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ANTHRAQUINONES: BIOACTIVE MULTIFACETED THERAPEUTIC AGENTS

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Anthraquinones: Bioactive Multifaceted Therapeutic Agents

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FOREWORD

The book series ‘Bentham Briefs in Biomedicine and Pharmacotherapy’ is dedicated to a comprehensive understanding of pharmacology and its role in treating different diseases. The third volume, ‘Anthraquinones: Bioactive Multifaceted Therapeutic Agents’ explores the realms of anthraquinones. These pharmacologically active molecules exhibit a diverse range of structural variations and different applications. Few enzymes in their biosynthetic pathways can bring out huge diversity as they can work on a large number of similar substrates having minor modifications at different positions. This book explores various aspects of anthraquinones, including their chemical structures, biosynthetic pathways, therapeutic potential, and potential applications in cancer treatment and nanotechnology. Anthraquinones are already in use for chemotherapy of various cancers. However, creating nanoparticles of these molecules brings out a new dimension in more effective delivery of these molecules, aimed at better effectiveness and reduced toxicity. Each chapter meticulously unravels the layers of complexity surrounding these compounds, offering a panoramic view of their current scientific and practical relevance. These chapters also illuminate the future pathways they may traverse, especially in the realm of nanotechnology-enhanced therapies. I am confident that this handbook will inspire readers to actively explore, critically analyze, and collaborate in order to further advance the understanding and utilization of anthraquinones in various fields.

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PREFACE

The exploration of anthraquinones, a class of naturally occurring aromatic compounds, represents a confluence of tradition and innovation, bridging millennia-old therapeutic practices with cutting-edge scientific research. In this third volume of the Bentham Briefs in Biomedicine and Pharmacotherapy series, titled "Anthraquinones: Bioactive Multifaceted Therapeutic Agents," we embark on a comprehensive examination of these compounds, renowned for their dynamic roles in the natural world and their therapeutic potential in medicine.

Anthraquinones, characterized by their distinctive aromatic structure, have been utilized since ancient times, most notably in traditional medicine and as natural dyes. Today, they are the subject of intensive scientific inquiry, particularly in the realm of pharmacology, where their diverse bioactivities including antimicrobial, anticancer, and anti-inflammatory effects offer promising avenues for new drug development. This volume aims to encapsulate the multifaceted nature of anthraquinones, from their chemical and biosynthetic properties to their therapeutic applications and emerging roles in nanotechnology-enhanced drug delivery.

The chapters presented herein are crafted by leading experts in the field, each delving into various aspects of anthraquinone research. The content ranges from detailed analyses of chemical structures and biosynthesis pathways to comprehensive reviews of the therapeutic uses and potential of anthraquinones, particularly in combating challenging diseases like cancer. Furthermore, the incorporation of nanotechnology in anthraquinone applications heralds a new era of precision medicine, where the delivery and efficacy of these compounds are significantly enhanced. We believe that this compilation not only serves as a repository of current knowledge but also as a catalyst for future research, inspiring continued exploration and innovation in the use of anthraquinones.

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CHAPTER 1

Anthraquinones: Integrated Perspectives on Analytical Methodologies and Functional Applications

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Abstract: Anthraquinones are aromatic organic compounds essential in both nature and industry, known for their diverse applications. Anthraquinones with a chemical formula of $C_{14}H_8O_2$ are commonly found in plants like *Aloe vera* and rhubarb, fungi, lichens (a symbiosis of fungi and algae), bacteria like *Streptomyces* species, and certain animals like crinoids and sponges. It has various biological functions such as antimicrobial properties and anticancer activities. Anthraquinones are synthesized through natural processes like the polyketide and shikimate pathways within plants and extracted using methods such as ultrasound-assisted extraction and super critical fluid extraction for their isolation and purification. In the medical field, anthraquinones play a crucial role in the development of drugs like anthracyclines for cancer and metformin for diabetes treatment, showcasing their therapeutic potential. Industrially, anthraquinones find application as natural dyes in textiles, imparting vibrant colors, and as additives in papermaking to enhance the strength and durability of paper products, highlighting their versatility in diverse industrial sectors. The utilization of analytical techniques such as ultraviolet-visible (UV-Vis) spectroscopy is essential for determining the absorption spectra of anthraquinones, while high-performance liquid chromatography is crucial for separating and quantifying individual compounds, emphasizing their indispensable roles in accurate anthraquinone analysis. The compound's significance extends beyond its bioactivities, playing a vital role in various industrial applications, which underscores the ongoing research and interest in exploiting its properties for innovative solutions in healthcare, manufacturing, and environmental sustainability.

Keywords: Anthraquinones, Biological activities, Biosynthesis, Chemical synthesis, Gas chromatography, High-performance liquid chromatography,

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Industrial applications, Mass spectrometry, Natural pigments, Polyketide pathway, Quinones, Shikimate pathway, Super critical fluid extraction, Ultrasound-assisted extraction.

INTRODUCTION

The group of quinones and their derivatives including benzoquinones and naphthoquinones, which constitute the large number of natural pigments are called anthraquinones. These are the aromatic organic compounds with the chemical formula $C_{14}H_8O_2$, where keto groups are located on the central ring (Fig. **1**). The compounds belonging to this class are abundantly produced from natural sources like plant parts such as roots, rhizomes, flowers, and fruits, while others are present in lichens, fungi, and animals [1].

Anthraquinones are of tremendous use in biological properties such as inhibiting bacterial and fungal growth and in industrial applications by acting as a natural dye and are used in bleaching pulp for papermaking. These are phenolic compounds widely present as a skeleton of 9,10-anthraquinone. The name anthraquinones was given by Carl Graebe and Libermann in the year 1868. The synthesis of these phenolic compounds includes the oxidation of anthracene in the presence of oxidant chromium (VI). These compounds are studied in plants belonging to the *Rubiaceae* family, such as *Morinda*, *Rubia*, and *Gallium* species. These quinones are derived from anthracenes and possess a broad spectrum of bioactivities such as anticancer, cathartic, anti-inflammatory, and diuretic, and also play a potential role in autoimmune diabetes [1–3]. Anthraquinones show their potential applications in various industries, such as in medicine, with their uses as drugs or as an anticancer agent.

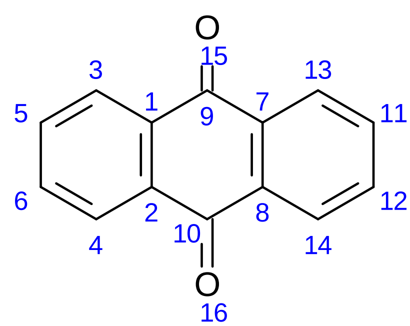

Fig. (1). Structure of anthraquinone.

BIOSYNTHESIS OF ANTHRAQUINONES: ENZYMATIC MECHANISMS AND GENETIC INSIGHTS

Anthraquinone synthesis includes 2 pathways *viz*. the polyketide pathway and the shikimate pathway.

Polyketide Pathway: This pathway is common in bacteria and fungi and is carried out in the presence of enzymes polyketide synthases that result in the formation of an intermediate during the anthraquinone synthesis (Fig. **2**) [4].

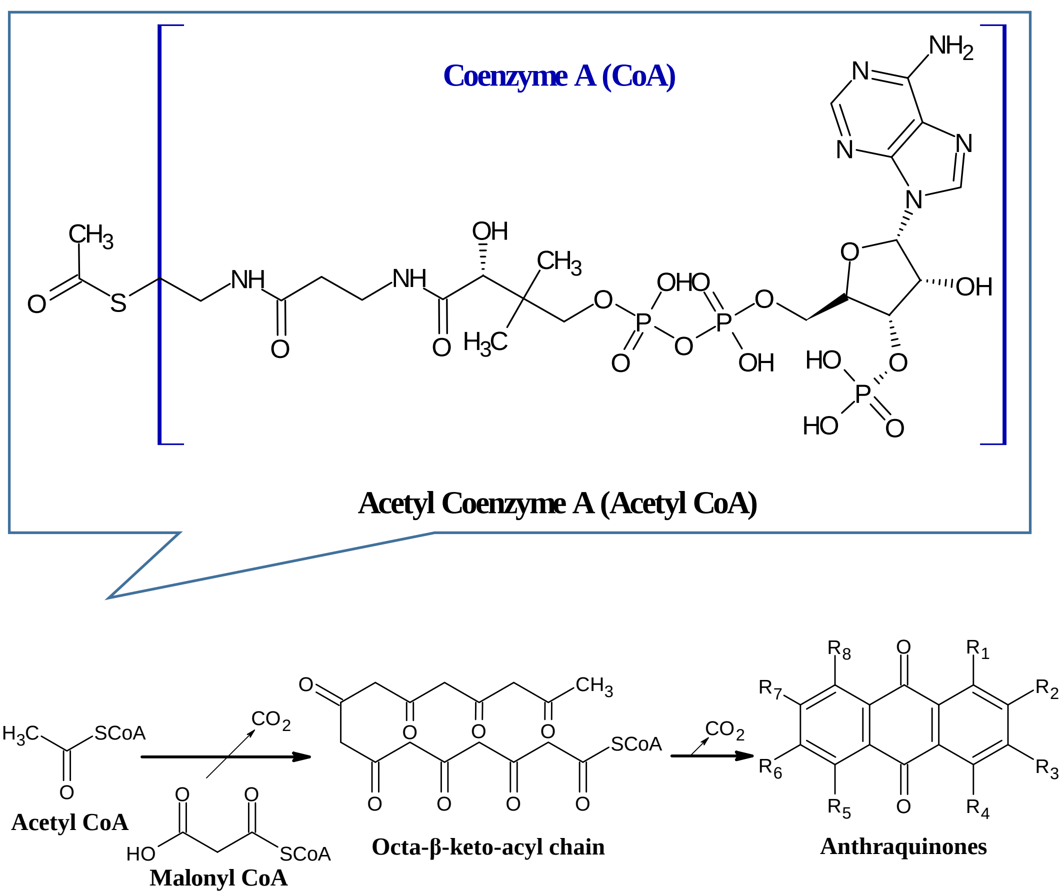

Fig. (2). The polyketide pathway.

Shikimate Pathway: α-ketoglutaric acid and shikimic acid result in the formation of o-succinoylbenzoic acid, which is further added to mevalonic acid and results in the formation of 1,2 dihydroxylated anthraquinones (Fig. **3**) [1].

CHAPTER 2

An Overview of Chemistry and Biosynthesis of Anthraquinones

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Abstract: Anthraquinones are a class of secondary metabolites, have garnered significant interest due to their diverse biological activities and various industrial applications. The derivatives of anthraquinones are widely distributed in nature, being found in numerous plants, fungi, and bacteria. The biosynthetic pathways leading to anthraquinones differ among various organisms, yet common underlying mechanisms can be observed. Enzymatic reactions play a pivotal role in the functionalization and diversification of anthraquinones. Cytochrome P450 monooxygenases, glycosyltransferases, and acyltransferases are key enzymes involved in modifying the basic anthraquinone skeleton, leading to a wide array of structurally distinct derivatives. Moreover, advances in genomic and proteomic technologies have facilitated the discovery of genes and enzymes responsible for anthraquinone biosynthesis. Genetic engineering and synthetic biology approaches have enabled the manipulation of biosynthetic pathways, paving the way for the production of novel anthraquinones with engineering and synthetic biology approaches have enabled the manipulation of biosynthetic pathways, paving the way for the production of novel anthraquinones with enhanced bioactivity and potential applications in pharmaceuticals, agrochemicals, and the dye industry. In the present work, we will focus on the different biosynthetic pathways for the biosynthesis of anthraquinones.

Keywords: Anthracene, Aromatic fused ring, Antioxidant properties, Dye industry, 9,10-anthraquinone, Mevalonate (MVA), Methyl erythritol phosphate (MEP) quinone, Polyketone pathway, Polygonaceae, Plant pigment, Polyketide biosynthesis, Shikimate pathway, Tricarboxylic acid (TCA).

INTRODUCTION

Anthraquinone is a prominent organic compound, known for its vibrant colors and diverse activities, which has captivated the attention of chemists, scientists, and industries for centuries [1]. Its name is derived from “anthracene”, a tricyclic aromatic hydrocarbon, and “quinone”, referring to the presence of a carbonyl group

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(C=O) in its chemical structure. Anthraquinone is characterized by a bicyclic core structure composed of three fused benzene rings with two ketone functional groups at adjacent carbon positions [2]. They are widely distributed in nature and play significant roles in various physiological activities. Along with their medicinal properties, natural anthraquinones are seeking attraction as an alternative to synthetic dyes which harm aquatic ecosystems [3, 4]. Anthraquinones are widely distributed in nature and can be found in various plants, fungi, and certain types of bacteria including Madder Root, Cinchona Bark, Rhubarb, and fungi [5, 6]. These are also found in various food sources of humans like cabbage, and beans, which provide around 0.04 to 36 mg of anthraquinone. The natural occurrence of anthraquinones highlights their significance in ecological and pharmacological contexts, as well as their potential as sources of bioactive compounds [7]. The chemical reactivity of anthraquinones is diverse, owing to their conjugated and electron-rich structure. They readily participate in a variety of chemical reactions (substitution, redox, cycloaddition, acid-base reactions, *etc*.), making them versatile building blocks for organic synthesis [8].

The versatility of anthraquinones extends to a wide range of applications across various fields, including chemistry (synthetic chemistry, analytical chemistry, and environmental chemistry), pharmaceuticals, dyes, biological research, and many more (Fig. **1**). Anthraquinones have garnered significant attention due to their diverse pharmacological properties, including anticancer, anti-inflammatory, antibacterial, and antioxidant effects [9, 10]. Anthraquinones are commonly found in many different organisms, ranging from bacteria and fungi to plants and some animals. In plants, anthraquinones are found in a wide range of species, especially in the families; *Rubiaceae*, *Polygonaceae*, *and Rhamnaceae* [11-13]. Understanding the biosynthetic pathways of anthraquinones is crucial for both natural product synthesis and biotechnological production. Anthraquinone biosynthesis primarily occurs in plants, fungi, and certain bacteria. The biosynthetic pathways are complex and involve multiple enzymatic reactions. In plants, the biosynthesis of anthraquinones typically begins with the shikimate pathway, a central metabolic route responsible for the synthesis of aromatic compounds. This pathway usually starts with the conversion of phosphoenolpyruvate and erythrose-4-phosphate into shikimate. The second pathway is chorismic acid conversion in which chorismic acid serves as a precursor for the formation of various aromatic compounds. In the context of anthraquinone biosynthesis, it undergoes a series of reactions involving enzymes like isochorismate synthase and isochorismate-pyruvate lyase to produce isochorismic acid, which is then converted into intermediates like 1,2-dihydroxyanthraquinone, which subsequently undergoes oxidation and cyclization reactions catalyzed by various enzymes. Once the anthraquinone skeleton is formed, various tailoring enzymes may further modify the structure [14-17]. These enzymes can introduce functional groups like hydroxyl, methyl, or glycosyl groups at specific positions on the anthraquinone ring system, yielding a wide range of anthraquinone derivatives with distinct properties. After biosynthesis, anthraquinones are often transported to specific cellular compartments, such as vacuoles, where they accumulate [18-20]. This compartmentalization helps prevent cellular damage from these often toxic compounds and also facilitates their storage for various purposes. In this context, this chapter provides an overview of the different biosynthetic pathways for the synthesis of anthraquinones.

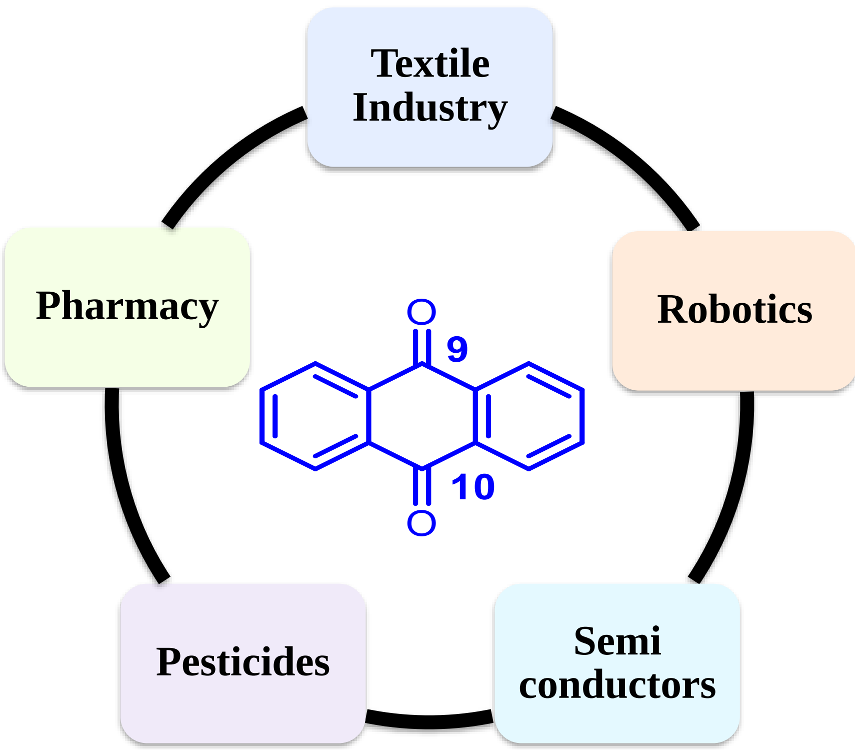

Fig. (1). Applications of anthraquinones in different fields.

GENERAL STRUCTURE AND CHEMISTRY

Anthraquinones are a class of organic compounds known as quinones and are characterized by a cyclic conjugated structure with alternating double bonds and oxygen atoms. The core structure of anthraquinone consists of three fused benzene rings, forming a tricyclic aromatic system [21]. The aromaticity of anthraquinone

CHAPTER 3

Anthraquinones as Bioactive Agents: Recent Trends and Developments in Phytotherapy

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Abstract: Anthraquinones are organic compounds and members of the Quinone family comprising 9, 10-anthracenedione core. Anthraquinone is a chemical scaffold that has been employed for many years in a variety of therapeutic applications such as antimicrobial, anticancer, diuretic, anti-inflammatory, and phytoestrogen activities. Anthraquinones are commonly produced as secondary metabolites in various higher plant species (senna, buckthorn, yellow dock) or they can either be synthesized using chemical routes such as the condensation of 1, 4-naphthoquinone with butadiene, naphthalene oxidation, anthracene oxidation, *etc*. Anthraquinones are used in various traditional and ethnomedical processes for the treatment of acute as well as chronic illness and are nowadays employed in modern pharmaceutical markets as a key bioactive agent. Hence, due to these properties, anthraquinone-based compounds are widely used in phytotherapy. Anthraquinones are unique in terms of their structure, chemical stability, biological properties, and industrial applications among all reported quinones, making them valuable in a wide range of drug formulations. The in-depth studies regarding the role of anthraquinones using *in vitro* and *in vivo* models need to be extensively explored for bioactive and phytotherapy applications. In addition to this, the safety and toxicity assessment need to be thoroughly investigated. The knowledge regarding its biochemical structure can pave the way to understanding its physiological and toxicological properties. The chapter dispenses compact knowledge regarding anthraquinones aspotential bioactive agents and their use as a therapeutic/health product.

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Keywords: Anthraquinones, Bioactive agents, Drug formulations, *In vivo*, *In vitro*, Medicinal plants, Toxicity studies.

INTRODUCTION

Anthraquinone, a captivating organic compound, has gained attention for its versatile applications in chemistry, pharmaceuticals, and the textile industry [1]. This aromatic compound is characterized by its unique structure, consisting of a fused aromatic ring system comprising three benzene rings and a ketone group. The term “anthraquinone” is derived from a Greek word, “anthos” meaning flower and “rhodo” meaning rose, signifying its initial discovery from the roots of madder plants, which have been employed for centuries in the production of vibrant red dyes. As time passed, the study of anthraquinone compounds expanded beyond their use in dyeing, revealing their presence in a diverse array of natural sources. Anthraquinones are frequently found in the roots, leaves, and stems of numerous plant species, including madder (*Rubia tinctorum*), rhubarb (*Rheum rhabarbarum*), and senna (*Senna alexandrina*) [2]. They are particularly abundant in plants belonging to families like *Polygonaceae*, *Rhamnaceae*, and *Juglandaceae*. More than 70 different types of anthraquinones have been identified. These compounds often serve as secondary metabolites in plants, playing essential roles in defense mechanisms against herbivores and pathogens [3]. Furthermore, anthraquinones have been identified in various fungi, notably in species belonging to the genera *Aspergillus* and *Penicillium*, where they contribute to the metabolic processes of these organisms [4]. These compounds have garnered significant interest from researchers due to their diverse biological functions, including hepatoprotective, antifungal, antibacterial, laxative, antioxidant, and anti-cancer properties. Anthraquinones have also been reported for their bioactive properties and use in phytotherapy [5-9]. In this exploration of anthraquinone, we will delve deeper into their origins and the diverse sources reported for their bioactive and phyto-therapeutic properties. Also, the study related to safety and toxicity assessment needs to be explored for its pharmaceutical applications. Beyond their role as natural products, anthraquinones have found applications in synthetic chemistry, pharmaceuticals, and as colorants in various industries [10]. This makes them a versatile and captivating class of compounds with a rich history and promising prospects for the future.

ANTHRAQUINONES AS BIOACTIVE AGENT

Anthraquinones are a group of chemical compounds that are found in a wide diversity of plants and have been explored for a range of bioactive properties [11].

The various biological activities that anthraquinones exhibit make them excellent candidates for use in medicine and other applications (Table **1**).

Antimicrobial Potential of Anthraquinone

Anthraquinones' antimicrobial abilities have been widely studied *in vitro* using both pure and crude forms [12]. Among the most studied anthraquinones found in nature include chrysophanol, aloe-emodin, emodin, rhein, and physcione reported for their *in vitro* antimicrobial activity. Anthraquinones, both extracted and isolated, were effective against various Gram-negative and Gram-positive bacteria including *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Neisseria gonorrhoeae*, MRSA strains of *Staphylococcus aureus* and *S. epidermitis* [11]. In literature, Wang *et al*. [13], isolated a new anthraquinone, 2-(dimethoxymethyl)-1-hydroxyanthracene-9,10-dione from the fermentation of *Aspergillus versicolor* derived from sea sediment. This anthraquinone showed strong inhibitory activity against MRSA strains and moderate activity against *Vibrio campbellii* due to the inhibition of topoisomerase-IV and AmpC β-lactamase. In literature, Song *et al*. [14] isolated two anthraquinone compounds *viz.* 3,8-dihydroxy-l-methylanthraquinon-2-carboxylic acid and 3,6,8-trihydroxy-1-methylanthraquinone-2-carboxylic acid from an actinobacterial strain named *Kitasatospora albolonga* R62. These compounds disrupted preformed MRSA biofilms, potentially by either killing or dispersing the biofilm cells. Similarly, Shupeniuk *et al*. [15] synthesized amino derivative fragments of anthraquinone using a Ullmann coupling reaction exhibiting an inhibitory effect against a wide range of Gram-positive and Gram-negative strains of clinical isolates *viz. Staphylococcus* spp., *Streptococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Providencia stuartii*, *Pseudomonas aeruginosa*, and fungal strain *Candida*. Antibacterial activity is due to the presence of benzoic acid inhibiting the active uptake of some amino and oxo acids [16]. Yirdaw and Kassa [17] reported the antibacterial activity of terpenoids and anthraquinones present in the methanol extracts from the root bark of *Ferula communis* (Apiaceae) against Gram-negative (*Salmonella typhi*, *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas erogenous*), and Gram-positive bacteria (*Staphylococcus aureus*). Zhuravleva *et al*. [18] isolated different anthraquinones namely Acruciquinones A to C from marine fungus *Asteromyces cruciatus* KMM 4696, which showed significant antimicrobial effects against *Staphylococcus aureus* and *Staphylococcus aureus*-infected human HaCaT keratinocytes. The antimicrobial activity of Acruciquinones A to C is due to the inhibition of sortase A and urease activity. Recently, Adekunle *et al.* [19] isolated two anthraquinone molecules from the extracts of *Morinda lucida viz.* 2-hydroxy-1-methoxy anthraquinone and 1,2-dihydroxyanthraquinone (Alizarin), which were found to

CHAPTER 4

Anthraquinone Derivatives as Potent Anti-Cancer Agents

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Abstract: Cancer is one of the high-mortality-causing diseases in the world. It causes a serious threat to mankind with an estimated 10 million deaths every year. Identifying novel drug candidates for the treatment of various types of cancer is a prime research area in medicinal chemistry. Even though many drug molecules are used in cancer treatment, they suffer from various drawbacks, such as low selectivity, toxicity, and resistance to new tumor cells. Hence, the search for novel anti-cancer agents is a continuous process in order to develop more efficient and less toxic chemotherapeutic agents. Among them, anthraquinone, a diketo derivative of anthracene, has gained much interest in the search for novel anticancer agents. Since anthraquinone is present in various natural products, it has diverse biological properties, which makes it a prominent scaffold in medicinal chemistry. Many anthraquinone classes of anticancer agents have been developed in the last decade and remain the first treatment option for cancer. The search for novel anthraquinone derivatives by the modification of the core structure or by the introduction of newer substituents to attain higher selectivity and efficacy has gained considerable interest recently. This book chapter concisely summarizes the anticancer activities of various anthraquinone derivatives reported by researchers, either derived from natural sources or synthetically prepared.

Keywords: Anthraquinone derivatives, Anti-cancer agents, Chemotherapy, Emodin derivatives, Heterocycles, Natural products.

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INTRODUCTION

The group of quinones and their derivatives including benzoquinones and naphthoquinones, which constitute the large number of natural pigments are called anthraquinones. These are the aromatic organic compounds with the chemical formula $C_{14}H_8O_2$, where keto groups are located on the central ring (Fig. **1**). The compounds belonging to this class are abundantly produced from natural sources like plant parts such as roots, rhizomes, flowers, and fruits, while others are present in lichens, fungi, and animals [1].

Cancer and the Need for New Chemotherapeutic Agents

Cancer is a highly assorted, multifactorial disease with a group of disorders characterized by abnormal cell growths in any part of the body, which is mainly caused by genetic and environmental factors [1]. The WHO highlighted that cancer is one of the leading causes of death in humans worldwide, and nearly 10 million mortalities were reported in 2020. That means one in every six deaths is due to cancer, which shows its brutal nature. Tobacco use, alcohol consumption, high body mass index, and low fruit and vegetable intake are the major causes of mortality from cancer [1]. Out of the 200 various types of cancers reported, lung, breast, stomach, colon and rectum, skin, and prostate cancers are the most common types found in humans. Most of the cancer types can be treated effectively only if they are detected in the early stages. It becomes more complicated in the final stages as the medication becomes ineffective and there is a possibility of recurrence after treatment.

Diagnosis of the correct types and stages of cancer is very much crucial for proper and effective treatment, because every cancer type requires a specific treatment protocol. Surgery, radiotherapy, and/or systemic therapy (chemotherapy, hormonal treatments, and targeted biological therapies) are commonly employed for curing the cancer based on the types of cancer and human beings treated. Most of the presently available cancer treatments are very expensive and cannot be afforded by a common man. Chemotherapeutic agents are the drugs used during chemotherapy, and it is one of the most common and effective cancer treatment options available. In general, cytotoxic agents destroy fast-growing cells, like cancer cells, and prevent them from multiplying. Non-selectivity of the chemotherapeutic agents and their side effects still remain a major source of concern. Neurotoxicity owing to present anti-cancer drugs can be resilient in the body even after the end of treatment, and it reduces the functional power and quality of life in cancer survivors. In their review article, Lustberg *et al*. wrote well about the possible side effects of cancer chemotherapeutic agents [2].

Most of the anti-cancer drugs are made up of synthetic compounds, either a single derivative or a combination of drugs. Taxoids, docetaxel (Taxotere), and paclitaxel (Taxol), among other well-known anticancer medications derived from natural products, will likely lead to the discovery of many more active molecules among the 300,000 plant species that are currently being studied [3]. Different cytotoxic agents fight cancer cells *via* different mechanisms, and many are still unknown to researchers. The development of new, efficient, cheaper, and selective anti-cancer agents with fewer side effects and different mechanisms of action is crucial to the fight against cancer and to reduce mortality. Hence, this review chapter emphasizes the progress in recent developments of anticancer drugs with respect to anthraquinone derivatives with the aim of developing new derivatives as anti-cancer agents.

Naturally Occurring Anthraquinones in Anticancer Drug Discovery

Anthraquinones (Fig. **1** (**1**)) are naturally occurring secondary metabolites in plants [4], fungi [5], and bacteria [6]. There are 3,798 anthraquinone derivatives reported in the PubChem database. Anthraquinones have been isolated from many plants belonging to the *Rubiaceae* [7], *Fabaceae*, *Ranunculaceae*, and *Asphodelaceae* families, and anthraquinones are active ingredients used in traditional Chinese medicines [8]. Although the exact mechanism of biosynthesis of anthraquinones in plants remains unclear, polyketide and shikimate pathways are the most important and widely accepted pathways [4]. Some of the most common anthraquinones, found in plants and microbes, are emodin (Fig. **1** (**2**)), aloe-emodin (Fig. **1** (**3**)), rhein (Fig. **1** (**4**)), chrysophanol (Fig. **1** (**5**)), alizarin (Fig. **1** (**6**)), quinizarin (Fig. **1** (**7**)), damnacanthal (Fig. **1** (**8**)), rubiadin (Fig. **1** (**9**)), purpurin (Fig. **1** (**10**)), physcion (Fig. **1** (**11**)), and danthron (Fig. **1** (**12**)). Anthraquinones have shown a wide range of pharmacological activities, including anti-inflammatory [9], antidiabetic [10], antimicrobial [11], antiviral [12], antimalarial [13], and antiplatelet [14] activities. Natural anthraquinones have been used as photosensitizers in photodynamic therapy of cancer [15].

Emodin is one of the important naturally occurring anthraquinone molecules that exhibit diverse applications in medicinal chemistry. It is isolated from various plants belonging to the *Rhamnaceae* [16], *Polygonaceae* [17], *Fabaceae* [18], and *Asteraceae* [19] families. It is also one of the fungal metabolites and is isolated from various fungal species like *Aspergillus* [20], *Cladosporium* [21], *Chaetomium* [22],

CHAPTER 5

Role of Nanotechnology in Anthraquinones-Mediated Disease Management

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Abstract: To maintain therapeutic efficacy while reducing toxicity and biocompatibility, innovative safety delivery techniques with improved nanotechnology are developed. Nanotechnology develops delivery systems that enhance the solubilizing and release quality of drugs, as well as their circulation time, which is important to enhance the therapeutic efficacy of drugs. Anthraquinones are organic substances that may be found in various plants, animals, and even some marine life. They are simple anthrones or bianthrones chemically speaking. They are used as pigments, dyes, and pharmaceuticals. Anthraquinone glycosides possess biological qualities including laxative, anti-inflammatory, anti-cancer, and antioxidants. Anthraquinones have certain drawbacks, such as their poor solubility in aqueous media, which restricts the routes of administration and lowers their bioavailability while also exhibiting a lower degree of selectivity for target tissues. It is speculated that anthraquinones and nanostructures work together. This chapter describes the application of nanotechnology in the treatment of anthraquinone-mediated diseases. The utilization of anthraquinone-loaded nanoparticles, nanocapsules, and nanocarriers in the treatment of various illnesses is highlighted.

Keywords: Anti-bacterial, Anthraquinones, Age macular diseases, Angiogenesis, Cancer, Chitosan, Diabetic nephropathy, Doxorubicin, Emodin, Liponanoparticles, Natural products, Nanocarriers, Nanoparticles, Nanotechnology, Peripheral vascular disease, Photosensitizers, Photodynamic, Rhein, Reactive oxygen species.

INTRODUCTION

For millennia, natural products have been a primary source of therapeutic agents. Nevertheless, the use of biologically active natural metabolites in pharmaceutical products and drug discovery is still a viable option. Living organisms in a variety of environments can develop various secondary metabolites, which can be useful

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to the organism and may have many applications for human beings Anthraquinone (AQ) is one of the main metabolites produced by various plants, marine organisms, and microorganisms, used in a broad range of applications, *e.g.*, colouring agents for foodstuffs as well as textile products which are therapeutic to different diseases [1,2]. Anthraquinones (Fig. **1**) originate from the compound known as 9,10-anthracenedione. The introduction of hydroxyl, methyl, carboxyl, and methoxy functional groups onto 9,10-anthracenedione leads to the generation of several anthraquinone derivatives, exhibiting various therapeutic properties (Fig. **2**) [1]. These are anthracene derivatives comprising three benzene rings and one or more hydroxyl groups that can combine with sugar molecules. Therefore, they occur in nature as anthraquinone glycosides. Anthracene compounds exist in oxidized (anthraquinone) or reduced (anthrones, anthranols) and dimer (dianthrones) forms in nature [3].

More than 75 naturally occurring AQs are identified from various natural sources which include algae, marine organisms, fungi, and medicinal plants belonging to distinct family groups. Researchers are interested in the AQ scaffold because of its broad spectrum of biological actions, which include antitumor, anti-inflammatory, anticancer, antimutagenic, anti-fungal, anti-viral, anti-malarial, anti-microbial, anti-platelet, antidiabetic, neuroprotective, antioxidant, anti-bacterial, laxative, *etc* (Table **1**) [4]. Many more biological properties have been recorded with different effects [5]. In addition to its biological activities, many natural and synthetic anthraquinones are finding applications in textiles, electronic goods, biochips, food, cosmetics, medicine, and imaging photocleavage protection groups [3].

In addition, the design of new techniques has shown that an effective nanoformulation can be produced by the combination of anthraquinones and nanostructures. A potential area of research in nanotechnology involves the creation of nanocarriers that encapsulate hydrophobic and lipophilic bioactive medicines. This will improve bioavailability and broaden the spectrum of delivery strategies. Because nanocarriers are bio-compatible and bio-degradable, they offer greater opportunities for innovation and early detection of many diseases [6].

Nanotechnology is the study of nanomaterials or structures less than 100 nm with high surface density and volume ratios that could change physical chemistry, and biological parameters in chemical compositions. Nanoscience has gained worldwide interest because of its potential for applications in pharmaceuticals, diagnostics, and disease treatment [7]. Nanomaterials have a variety of qualities and characteristics, such as the required size, greater solubility, easier passage over biological barriers or an improvement in reactivity. New ambitions to tackle today's human challenges have arisen from the use of nanotechnology. The use of nanotechnology also benefits the pharmaceutical and medical industry, resulting in new products being launched on the market [8].

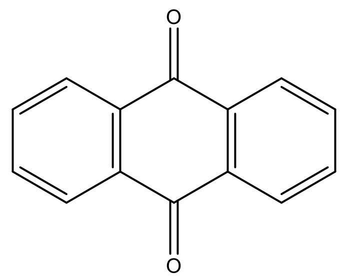

Fig. (1). Anthraquinone structure.

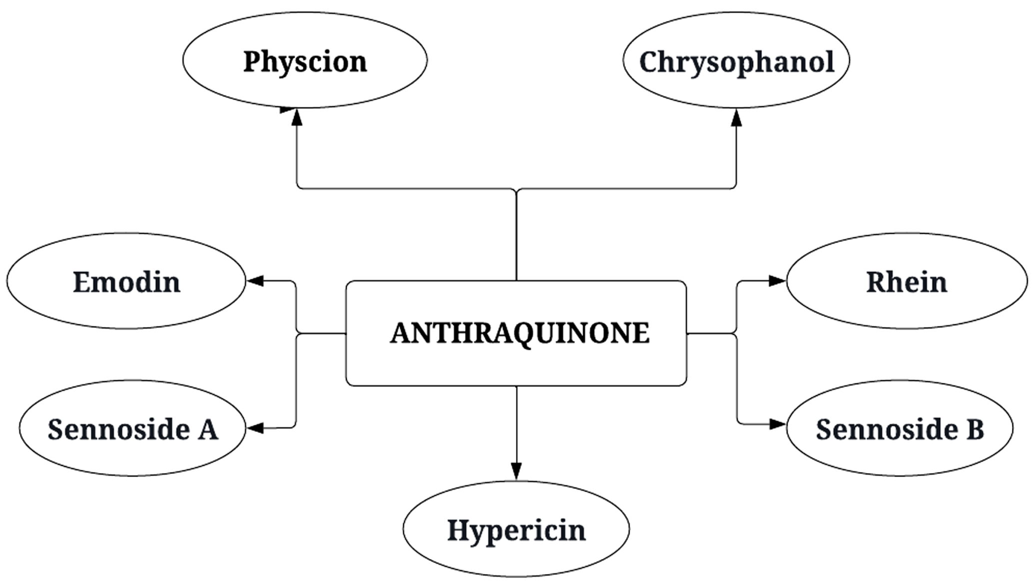

Fig. (2). Derivatives of Anthraquinone.

Toxicity of Anthraquinone

Anthraquinones are recognized for their diverse toxicological effects, which pose risks to both human health and environmental integrity. The degree of toxicity associated with these compounds can vary markedly based on the specific anthraquinone derivative and the levels of exposure involved. Certain derivatives have been classified as potential carcinogens, indicating their possible role in cancer

CHAPTER 6

Anthraquinone-Based Nanomaterials: Emerging Strategies in Cancer Therapy

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Abstract: Anthraquinone-based nanomaterials (ANMs) have recently garnered considerable attention due to their potential applications in cancer therapy. Anthraquinones are characterized by their tricyclic aromatic structure, which can be modified and incorporated into nanomaterials for various therapeutic purposes in cancer treatment. There are several ways in which ANMs are currently being investigated for cancer therapy such as improved drug delivery systems, photothermal therapy, photodynamic therapy, imaging agents (anti-cancer agents), combination therapy, and biomarker detection. It is important to highlight that ongoing research in the field of nanomedicine is continuously advancing, and the exploration of ANMs for cancer therapy is a rapidly evolving area. Recent studies reported in the literature show that ANMs effectively inhibit cancer by reactive oxygen species formation, paraptosis, autophagy, apoptosis, and various cell signaling pathways. Furthermore, before these ANMs can be extensively utilized in cancer therapy, regulatory approval and clinical trials are mandatory steps in the process. The chapter outlines a comprehensive overview of ANMs, highlighting their potential use for therapeutic, cancer therapy, and various health products.

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Keywords: Anthraquinone-based nanomaterials, Cancer therapy, Drug delivery systems, Nanomedicine, Photothermal therapy.

INTRODUCTION

Anthraquinone, derived from Rubia and other higher plant sources, is a tricyclic compound reported for its antioxidant properties [1-3]. It finds a wide range of applications in both industrial and medical fields due to functional activity. These compounds are derivatives of 9,10-anthracenedione, which offer several therapeutic effects in humans exhibiting antibacterial, antitrypanosomal, and antineoplastic activities [4]. Additionally, they also inhibit lipid peroxidation, intestinal motility, and human telomerase activity. Anthraquinone-based nanomaterials (ANMs) have demonstrated hepatoprotective, renal calculi elimination, immunomodulatory, anti-inflammatory, calcium channel antagonistic, antithrombotic, and DNA binding properties in both animals and humans [5]. Recent studies have shown that ANMs isolated from flowers and roots exhibit *in vitro* antitumor effects on human cancer cell lines [6-7]. These findings underscore their potential to activate antiproliferative activity and induce cytotoxic effects on these cancer cells. ANMs are recognized for their ability to induce apoptosis in various human cancer cell lines, including lung adenocarcinoma A549, myelogenous leukemia HL-60, lung squamous carcinoma CH27, cervical carcinoma HeLa cells, neuroblastoma IMR-32, bladder cancer T24, and hepatoma HepG2 cells [8]. Anthraquinone also inhibits the uptake of glucose in tumor cells, leading to alterations in membrane-associated functions that ultimately induce cell death [9].

Cancer is the second leading cause of death, with projections indicating over 21.7 million new cases and 13 million deaths attributed to this disease by 2030 [10,11]. Contemporary anticancer drugs face a lot of challenges, encompassing concerns related to their selectivity, resistance, toxicity, and limited therapeutic window. The focus has shifted to developing highly selective and potent drugs that minimize side effects. These drugs target specific factors, including DNA, topoisomerases, telomerase, MMPs, kinases, ectonucleotidase, and quinone reductase [12]. The pharmaceutical industry is placing a growing focus on targeted therapies, which is propelling the progress of novel drug formulations. The introduction of nanotechnology has brought about a revolution in drug delivery, resulting in enhanced solubility, increased bioavailability, and a reduction in toxicity [13-17]. Both natural and synthetic nanoparticles are gaining recognition and popularity because of their capability to precisely target drug delivery and improve the controlled release of medications. Within the field of cancer treatment, nanoparticle-based delivery systems have made substantial advancements, effectively reducing toxicity and precision-based targeting only cancer cells [18-21]. Doxorubicin (DOX) is a modern Anthraquinone derivative that is being studied intensively in the field of nanotechnology to cure various tumors (Fig. **1**) [22]. A heterobifunctional linker was used to create an artificial recombinant chimeric polypeptide (CP)-based near-monodisperse nanoparticle containing DOX at Cys residues. In solid tumors, CP-DOX nanoparticles are reported to accumulate preferentially.

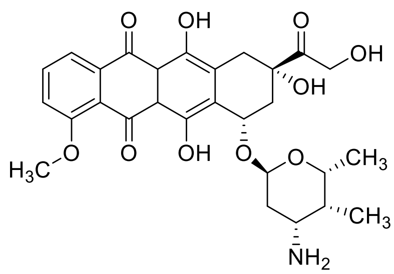

Fig. (1). Structure of Doxorubicin.

The scope of ANMs has gained significant attention in the field of cancer therapy due to their unique properties and potential applications due to their planar and aromatic ring structure making it easy to form various functionalized nanoscale structures. These nanomaterials have shown promise in several aspects of cancer therapy, and their scope includes, drug delivery systems, imaging agents, photothermal therapy (PTT), photodynamic therapy (PDT), reactive oxygen species (ROS) modulation, multimodal therapy, targeted therapies, overcoming drug resistance, nanotoxicology and biocompatibility. The potential of ANMs in cancer therapy is continuously evolving, as ongoing research strives to refine their properties and expand their applications. With increasing research efforts and the development of novel derivatives, the potential for these nanomaterials to bring about revolutionary changes in cancer therapy is on a steady path of expansion.

This chapter highlights the medicinal importance of natural anthraquinone-based nanoparticles specifically focusing on their role in anticancer activities. The creation of thoughtfully designed ANMs can pave the way for innovative approaches in chemotherapy. Various diverse nanoparticle formulations have been researched for cancer therapy and its applications in the healthcare sector. In addition to this, ongoing collaboration between scientists, engineers, healthcare professionals, and regulatory agencies will be vital in realizing these future applications.

SUBJECT INDEX

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