shape and size on a nanometer scale' [1]. In 1959, the renowned physicist and Nobel laureate Richard Feynman put forth the idea of 'nanotechnology' in his celebrated Caltech lecture titled "There's Plenty of room at the bottom" [2]. Feynman presented the vision of printing the complete encyclopedia on the tip of a pin. However, in 1974 the first one to use and define the term 'Nanotechnology' was Norio Taniguchi, a Japanese scientist, who said that "nanotechnology mainly deals with the processing of separation, consolidation, and deformation of materials by one atom or one molecule" [3].

Nanotechnology and Cancer Research

Cancer has been one of the gravest challenges of the 21st century. It is one complex disease characterized by uncontrolled growth and proliferation of cells. The causal factors may be genetic, epigenetic, external, and environmental [4]. Considering the complicated nature of this disease, the treatment is also not straightforward. It is treated by chemotherapy, hormone therapy, surgery, radiation, immunotherapy,and sometimes through clinical trials [4]. However, these treatments are very expensive, and the chances of patient survival aren't as high as they should be.

At present, conventional oncological therapies suffer from the drawback of being non-targeted, meaning that the existing radio and chemo treatment kills the normal cells along with cancerous cells. This in turn, has a detrimental effect on the patient leading to further weakening his/her immune system. Also, these conventional methods lack target cell specificity. Scientists all over the world have been searching for alternative approaches to kill cancerous cells. Nanotechnology, owing to its site-specificity and target-oriented nature, offers the boon of providing a targeted means of eradicating cancerous cells without harming healthy body cells.

Over the decades, the scope and application of nanotechnology have increased exponentially. Today, nanotechnology has touched almost every domain of pure and applied science, engineering, and technology. The field of medical sciences has by far been the most benefited. This is evident in the emergence of

nanomedicine, a branch of medicine that relies on the application of concepts and techniques of nanotechnology for the detection, diagnosis, treatment, and prevention of disease. Nanoparticles, nanocomposites, nanorobots, and nano clusters are the pillars of nanomedicine. In this chapter, we will be discussing in detail nanoparticles, their synthesis, utility, and challenges associated with their applications.

Nanoparticles are hundred to ten thousand times tinier than cells in the human body (Fig. **1**). We can safely assume that their size is like large biomolecules like enzymes and certain receptors. Nanoparticles can easily diffuse in and out of the blood vessels and enter cells to interact with the targeted biomolecule or marker. This minute scale of interaction enables disease detection at an early stage. Also, drugs are delivered in a targeted manner.

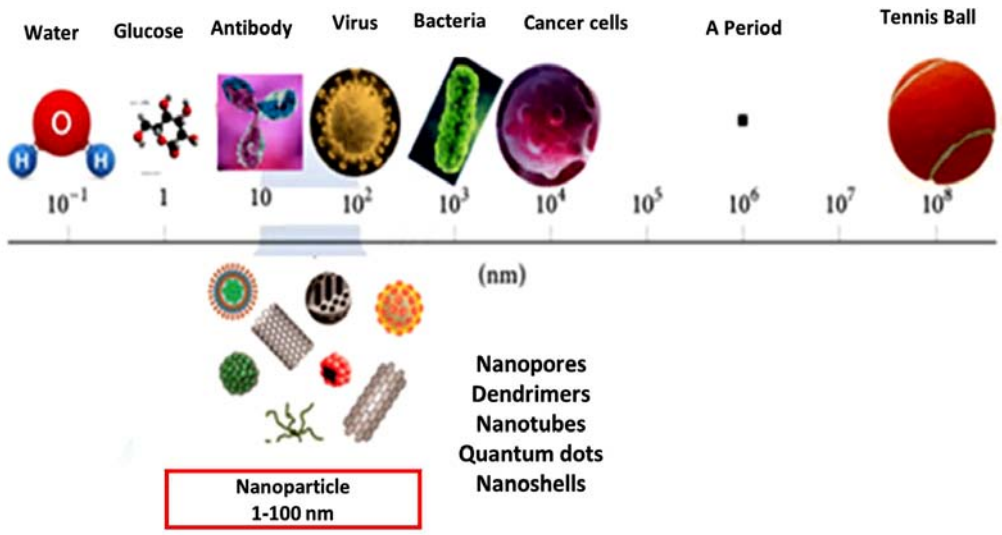

Fig. (1). A comparative scale to give an idea about the size of nanoparticles [11, 12].

Both lifesaving as well as life-threatening biological processes occur at the nanoscale. Thus, nanoparticles can help trace a disease at the earliest stages of abnormality inside any tissue. This is particularly helpful in cancer theranostics as it provides a lot of time for the doctors to decide the future course of the therapy, further increasing the chances of patient survival. Nanotechnology has provided researchers and doctors with the ability to analyze and modify biomacromolecules in real-time. Scientists can now detect oncogenic changes at the molecular level rapidly and sensitively.

CHAPTER 3

Algal Polysaccharides as Promising Anticancer Agents

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Abstract: There is a growing demand for the development of new anticancer drugs owing to the worldwide increase in cancer mortality. Algal polysaccharides, such as fucoidan, alginate, laminarin, carrageenan, porphyran, ulvan and calcium spirulan, have been recognized as natural products with potential good anticancer properties against a variety of cancer cell lines *in vitro* and *in vivo*. Therefore, they can be used for the development of natural anticancer drugs with fewer side effects than synthetic ones. Additionally, algal polysaccharides can be used as an adjuvant treatment to mitigate undesirable side effects and promote the anticancer properties of clinical anticancer drugs. This chapter focuses on the recent anticancer properties of algal polysaccharides from different algal groups as well as their mode of action.

Keywords: Adjuvant activity, Anticancer mechanism, Alginate, Ascophyllan, Calcium spirulan, Carrageenan, Fucoidan, Laminarin, Porphyran, Structure-activity relationship, Ulvan.

INTRODUCTION

Cancer is a pathological condition in which malignant cells grow uncontrollably and can spread to the adjacent tissue or other parts of the human body. The World Health Organization (WHO) ranked cancer as the second highest cause of mortality worldwide, after heart diseases. It was estimated that cancer could end the life of ~ 9.6 million people annually [1]. The development of drug resistance and adverse side effects are the major problems associated with chemotherapeutic approaches to cancer treatment [2]. Therefore, there is an insistent need for the development of new anticancer agents, especially because the number of cancer mortalities will increase dramatically in the upcoming years [3]. Hence, there is a growing demand to find new alternative drugs from natural sources that can affect the cancer cells without having any adverse effects on the normal cells.

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Algae are a diverse group of organisms rich in bioactive compounds, such as polysaccharides. Algal polysaccharides are gradually recognized as anticancer agents due to their low toxicity to normal cells as well as high efficiency against different cancer types [4]. Different algal phyla and genera are characterized by different groups of polysaccharides. For example, brown algae (Phaeophyta) members contain cellulose, fucoidan, ascophyllan, sargassan, alginate, and laminarin; red algae (Rhodophyta) genera contain cellulose, agar, agarose, carrageenan, porphyran, sulphated galactans, and floridean starch; while green algae (Chlorophyta) contain cellulose, starch, ulvan, sulphated rhamnan, sulphated galactans and xylans [4 - 11].

Algal polysaccharides can kill cancer cells through indirect or direct methods. The indirect mechanisms include the promotion or activation of the immune cells to fight malignant cells. While the direct mechanisms involve apoptosis, cell cycle arrest, anti-angiogenesis, and inhibition of cellular invasion and migration [12]. Apoptosis or programmed cell death is the process that maintains the balance between the new cell formation and cell death. Therefore, when the normal cells fail to follow normal apoptotic pathways, this leads to a suitable environment for gene mutation and pathogenesis of cancer cells. Previous studies have proved that different algal polysaccharides could restore the balance and induce apoptosis in cancer cells through different mechanisms [13]. A cell cycle during division consists of G0 (quiescence), G1 phase (growth), S phase (DNA synthesis), G2 (growth and preparation for mitosis), and M phase (mitosis). Algal polysaccharides can arrest cancer cells in different phases during proliferation [14]. In general, cancer cells can disseminate from the primary tumor to the surrounding tissues or other parts of the body; this is a multistage process and is known as metastasis. While angiogenesis is the process of the development of new blood vessels, which is important in normal physiological processes, such as embryonic growth and wound healing. Uncontrolled angiogenesis arises in several pathological states, including tumor growth. Algal polysaccharides can exhibit antitumor potential against cancer cells by inhibiting their angiogenesis and metastasis processes [14, 15]. Taken together, this chapter focuses on recent studies aimed at discovering the anticancer properties of different algal polysaccharides and their potential molecular mechanisms.

FUCOIDAN

Fucoidan Structure

Fucoidans are fucose-rich sulphated polysaccharides, which represent one of the main structural components in the cell wall and intracellular matrix of brown algae. Fucoidans are heteropolysaccharides with α-L-fucose as the main

monomer, and other residues may include glucose, galactose, guluronic acid, xylose, mannose, arabinose, and rhamnose [4, 9, 16, 17]. Sulphate groups in the fucoidans are attached to the C-2 or C-6 of fucose residues (Fig. **1**). Fucoidans are classified based on their structural variations into different types, including

1. Fucoidans or fucans in which fucose residues are linked by α-(1,3)-glycosidic bonds. They mainly occur in the order Laminariales.
2. Fucoidans in which fucose residues are linked by α-(1,3) and α-(1,4)-glycosidic bonds. They mainly occur in the order Fucales.
3. Fucoidans or galactofucans in which fucose and galactose residues are the main components. They can be found in the members of the family Sargassaceae and Laminariaceae.
4. Fucoidans with different molar ratios of fucose, mannose, xylose, galactose, arabinose, and uronic acids.

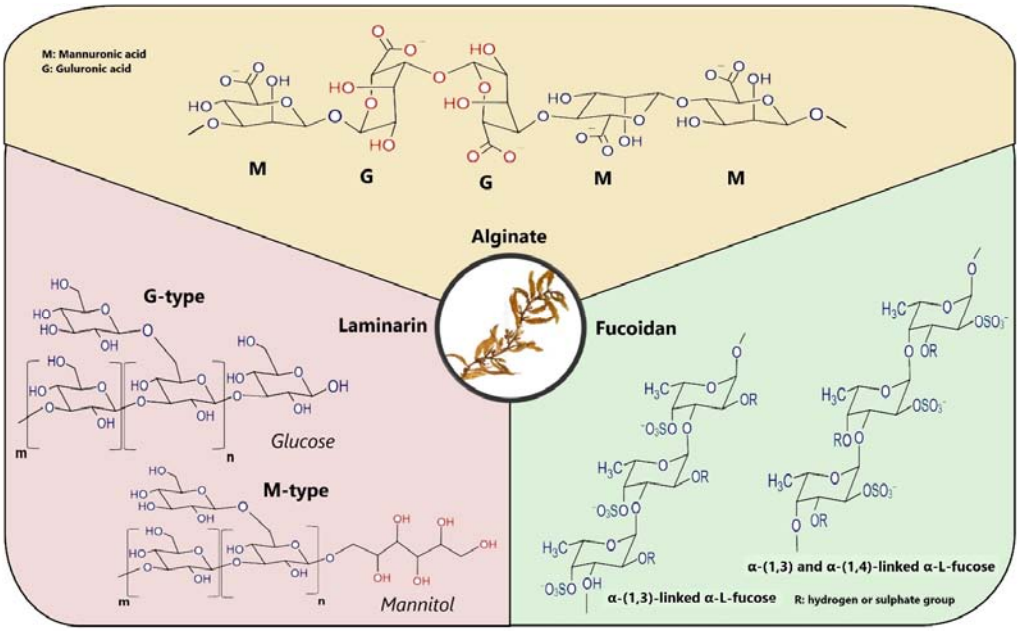

Fig. (1). Chemical structure of the main polysaccharides from brown macroalgae.

Fucoidans have countless promising bioactivities, including anticancer and antitumor; therefore, they may be recognized as a treasure of the sea. Additionally, they represent the most studied group of algal polysaccharides in relation to their various bioactivities [4, 18].

CHAPTER 4

Cardiotoxicity Caused by Doxorubicin and Trastuzumab: Current Understanding for Future Preventive Strategies

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Abstract: Cancers and cardiovascular disease continue to be leading causes of mortality worldwide despite unrelenting efforts to improve therapeutic strategies in both. Ironically, cardiac adverse effects of anticancer drugs result in an ever-increasing proportion of deaths in cancer survivors. Doxorubicin, one of the earliest anthracycline chemotherapeutic agents which has been in clinical use since the 1970s, is notorious for causing cumulative dose-dependent irreversible cardiac damage, traditionally termed "type I" cancer therapy-related cardiotoxicity. In the late 1990s, the approval of trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), initiated an era of targeted anticancer therapy with the hope of eradicating off-target adverse effects. Unfortunately, trastuzumab treatment leads to the distinctive "type II" cancer therapy-related cardiotoxicity. As an acknowledged type I and type II cardiotoxic anticancer agents, doxorubicin and trastuzumab have been intensely investigated with regard to the complex mechanisms of their effects on the heart, yet complete understanding remains elusive. This chapter comprehensively summarizes current mechanistic insights regarding the cardiotoxicity of doxorubicin and trastuzumab, encompassing the pathophysiology of contractile dysfunction (cardiomyopathy) and electrical disturbance (arrhythmia). Gaps in knowledge and recommendations for future advances are also discussed to encourage further investigation in the field, with the ultimate goal being the effective prevention and/or treatment of cancer therapy-induced cardiac complications.

Keywords: Arrhythmia, Cancer, Cardiotoxicity, Cardio-oncology, Chemotherapy, Doxorubicin, HER2, Heart failure, Trastuzumab, Targeted therapy.

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INTRODUCTION

Cancers and cardiovascular diseases have been a substantial global health burden for many years and remain the leading causes of mortality [1 - 3]. Although the use of efficacious anticancer agents has greatly enhanced survival rates from malignancy, the medications themselves impose off-target damage to various vital organs including the heart. This impact is evidenced by the increasing number of cancer survivors dying from cardiac causes as well as by the establishment of cardio-oncology, a subspecialty devoted to cardiovascular care in cancer patients [4, 5].

Doxorubicin (also known as hydroxydaunorubicin, hydroxydaunomycin, or Adriamycin®) is a 14-hydroxy derivative of daunorubicin, an anthracycline compound produced by the soil-dwelling bacterium *Streptomyces peucetius* var. *caesius* [6]. Since the 1970s, this anticancer agent has been commonly used against a wide range of malignancy types, either as a first-line monotherapy or in combination with other drugs and treatment modalities (*e.g.*, radiotherapy and surgery). The potent oncosuppressive effect of doxorubicin results primarily from the disruption of cell proliferation *via* deoxyribonucleic acid (DNA) base pair intercalation, inhibition of topoisomerase IIα, and oxidative damage to macromolecules [7]. However, cellular injury caused by doxorubicin is neither specific nor limited to tumor cells. It is well recognized that doxorubicin can cause cumulative dose-dependent irreversible cardiac dysfunction, which was defined by Ewer and Lipman in 2005 as “type I” cancer therapy-related cardiotoxicity [8].

Trastuzumab (also known as Herceptin®) is a monoclonal antibody that recognizes and inhibits human epidermal growth factor receptor 2 (HER2; also known as HER2/neu or ERBB2), a tyrosine kinase responsible for aggressive growth/proliferation of certain breast and gastrointestinal cancers [9]. Since the beginning of its use in the late 1990s, trastuzumab has greatly improved the survival of patients with HER2-positive neoplasms [10]. Despite being an antibody-based targeted therapy, trastuzumab is still capable of inducing cardiotoxicity. Unlike doxorubicin, trastuzumab leads to cardiac dysfunction that does not correlate with dosage and is generally reversible upon treatment interruption or cessation. Recognizing these distinctive features, Ewer and Lipman have coined the term “type II” cancer therapy-related cardiotoxicity to describe trastuzumab-induced cardiac dysfunction [8].

Although the terminology continues to be refined as new insights emerge and different classifications have been proposed by others [11, 12], the traditional classifications by Ewer and Lippman are still commonly used. Doxorubicin and

trastuzumab serve as the prototypes for each category of this classification scheme and therefore have been extensively investigated. Nevertheless, the understanding of the complex pathophysiological processes leading to the cardiac adverse effects of these drugs remains incomplete. This chapter summarizes current mechanistic insights regarding cardiac contractile dysfunction and arrhythmias caused by doxorubicin and trastuzumab. Future research directions are also suggested to encourage further investigations that will lead to more effective preventive and treatment strategies against cancer therapy-related cardiotoxicity.

CARDIOTOXICITY OF DOXORUBICIN

Clinical Features of Cardiotoxicity Caused by Doxorubicin

The prevalence of cardiac complications in doxorubicin-treated patients varies widely (from 0% to more than 50%) depending on the populations investigated and the diagnostic criteria [13]. Manifestations of acute cardiotoxicity (defined as cardiac adverse effects occurring within 1-2 weeks of the onset of treatment) include arrhythmias, pericarditis, myocarditis, and acute heart failure [14 - 16]. However, such acute events are rare in comparison with chronic cardiotoxicity, which generally emerges and progresses in an irreversible cumulative dose-dependent manner [16]. Similar to the progression of most diseases, chronic doxorubicin-induced cardiotoxicity results in histopathological changes (cardiomyocyte vacuolization, myofibrillar disarray, cellular demise, and fibrosis) as well as subclinical functional abnormalities that precede the symptomatic heart failure [17, 18]. At a cumulative dose of 200 mg/m^2, doxorubicin treatment resulted in contractile dysfunction detectable by multiple-gated acquisition (MUGA) radionuclide ventriculography [18]. The cumulative dose corresponding to a 5% incidence of overt heart failure is approximated to be 400-450 mg/m^2 [19].

Doxorubicin not only impairs the mechanical functioning of the heart but also perturbs cardiac electrical activities in both acute and chronic situations. Ectopic beats, either of supraventricular or ventricular origin, frequently occur in patients receiving doxorubicin [20 - 22]. Prolongation and increased dispersion of the QT interval, electrocardiographic (ECG) findings that reflect aberrant ventricular repolarization, are well-documented in doxorubicin-treated cancer patients [23 - 27]. Doxorubicin-induced QT abnormalities can be either asymptomatic or associated with clinically significant arrhythmic events such as syncopal episodes and sudden cardiac death [28]. Heterogeneous myocardial repolarization serves as a substrate for reentrant tachyarrhythmias ranging from non-sustained ventricular tachycardia (VT) to life-threatening VT and ventricular fibrillation (VF) [28]. An association between doxorubicin treatment and atrial fibrillation, an arrhythmia

CHAPTER 5

Emodin: Anticancer Agent

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Abstract: Cancer is a serious health issue that remains a significant cause of mortality around the world. Psychosocial support, surgery, radiation, and chemotherapy are common cancer treatments. However, because of the rising rate of cancer-related mortality and the adverse or toxic side effects of cancer chemotherapy and radiation therapy, new anticancer compounds obtained from nature, particularly plants, are currently being researched. Phytochemicals, which are naturally occurring plant substances, are important sources for new drugs and cancer treatment. Phytochemicals are selective in their actions, acting only on tumour cells and not on healthy cells. These phytochemicals act by modulating molecular pathways involved in cancer growth and progression. Anthraquinones are a class of phytochemicals that have a wide range of biological functions as well as anticancer action. Emodin is a natural anthraquinone derivative found in *Rheum palmatum*, *Polygonum cuspidatum*, *Polygonum multiflorum* and among other commonly used Chinese medicinal plants. Evidence indicates that emodin has a wide spectrum of pharmacological properties, including hepatoprotective, antiinflammatory, antioxidant and antimicrobial activities. Emodin has also been reported to have anticancer properties in a variety of malignancies, including lung, liver, and pancreatic tumours. Anticancer properties of emodin have been studied in a variety of biological pathways. This chapter aims to comprehensively summarize the anti-proliferative and anti-carcinogenic properties of emodin.

Keywords: Anthraquinones, Antiinflammatory, Antioxidant, Anticancer, Breast cancer, Cancer, Emodin, Lung cancer, Nanoformulation, Phytochemicals, Rhubarbs, Tyrosine kinase inhibitor.

INTRODUCTION

Cancer is a group of disorders in which abnormal cells develop and spread uncontrollably. It is possible that death will follow if the spread is not controlled. Although the aetiology of many cancers, especially those that arise in children, is unknown, there are numerous recognised cancer causes, including lifestyle variab-

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les like tobacco use and excess body weight, as well as non-modifiable factors such as inherited genetic mutations, hormones and immunological disorders. These risk factors may work in concert or in concert with one another to initiate and/or encourage cancer growth [1]. Cancer is the world's largest cause of death, with approximately 10 million deaths estimated by 2020 [2]. Chemotherapeutic drugs derived from plants are a promising cancer treatment strategy because they are generally less toxic to normal cells than synthetic chemotherapeutic agents [3]. Emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) is a naturally occurring anthraquinone derivative found in several well-known herbal medicines. It's a protein tyrosine kinase inhibitor as well as an anticancer medicine that works on a variety of tumour cells, including lung, breast, liver, and ovarian cancer cells. Its involvement in combination chemotherapy with various allopathic drugs has recently been investigated in order to reduce toxicity and increase efficacy. *In vitro* and *in vivo* models, Emodin has anti-ulcer, anti-inflammatory, hepatoprotective, neuroprotective, antibacterial, muscle relaxant, immunosuppressive, and anti-fibrotic properties in addition to its antineoplastic action [4]. Emodin (Fig. **1**) is capable of reducing cellular proliferation, inducing apoptosis, and preventing metastasis [5].

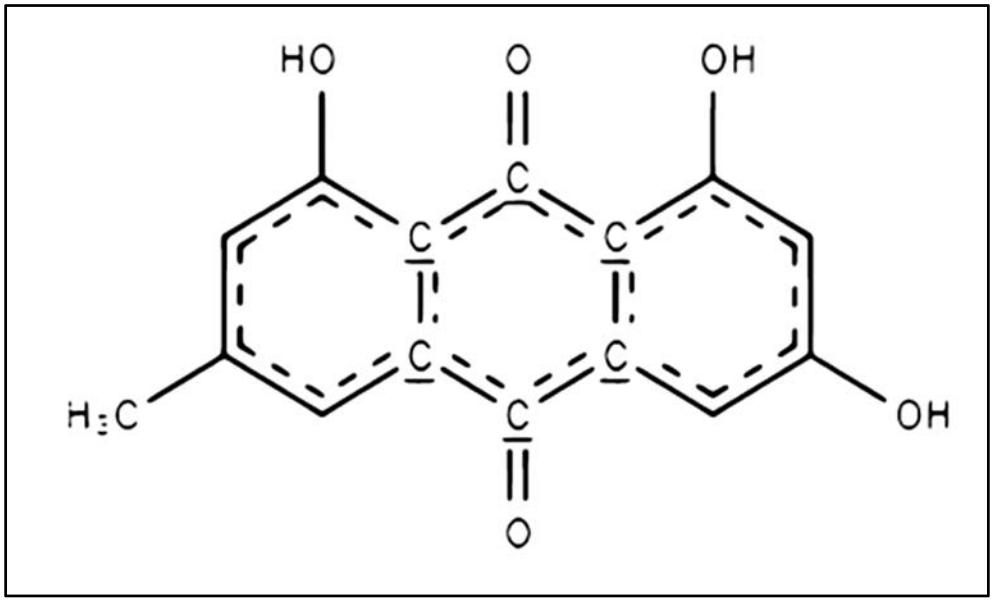

Fig. (1). Chemical structure of emodin.

Emodin is a member of the anthraquinones, which are the biggest group of natural quinones with over 170 molecules. Lower fungi, particularly Penicillium and Aspergillus species, and lichens contain more than half of the natural

anthraquinones. Others can be found in higher plants and, in rare occasions, insects. Anthraquinones are abundant in the Rubiaceae, Rhamnaceae, Fabaceae, Polygonaceae, Bignoniaceae, Verbenaceae, Scrophulariaceae, and Liliaceae families. In the Polygonaceae and Rhamnaceae, anthraquinone is produced by the acetate-malonate pathway, while in the Bignoniaceae and Verbenaceae, it is produced *via* O-succinylbenzoic acid. Anthracene ring (tricyclic aromatic) with two ketone groups in positions C9 and C10 is the basic chemical structure of anthraquinone (Fig. **2**). Anthraquinones are typically found in plants as sugar derivatives (glycosides), although the free form (aglycones) is also extensively distributed. Emodin, rhein, chrysophanol, aloe-emodin, and physcion are some of the most frequent anthraquinone aglycones found in higher plants like rhubarbs (Fig. **3**). Originally, emodin was believed to be more common in bark and roots [6]. Emodin comes in the form of orange needles (Fig. **4**) or powder [7].

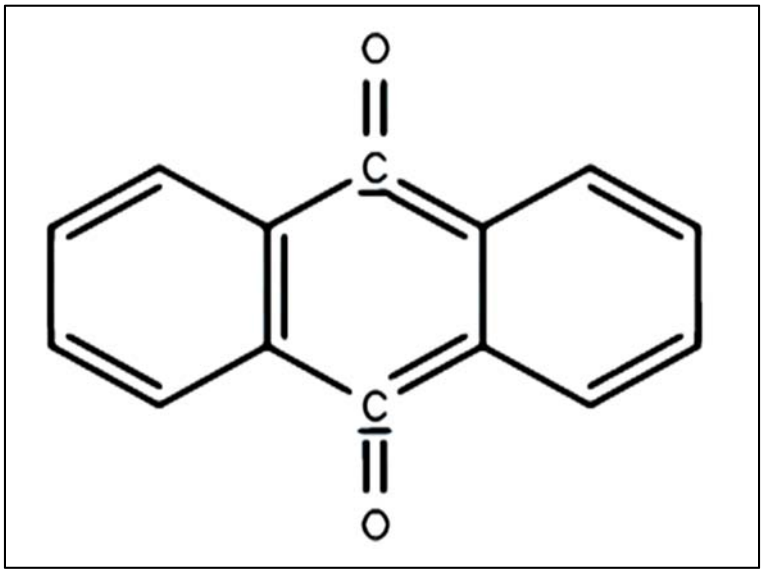

Fig. (2). General Chemical Structure of Anthraquinone.

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PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.