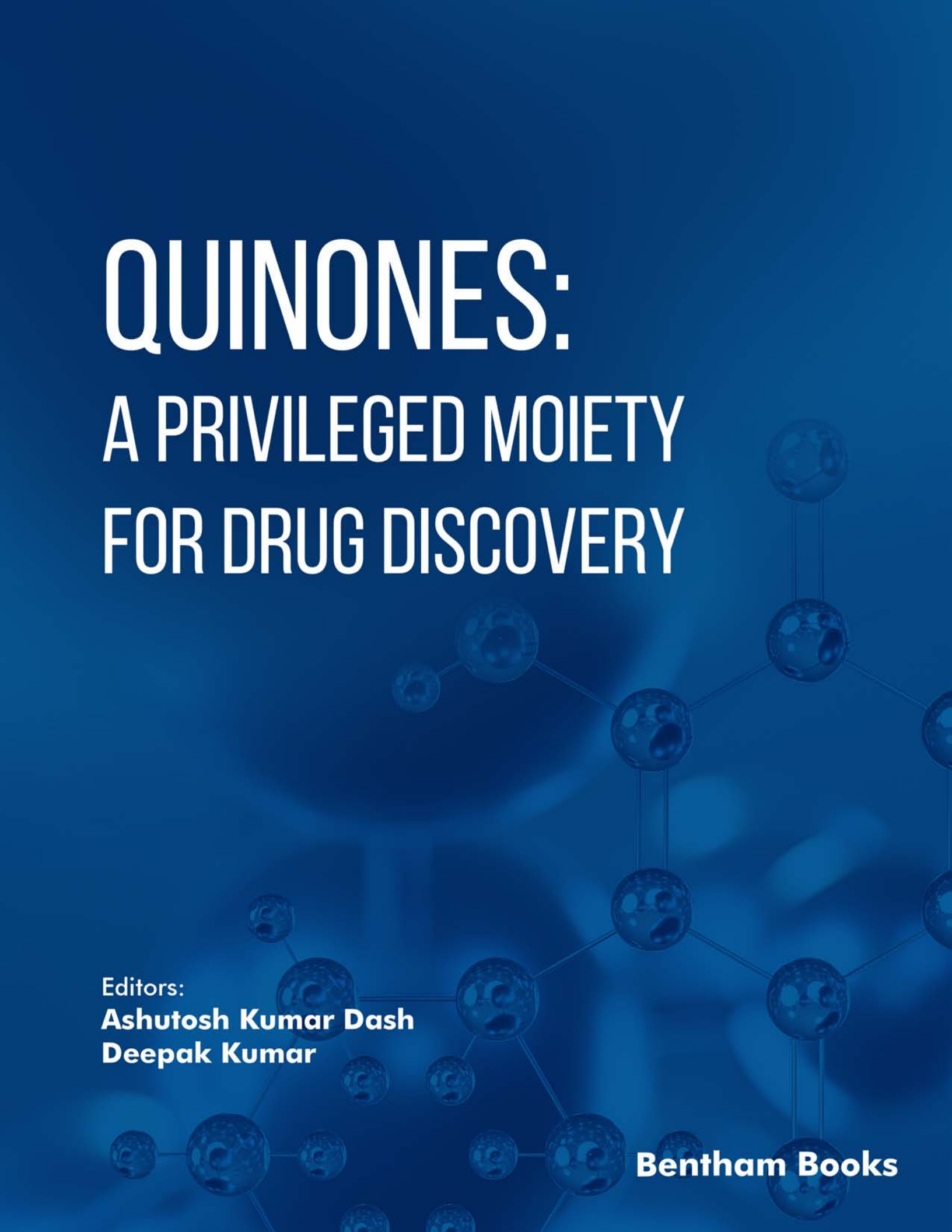
QUINONES:
A PRIVILEGED MOIETY FOR DRUG DISCOVERY



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PREFACE

Quinones constitute a major class of organic compounds that contain conjugated cyclic dione structures prevalent both in natural as well as synthetic organic chemistry. Naturally, quinones are rich in angiosperms, fungi (including lichens), bacteria, algae, ferns, conifers, sponges, *etc*., and also in human beings. Hence, a lot of traditional Asian therapies include quinone as Ayurvedic medicine. These can be frequently accessed from reactive aromatic compounds, such as phenols or catechols, very easily. The topic "Quinone derivatives as drug candidates" is a vital point of discussion as they have a unique property to bind to multiple targets with excellent affinity. They are electrophilically reactive and covalently bind to nucleophilic sites within cells through the formation of oxidized cellular macromolecules, including lipids, proteins, and DNA. Hence, we can consider it as a privileged moiety for potential pharmacological activities. Due to its high redox ability, semiquinone radical can construct ROS (reactive oxygen species). Quinones are cast-off for electron and proton transport (Co-enzymes/ Cofactors) and are extremely tunable and versatile in function. With regard to biological activities, quinones and their derivatives have been proclaimed as antitumor, antibacterial, antifungal, antiviral, antimalarial, anti-AD, and anti-epileptic agents. They have various mechanisms of action for biological activities, including ROS, GSH, NADPH, P450s, (COX-2), glutathione S-transferase (GST), (NQO1), DNA, *etc*., as receptors. If we collect quinone containing marketed drugs, we will get n-number. Some of them are Atovaquone, Flaviolin, buparvaquone, Seratrodast, doxorubicin, Emodin, mitomycins, Duroquinone, Mitoxantrone, Porfiromycin, Parvaquone, Valrubicin, *etc*. Quinones assist as indicators that transform in physical presence, hence used as dyes. The negative side of quinone is also an important point of discussion, such as toxicity profile (quinone toxicity can arise because of their use as well as by the metabolism of other drugs and various environmental toxins or dietary constituents). Quinones as drugs can also considered for organisms other than human beings, such as plants. Antifungal drugs include Chlonil, chlorothalonil, *etc*. Some napthoquinones (Duniones) have been marketed as insecticides, pesticides, *etc*. Some drug-like molecules containing quinones are under FDA approval, *viz* vatiquinone from PTC Therapeutics, which will be used against epilepsy. The modern trends of quinones are discussed as a concluding chapter of the book.

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CHAPTER 1

Importance of Quinones in Drug Discovery

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Abstract: Quinones, which are cyclic chemical molecules, have attracted considerable interest in the field of drug discovery because of their wide range of pharmacological effects and structural flexibility. This study examines the diverse functions of quinones in several therapeutic domains, encompassing their antioxidant, anti-diabetic, anti-inflammatory, anti-Alzheimer, and antibacterial properties. Having redox activity means that quinones can change important signalling pathways and create reactive oxygen species (ROS). This makes them effective against cancer cells and also protects against damage caused by oxidative stress. In preclinical studies, both natural and artificial quinone derivatives have publicised promising results. They act as antioxidants, getting rid of free radicals and stopping lipid peroxidation. Moreover, quinones have shown promise in the treatment of diabetes by blocking crucial enzymes and decreasing high blood sugar levels after meals. Quinones have anti-inflammatory properties because they are involved in the diminution of pro-inflammatory mediators and reduce oedema volume. Quinone derivatives have demonstrated reduction of β-amyloid aggregation, acetylcholinesterase activity, and monoamine oxidase in Alzheimer's disease research, suggesting them as possible multitarget-directed ligands for Alzheimer's disease treatment. Quinones also have antibacterial action against a variety of harmful microorganisms, indicating that they have the potential to tackle infectious disorders. Overall, quinones and their derivatives represent attractive possibilities for drug development across diverse therapeutic domains, emphasising their importance in advancing pharmaceutical research and solving unmet medical needs.

Keywords: Quinone, drug, drug discovery, disease.

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INTRODUCTION

The quest for novel therapeutic agents to address the myriads of human ailments necessitates exploration into diverse chemical classes. Quinones, owing to their unique structural attributes and pharmacological properties, have garnered considerable attention in drug discovery endeavours. Quinones exhibit a wide array of biological activities, making them versatile candidates for drug development [1, 2]. Quinones are capable of interacting with various cellular components, such as proteins and enzymes, due to their redox activity, thereby influencing essential signalling pathways. Furthermore, their ability to undergo redox cycling makes them effective generators of reactive oxygen species (ROS), which can induce cytotoxic effects in cancer cells. Additionally, quinones possess intrinsic antioxidant properties, enabling them to scavenge free radicals and alleviate oxidative stress-induced damage. This dual functionality of quinones, serving both as prooxidants and antioxidants, highlights their intricate role in cellular homeostasis and the pathogenesis of diseases [3]. It is well documented that quinone moiety in vitamins K_1 and K_2 is chiefly responsible for various biological activities [4]. Furthermore, quinones have been implicated in the inhibition of key enzymes involved in disease progression, such as topoisomerases and kinases, highlighting their potential as therapeutic agents. In addition to their direct pharmacological effects, quinones can also serve as versatile pharmacophores for drug discovery [5]. Quinones play multifaceted roles in cellular processes and pharmacology. Acting as electron carriers in cellular respiration and oxidative phosphorylation, they facilitate energy production. Additionally, quinones act as electrophiles, forming covalent bonds with nucleophilic residues in target proteins, a mechanism commonly exploited in designing enzyme inhibitors. Moreover, they participate in Michael addition reactions, enabling the conjugation of biologically active moieties to the quinone scaffold, thus imparting additional pharmacological properties. Beyond pharmacology, quinones are indispensable across scientific domains serving in electron transfer and photochemical processes with applications ranging from catalysts to energy storage [6]. Found abundantly in nature, sourced from plants, animals, bacteria, and fungi, they serve as building blocks for various technological advancements [7, 8]. In the pharmaceutical industry, quinone derivatives are crucial in drug development, offering promising pharmacological effects, including anticancer, antioxidant, antimicrobial, and anti-inflammatory activities. They form a major class of anticancer cytotoxins. One example is daunorubicin, which is antileukemic [9]. Additionally, in herbal medicine, quinone derivatives contribute to remedies for ailments, such as purgative (sennosides), antimicrobial and antiparasitic (rhein and saprorthoquinone, atovaquone), anti-tumor (emodin and juglone), and anti-cardiovascular disease (tanshinone), as well as in the inhibition of PGE2 biosynthesis (arnebinone and

arnebifuranone). Furthermore, the natural world offers intriguing discoveries, such as *Malbranchea cinnamomea*, a thermophilic fungus capable of producing quinone antibiotics, highlighting the potential for novel pharmaceutical interventions derived from these compounds [10].

Quinones and their derivatives are essential and adaptable compounds that have far-reaching implications across scientific fields. Their multifaceted characteristics, spanning from fundamental chemical processes to advanced medical applications, underscore their enduring significance in advancing knowledge and meeting societal needs. In drug discovery, their wide-ranging biological activities, redox capabilities, structural flexibility, and potential as pharmacophores offer promise for creating innovative therapies for diverse diseases, including cancer, infectious diseases, and neurodegenerative disorders. Consequently, quinones remain pivotal in shaping and innovating various disciplines, showcasing their profound influence on both science and society.

CHEMISTRY OF QUINONE

Quinones constitute a group of cyclic organic compounds featuring a six-membered unsaturated ring where two oxygen atoms are bonded as carbonyl groups [11]. Quinone-based compounds exhibit thermal stability due to their aromatic ring structure, which enables them to maintain their integrity under heat. These compounds display reactivity because of the electron-rich regions present within their molecular structure. Additionally, the inclusion of oxygen atoms as heteroatoms enhances their reactivity against disease-causing microorganisms. Their ring structure being electron-rich allows them to undergo electrophilic substitution reactions, while the ketonic carbonyl carbon's electron deficiency adds to their versatility. This dual nature makes quinones highly active and promising candidates for fighting various disease conditions. Moreover, their propensity to undergo tautomerization, transitioning between quinone and hydroquinone forms, contributes to their variability in properties and reactivity [12]. When quinones are combined with heteroatoms like nitrogen, halogens, or sulphur to create medicinal compounds, they tend to exhibit enhanced bioactivity compared to standard molecules. The presence of these heteroatomic groups on the quinone structure introduces electron-donating or electron-withdrawing effects through resonance and inductive effects. This alters the reactivity of the compound, consequently influencing its pharmacokinetics and pharmacodynamics [13]. According to the Hammett equation concept, these effects lead to qualitative and quantitative changes in the activity of the compounds. Such changes in activity are attributed to variations in the sigma and rho values of the additional groups present in the compound, as well as their positioning and stereochemistry [14].

CHAPTER 2

Chemistry and Synthesis of Quinones and their Derivatives

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Abstract: Quinones are a group of organic compounds that have a wide range of chemical properties and applications in various fields, such as pharmaceuticals, materials science, and organic synthesis. They are highly versatile and can be modified to produce derivatives with unique properties. This chapter presents a comprehensive and current overview of the chemistry and synthesis of quinones and their derivatives. It serves as an invaluable resource for chemists, researchers, and scientists who are interested in exploring the diverse aspects of this significant class of organic compounds.

Keywords: Derivatives of quinone, Synthesis of quinone, Quinone.

INTRODUCTION

Quinones are fascinating chemical structures composed of a nonaromatic ring and two carbonyl functional groups positioned at either the 1 & 2 or 1 & 4 relative to one another [1 - 4]. Quinones have garnered significant scientific attention since their fundamental structure was revealed in 1838 [5, 6].

Quinones have a crucial function in photosynthesis by carrying electrons. They are a type of molecule that works as vitamins and can help prevent and treat various illnesses, such as cardiovascular diseases and osteoporosis. Quinones can also enhance overall health conditions due to their antioxidant properties [7]. Several cancer-fighting drugs that have either been clinically approved or are

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Ashutosh Kumar Dash & Deepak Kumar (Eds.)

currently in clinical trials are made up of quinone-related compounds. Quinones, which can be produced from air pollutants, also have toxicological effects.

Quinones can activate rapid redox cycles, which enables them to form bonds with hydroxyl, thiol, and amine groups [8]. Furthermore, several quinones have anti-inflammatory [9, 10], anti-osteoarthritis [11], antibiotic [12], antimicrobial [13], antioxidant [14], and anticancer potential (Fig. **1**) [14-16]. While the exact mechanism by which they operate remains incompletely elucidated, speculation suggests that DNA is their primary target. Some proteins participate in alkylation or intercalation with DNA, while others catalyze double-strand DNA breaks and also serve in DNA cleavage through the actions of both DNA topoisomerase I and II [17].

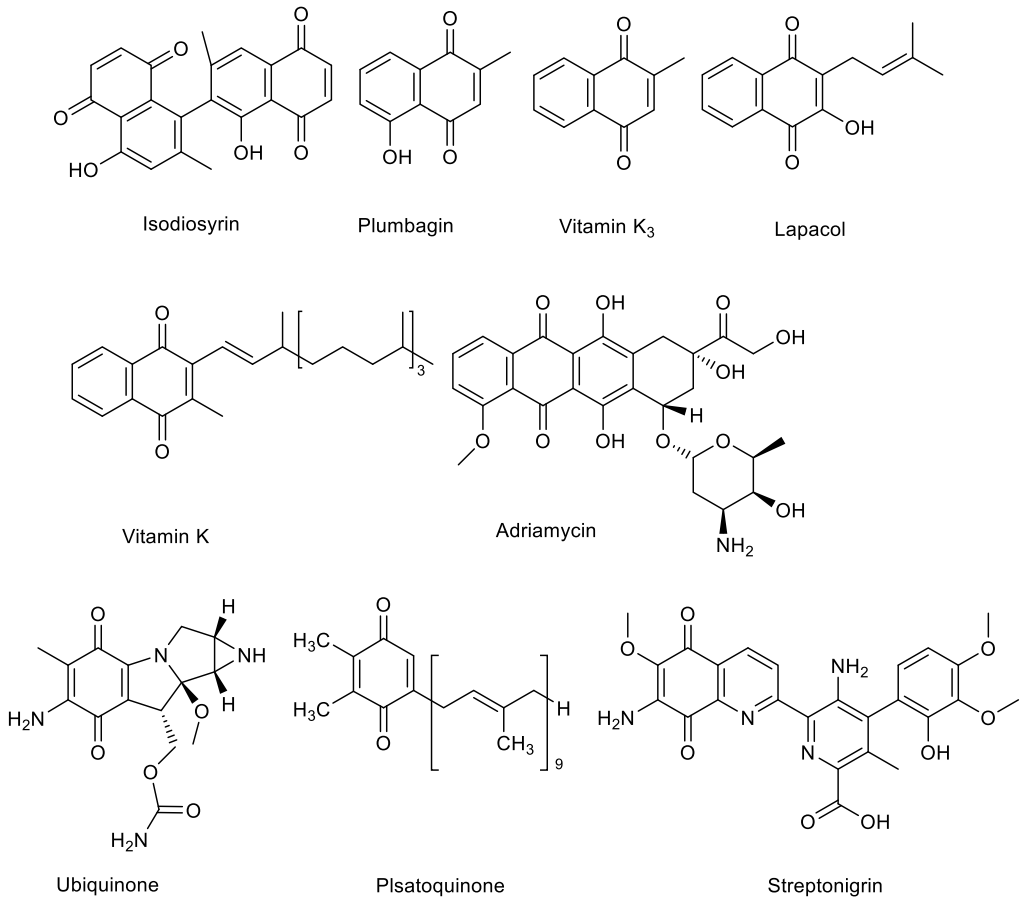

Fig. (1). Some naturally occurring quinone derivatives [25 - 27].

Quinones and their derivatives are essential in chemical, environmental, and pharmaceutical applications because of their distinct physical and chemical characteristics [18]. Quinones and their derivatives possess unique physical and chemical properties that make them essential for chemical, environmental, and pharmaceutical applications [19 - 21].

Furthermore, quinones serve as key components in the synthesis of functional materials, such as conducting polymers, organic dyes, and photoactive molecules, enabling applications in optoelectronics, photovoltaics, and sensor technologies [22]. Their redox chemistry has also been harnessed for energy storage devices, electrochemical sensors, and catalytic transformations, underscoring the multifaceted nature of quinone reactivity and its relevance to modern technological challenges [23, 24].

In this chapter, we explore the chemistry of quinones and their derivatives, underlying their reactivity, synthetic strategies for their preparation, and the myriad applications that exploit their unique properties. Through a comprehensive examination of quinone chemistry, we aim to illuminate the diverse facets of this fascinating class of compounds and highlight their enduring impact on science and technology.

Structure and Chemistry of Quinone

Quinones are colored compounds with a basic benzoquinone chromophore structure consisting of two carbonyl functional groups associated with two C=C bonds. Anthraquinones, benzoquinones, and naphthoquinones are the three primary classes of quinones, distinguished by their respective one, two, and three-ring structures. Benzoquinone is an essential component of quinones; specifically, 1,4-benzoquinone (4-benzoquinone) is a non-aromatic substance that may be readily reduced to produce hydroquinone [28]. Benzoquinone units play a crucial role as fundamental units in both the biosynthesis of biologically active chemicals and quinone synthesis. Anthraquinones are compounds characterized by the attachment of 1,4-benzoquinones to one or more C_6H_6 rings on a 2,3-carbon position. Two carbonyl groups are located at a single benzene ring in the naphthoquinone structure, usually in the ortho or para position [29, 30]. Naphthoquinones hold α- and β-unsaturated carbonyl functional groups. The electron delocalization facilitated by the presence of carbonyl groups and double bonds results in strong coloring in the visible spectrum. Anthraquinones, which belong to the third family of quinones, are molecules that consist of the anthracene nucleus and two carbonyl groups, often located on the B-ring. Due to the ability of quinone structures to accommodate various substitution patterns, there are several derivatives found in nature, particularly for anthraquinones.

CHAPTER 3

Identification Techniques of Natural and Synthetic Quinones Using Various Methods

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Abstract: Quinones are intriguing substances with distinctive properties and several significant biological and chemical functions and applications. Quinones are found in many parts of nature, including the tissues of plants and animals. They have several important roles in biological systems, for example, in the electron transport process to preserve plants' and animals' biological processes, in the form of plastoquinone and phylloquinone to be a part of photosynthesis in plants, and in the posttranslational modification of proteins and others. On essentiality grounds, they need to be detected and determined from the natural and synthetic samples. This chapter incorporates the detection and determination methods for various natural and synthetic quinones, viz., titrimetric methods, spectrophotometric methods, HPLC-based methods, and GC-M--based methods.

Keywords: GC-MS, HPLC, Titrimetric methods, Quinones.

INTRODUCTION

A special class of chemical molecules known as quinones is generated from aromatic compounds such as naphthalene or benzene. Quinones are composed of two carbonyl bonds formed when two oxygen atoms are replaced by two hydrogen atoms in a six-membered core benzene ring [1]. Quinones are a class of biological pigments that are present in many different types of living things, including fungi, bacteria, higher plants, and a few mammals [2]. They can be found in nature in a variety of forms, including polycyclic quinones, benzoquinones, naphthoquinones, and anthraquinones. Quinones have displayed multiple applications, including biological (antibacterial, anticancer, antimalarial, antioxidant, and anti-inflammatory properties) [3]. They are used as natural colorants in the fabric industry as they exert antifungal, anti-insecticide, anti-

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bacterial, and anti-UV properties to the fabric, particularly for the textile industry [2]. Their low cost, sustainability, and strong environmental stability make them an attractive material for supercapacitors [4]. They are used as an oxidant in several organic oxidations in the form of *p*-quinone oxidations (DDQ and chloranil for hydride abstraction) [5]. They also have biological functions (oxidative phosphorylation [6], electron transport, and bioenergetic transport processes) [7] and are used as cathodic materials for lithium-ion batteries as their ability to undergo reversible self-redox reaction makes them indispensable for efficient energy storage [8].

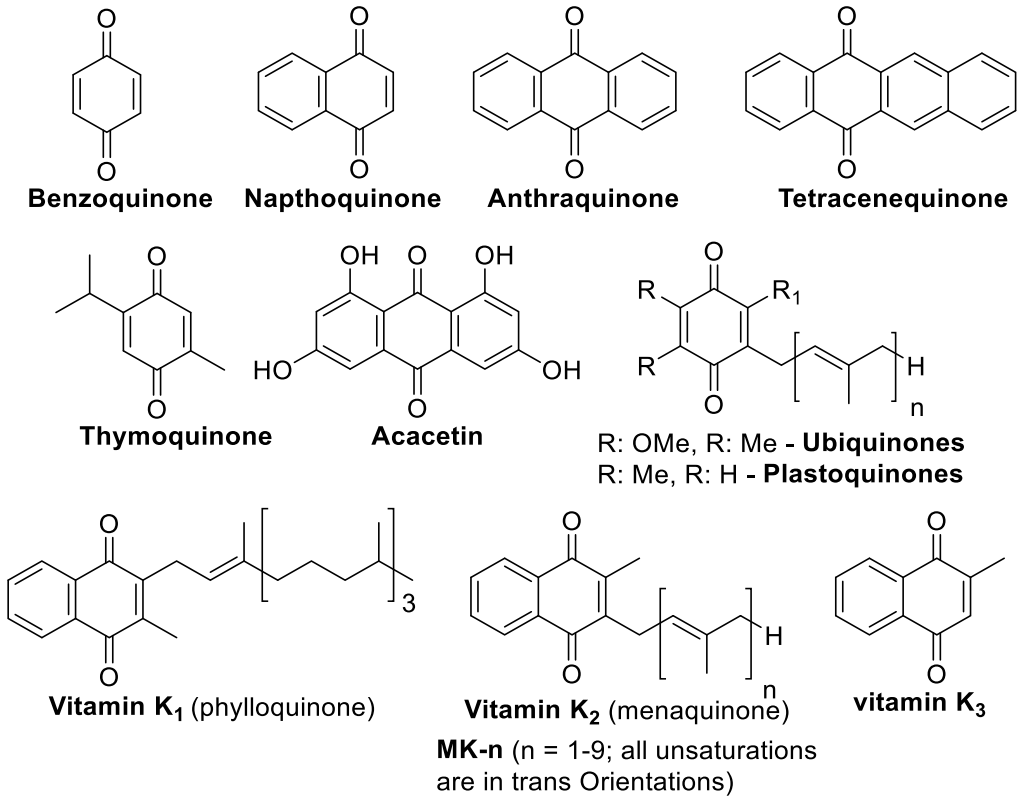

Fig. (1). Different quinone structures.

THE BIOLOGICAL, SYNTHETIC, AND INDUSTRIAL IMPORTANCE OF QUINONES

The quinones are one of the important classes of natural molecules with a variety of useful applications in biological systems. Almost all types of aerobic species, including bacteria, higher plants, and animals, contain ubiquinones (n = 1–12). They are present in mitochondria and play a major role in the electron transport

mechanism in the respiratory chain [9]. On the other hand, chloroplasts of green plants encompass plastoquinones (plastoquinone; n=9), which are generally involved in electron transport pathways during photosynthesis [10]. In addition, vitamin K consists of a structurally related class of 2-methyl-1,4-naphthoquinone derivatives with the side chains containing either isoprenoid units (menaquinones (MKs), vitamin K_2) or a side chain containing phytyl unit (phylloquinone; vitamin K_1) [11]. It was previously established that vitamin K is advantageous for bone formation, metabolism, and blood coagulation [12]. Additionally, vitamin K displays imperative clinical applications like treating osteoporosis, arterial calcification [13], and vitamin K insufficiency. There are other anthraquinone molecules, for example, doxorubicin (DXR) antibiotic, which have been utilized in the clinical treatment of malignant tumors [14]. Rhein (the main active ingredient in rhubarb, a traditional Chinese herb) is an immunosuppressive and anti-inflammatory molecule [15].

Adversely, quinones have also been considered a class of toxins that can have a wide range of harmful effects on living cells; for instance, they produce reactive oxygen species (ROS) in biological systems through their redox cycle, initiating several types of oxidative damage; for example, to DNA, proteins, and others [16, 17]. Moreover, the atmosphere contains polycyclic aromatic hydrocarbon quinones (PAHQ), as it is believed that the photo-oxidation of polycyclic aromatic hydrocarbons takes place, which are generally discharged by motor vehicle engines into the environment. These PAHQs cause the pathogenesis of respiratory diseases [18].

Apart from the wide spectrum of biological interests, quinones and their derivatives have beenproven to exhibit extensive applications in diverse fields owing to their special chemical characteristics. Quinone has been employed as a dienophile in a stream of Diels-Alder reactions [19] as Michael donors/acceptors and 1,3-dipolarophiles [20] for decades and used in the synthesis of several natural products and stereo-selective complex molecules. In addition, ortho-quinone methides are imperative synthetic intermediates and used in enantioselective nucleophilic addition reactions [21]. As quinones have an additional nature to undergo reversible reduction and oxidation reactions, they are essential for effective energy storage devices and battery making [22]. Anaquinone, 1,4-naphthoquinone (NQ), and 1,4-benzoquinone are important organic cathodes thathave already been used in a number of metal-organic systems, and they are capable materials for the making of multivalent batteries such as Li, Na, K, Mg, Al, and others [23].

CHAPTER 4

Quinone in Traditional Therapy and Nutraceutical Use

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Abstract: Quinones are a distinct group in chemistry, having a wide range of chemical and biological properties. These are extensively cast off as traditional medicines, such as anticancer, anti-inflammatory, antibacterial, *etc*. Plants such as Henna, Rhubarb, and Aloe vera possess quinones as active ingredients, which developed diverse medicinal possessions. Traditional uses and nutraceutical ethics have been enriched owing to the molecule. The biological application of quinones is discussed.

Keywords: Biological use, Nutraceuticals, Traditional use, Quinone.

INTRODUCTION

Quinones are a prominent class of organic compounds that hold significant importance in a multitude of biological processes. They are characterized by their fully conjugated cyclic dione structure, which consists of a ring system with two ketone (carbonyl) groups. This unique structure allows quinones to participate in various redox reactions, making them essential in biochemical pathways [1]. Quinones are naturally abundant, especially in the plant kingdom, where they play critical roles in photosynthesis, respiration, and defense mechanisms.

Historically, quinones have been utilized in traditional medicine for centuries. Their presence in medicinal plants has been exploited for their therapeutic properties long before the advent of modern pharmaceuticals. For example, quinones like coenzyme Q10 are vital for cellular energy production, while others, such as vitamin K, are crucial for blood clotting processes [2].

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In recent years, the scientific community has shown a growing interest in the potential of quinones as nutraceuticals. These compounds are widely distributed

in nature and found in various plants, fungi, bacteria, and marine organisms. The natural occurrence and biological significance of quinones make them valuable candidates for nutraceutical applications, offering potential health benefits beyond basic nutrition [3]. Nutraceuticals are food-derived products that offer health benefits beyond basic nutrition. The interest in quinones is largely due to their impressive range of bioactive properties, including antioxidant, anti-inflammatory, and anticancer activities. Ongoing research and development are essential to fully understand their mechanisms of action, optimize their bioavailability, and integrate them effectively into nutraceutical products. As science continues to uncover the therapeutic potential of quinones, their role in promoting health and preventing disease is likely to expand, making them an exciting area of focus in the nutraceutical industry [4].

ANTIOXIDANT PROPERTIES

Quinones are renowned for their ability to neutralize free radicals, thereby preventing oxidative stress and cellular damage and protecting biological systems from damage. This antioxidant property is particularly crucial in defending cells from the harmful effects of reactive oxygen species (ROS), which are linked to aging and various chronic diseases [5]. Quinones can substitute between their oxidized (quinone) and reduced (hydroquinone or semiquinone) forms. This redox cycling allows quinones to act as electron acceptors and donors, neutralizing ROS and preventing oxidative damage to cellular components. Quinones can directly scavenge free radicals, such as superoxide anions, hydroxyl radicals, and peroxyl radicals [6]. By donating electrons or hydrogen atoms, quinones neutralize these reactive species, reducing their potential to cause cellular damage. Some quinones can chelate transition metals like iron and copper, which are catalysts in the formation of highly reactive hydroxyl radicals *via* the Fenton reaction. By binding these metals, quinones prevent the catalysis of ROS production. The ability of quinones to undergo redox cycling, scavenge free radicals, and chelate metals underpins their effectiveness as antioxidants.

ANTI-INFLAMMATORY EFFECTS

Inflammation is a biological response to harmful stimuli, but chronic inflammation can lead to various health issues, including autoimmune diseases and cancer. Quinones have been found to exhibit anti-inflammatory effects by modulating pathways that reduce inflammation and inhibit the production of pro-inflammatory cytokines. Quinones can suppress the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins

(IL-1β, IL-6), and interferon-gamma (IFN-γ) [7, 8]. This inhibition helps reduce the overall inflammatory response. NF-κB is a key transcription factor that regulates the expression of various inflammatory genes. Quinones can inhibit the activation of NF-κB, thereby reducing the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules [9]. Quinones can inhibit the activity of COX and LOX enzymes, which are involved in the synthesis of pro-inflammatory eicosanoids such as prostaglandins and leukotrienes [10]. This suppression leads to reduced inflammation and pain. The nuclear factor erythroid 2–related factor 2 (Nrf2) pathway plays a critical role in the cellular antioxidant response. Quinones can activate Nrf2, leading to the upregulation of antioxidant enzymes and suppression of inflammation. Quinones can affect the MAPK signaling pathways, which are involved in the regulation of inflammatory responses [11]. By modulating these pathways, quinones help in reducing the expression of inflammatory mediators. Their ability to modulate key inflammatory pathways, such as NF-κB, COX, LOX, Nrf2, and MAPK, underpins their effectiveness as anti-inflammatory agents.

ANTICANCER POTENTIAL

The anticancer properties of quinones are among the most promising. They can induce apoptosis (programmed cell death) in cancer cells, inhibit cell proliferation, and interfere with tumor growth and metastasis. These effects are mediated through various mechanisms, including the generation of ROS to selectively target cancer cells and the inhibition of key signaling pathways involved in cancer progression. Due to these multifaceted properties, quinones are being extensively studied for their potential applications in health and medicine. Their role as antioxidants, anti-inflammatory agents, and anticancer compounds highlights their importance in the development of new therapeutic strategies and health supplements [12, 13]. As research continues to uncover the diverse benefits of quinones, their incorporation into modern healthcare and nutraceutical products is likely to expand, offering new avenues for enhancing human health and well-being. Some quinones can intercalate into the DNA double helix, disrupting the DNA structure and interfering with DNA replication and transcription. Certain quinones can form covalent bonds with DNA, causing DNA alkylation. This can lead to DNA cross-linking and strand breaks, further inhibiting DNA synthesis and triggering cell death mechanisms. Topoisomerases are enzymes that regulate the overwinding or underwinding of DNA during replication and transcription [14, 15]. Quinones, such as anthraquinones like doxorubicin, can inhibit topoisomerase II, preventing the enzyme from re-ligating DNA strands after they have been cut. This inhibition results in the accumulation of DNA breaks, leading to apoptosis [16]. Quinones can modulate the cellular redox balance by interacting with cellular thiols and other antioxidant systems. This disruption can deplete

CHAPTER 5

Efficient Synthesis of Quinone-Based Glycohybrids

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Abstract: Quinones are redox-active cyclic chemical compounds with two carbonyl groups in a six-membered ring structure, either contiguous or apart. Quinones are a diverse group of natural compounds that have gained attention for their pharmacological properties. This book chapter focuses on the design and synthesis of natural product-inspired quinone-based glycohybrids. Glycohybrids can have a broad variety of structural and functional properties, including protein-carbohydrate interactions that are essential for the biology of mammals and some disease states. These glycohybrids are designed based on the structures of bioactive aryl glycosides and quinones, aiming to enhance their binding affinity, enhanced bioavailability, high water solubility, low toxicity, and specificity toward cancer-related protein targets. This book chapter consistsof the literature from January 2017 to December 2023 and provides an overview of recent developments in the chemical synthesis of glycohybrids based on natural product scaffold of quinones.

Keywords: 1,4-naphthoquinone, Anticancer, Antiradical, Click chemistry glycohybrids, Cytotoxicity, Glycohybrids, Natural products, Synthetic methods, Quinone.

INTRODUCTION

Quinones are colored substances containing a basic benzoquinone chromophore composed of two carbonyl groups joined by two carbon-carbon double bonds. The quinone dyes are composed of fused benzenoid quinoid ring complexes that have enough conjugation to provide color. The three primary classes of quinones are benzoquinones (**A)**, benzoquinones (**B),** and anthraquinones (**C),** which have 1, 2, and 3-ring structures, respectively, as shown in (Fig. **1**). The fundamental building block of quinone molecules is benzoquinone [1]. Chemically, 1,4-benzoquinone, commonly known as para-benzoquinone, is a non-aromatic substance that reduces readily to hydroquinone [2]. Benzoquinone units are

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essential moieties to produce biologically active chemicals and act as building blocks in quinone synthesis [1].

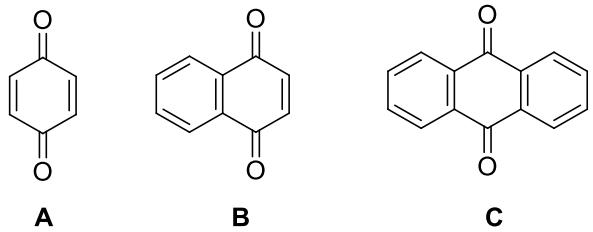

Fig. (1). Chemical structure of benzoquinone **A**, naphthoquinone **B,** and anthraquinone **C**.

Naphthoquinones are compounds that have para-benzoquinones bound to an additional benzene ring at position 2,3-C (carbon). Two carbonyl groups are present on one benzene ring in the naphthoquinone structure (Fig. **1b**), usually in the o- or p-orientation [3]. Naphthoquinones also have α- and β-unsaturated carbonyls. The visible region exhibits significant coloration due to extended electron delocalization across carbonyl groups and double bonds [4].

Nature is full of naphthoquinones [5, 6], which are typically found as glycosides that may be separated from bacteria, fungi, plants, and marine invertebrates [7, 8]. The pharmacological activity [9 - 11] and diverse synthesis techniques of naphthoquinones, including their anticancer, antibacterial, antifungal, and anti-inflammatory properties, have been documented in recent years [12 - 14]. The solubility and activity of naphthoquinones will increase as they convert to naphthoquinone glycosides, and new activity may even develop, offering a new method for obtaining novel compounds with a range of biological activities [15 - 17]. According to reports, the anticancer activities of 1,4-naphthoquinone could be enhanced by the inclusion of acetylated D-glucose and D-galactose residues [18a-b]. One example of this would be the acetylated glycosides of lapachol [19]. Thus, the synthesis of 1,4-naphthoquinone glycosides is a powerful approach to finding novel compounds with strong biological activity [20].

The third class of quinones, known as anthraquinones, are compounds containing the anthracene nucleus with two carbonyl groups. They are derived from the tricyclic aromatic chemical molecule 9,10-dioxoanthracene ($C_{14}H_8O_2$) (Fig. **1**), which has a fundamental structure. Anthraquinones are found in fungi, lichens, and plants. Hydroxyanthraquinoids absorb visible light and are therefore colored. Alizarin is a prominent red dye used in the fabric industry. It has anthraquinone moiety.

There are hundreds of derivatives in nature due to quinone structures' ability to accommodate various substitution sequences, particularly for anthraquinones. A

quinone compound's color is often determined by the location, kind, and quantity of hydroxyl and electron-donating/accepting elements, commonly known as auxochromes, as well as by the many rings that affect steric effects and intramolecular hydrogen bonding.

Quinones are important secondary metabolites that play a crucial role in photosynthesis and respiration processes in plants. These activities include electron transport and oxidative phosphorylation. These substances frequently serve as mediators between a plant and its surroundings and oversee energy transduction, color, signaling, defense, scent, and favor. Some of the natural quinone components with antifungal, antibacterial, antioxidant, anti-cancer, anti-inflammatory, laxative, and anti-allergen properties have been employed in pharmacology to cause cytoprotection in humans [21-23a-b].

It is known that glycohybrids are an important class of molecules that exhibit diverse biological activities and are present as structural motifs in many natural products. Glycohybrid structures are formed by linking/connecting heterocyclic rings or hydrocarbon chains and carbohydrate moieties with biologically relevant molecules without changing their initial structure much. These molecules are known as glycohybrids [24a-b]. Linking or merging carbohydrates with bioactive molecules provides a viable source for chemical libraries in drug discovery and development [25]. The glycosylation of bioactive molecules of both synthetic and natural origin most often improves the pharmacological properties and ADMET parameters of the drug. Thus glycoconjugation has emerged as one of the most effective approaches for targeting cancerous cells by linking or merging the pharmacophoric moiety to the glycosyl/carbohydrate unit [25].

Glycohybrid molecules are used in the creation of pharmaceuticals due to their biological activity, high diversity, improved pharmacokinetic and pharmacodynamic properties [26, 27], molecular recognition, intracellular functions, enhanced bioavailability, high water solubility, and low toxicity [28, 29].

Numerous medicinal chemists worldwide have combined organic molecules quinone with carbohydrates, resulting in the production of novel glycohybrids (**D-I**), as shown in (Fig. **2**), with varying structural and functional features [30, 31]. These innovative glycohybrids may exhibit enhanced biological activity or prove to be more efficient, safe, and affordable as potential pharmaceutical candidates. On the basis of these innovations, we have chosen to review and investigate the literature about the recently reported synthesis of quinone-based glycohybrids and their related biological activities. These recent literature reports covering the years 2017-2023 are presented here in this book chapter.

CHAPTER 6

Pharmacodynamics of Quinones and their Derivatives

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Abstract: Quinones and their derivatives are a diverse group of compounds with significant pharmacological potential rooted in their unique redox properties and ability to interact with various biomolecules. This chapter explores the pharmacodynamics of quinones, highlighting their mechanisms of action, including electron transfer, generation of reactive oxygen species (ROS), and interactions with DNA, proteins, and lipids. These mechanisms underpin their therapeutic applications in oncology, antibacterial and antifungal treatments, antiviral therapies, and other medical areas such as anti-inflammatory and neuroprotective interventions. Despite their promise, the development of quinone-based drugs is challenged by issues of stability, solubility, and toxicity. Advances in drug delivery systems, such as nanoparticles and liposomes, and the creation of novel quinone derivatives are critical to overcoming these obstacles. Moreover, the potential for personalized medicine, leveraging genetic profiling and biomarkers, represents a transformative approach to optimizing quinone therapies. The chapter also addresses the current regulatory and safety considerations in quinone drug development and highlights future research directions, including combination therapies and the use of artificial intelligence in drug discovery. Overall, while challenges remain, ongoing innovations and research efforts are poised to enhance the therapeutic efficacy and safety of quinone-based drugs, unlocking their full potential in modern medicine.

Keywords: Anticancer therapy, Drug delivery systems, Pharmacodynamics, Personalized medicine, Reactive oxygen species, Quinones.

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INTRODUCTION

Quinones are a class of organic compounds that are characterized by a fully conjugated cyclic dione structure. Structurally, quinones are derived from aromatic compounds like benzene, naphthalene, or anthracene, where two hydrogen atoms on the ring are replaced by oxygen atoms, creating a system of alternating double bonds. This conjugated system is responsible for the distinctive chemical properties and reactivity of quinones. The general formula for quinones can be represented as $C_6H_4O_2$ for benzoquinones, but this can vary based on the type and complexity of the parent aromatic system [1].

Quinones are known for their ability to participate in redox reactions, which is a key feature underlying their biological and pharmacological activities. The redox cycling of quinones involves the reversible reduction of quinones to hydroquinones (quinols), which can then be reoxidized back to quinones. This redox activity allows quinones to participate in various biochemical processes, including electron transport chains and redox signaling pathways.

The aromaticity of quinones also contributes to their chemical stability and reactivity. The delocalized π-electron system across the conjugated dione structure makes quinones relatively stable compounds yet reactive enough to interact with biological molecules and participate in electron transfer reactions.

Quinones are naturally occurring in many plants, fungi, and bacteria. They are often involved in pigmentation (*e.g.*, anthraquinones in madder root), defense mechanisms (*e.g.*, juglone in walnut trees), and cellular respiration (*e.g.*, ubiquinones in the mitochondrial electron transport chain).

In synthetic chemistry, quinones are typically produced through the oxidation of phenols or anilines. For example, the industrial production of benzoquinone often involves the oxidation of hydroquinone (1,4-dihydroxybenzene) using oxidizing agents like hydrogen peroxide or ferric chloride.

Quinones play crucial roles in various biological processes. One of the most well-known quinones, ubiquinone (coenzyme Q), is vital for the electron transport chain and ATP synthesis in mitochondria. Vitamin K, another important quinone, is essential for blood clotting and bone health. The redox properties of quinones enable them to function as electron carriers in biological systems.

Pharmacologically, quinones and their derivatives exhibit a range of activities, including anticancer, antimicrobial, anti-inflammatory, and antioxidant effects. Their ability to generate reactive oxygen species (ROS) through redox cycling

makes them useful in targeting cancer cells, which are often more susceptible to oxidative stress than normal cells [2, 3].

HISTORICAL BACKGROUND AND DISCOVERY

The discovery and study of quinones date back to the early 19th century. The first quinone, benzoquinone, was identified by Carl Wilhelm Scheele in 1786. However, it was not until the 1830s that Friedrich Wohler and Justus von Liebig elucidated the structure of quinones through their pioneering work in organic chemistry. Their research laid the foundation for understanding the chemical properties and reactivity of quinones, leading to the synthesis of numerous quinone derivatives and the exploration of their applications in various fields [4].

SIGNIFICANCE IN PHARMACOLOGY AND MEDICINE

Quinones and their derivatives have significant importance in pharmacology and medicine due to their wide range of biological activities. They exhibit various pharmacodynamic properties, including antimicrobial, anticancer, anti-inflammatory, and antioxidant effects. The biological activity of quinones is primarily attributed to their ability to undergo redox cycling, generating reactive oxygen species (ROS) that can induce oxidative stress and modulate cellular signaling pathways. This unique redox behavior makes quinones promising candidates for therapeutic applications in treating diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions.

Furthermore, quinones are integral components of several vital biochemical processes. For instance, ubiquinone (coenzyme Q) plays a crucial role in the electron transport chain and ATP synthesis in cellular respiration. Similarly, vitamin K, a naphthoquinone derivative, is essential for blood coagulation and bone metabolism. The diverse pharmacological potential and therapeutic applications of quinones underscore their significance in modern medicine and ongoing biomedical research [5].

CHEMICAL STRUCTURE AND CLASSIFICATION

Basic Chemical Structure of Quinones

Quinones are characterized by a fully conjugated cyclic dione structure, typically involving an aromatic ring system where two carbonyl groups (C=O) replace two hydrogen atoms. This conjugation creates a system of alternating double bonds, giving quinones their distinctive reactivity and stability. The simplest quinone, benzoquinone, has the formula $C_6H_4O_2$, with the general structure for quinones

CHAPTER 7

Synthetic and Natural Quinones as Drug Candidates

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Abstract: Quinones are a group of organic compounds that have a wide range of chemical properties and applications in various fields, such as pharmaceuticals, materials science, and organic synthesis. They are highly versatile and can be modified to produce derivatives with unique properties. This chapter presents a comprehensive and current overview of the chemistry and synthesis of quinones and their derivatives. It serves as an invaluable resource for chemists, researchers, and scientists who are interested in exploring the diverse aspects of this significant class of organic compounds.

Keywords: Mitochondrial activity, Natural naphthoquinones, Oxidative stress, Parkinson's disease, Ubiquinone.

INTRODUCTION

Quinones are a substantial class of naturally occurring intramolecular unsaturated cyclic diketone structures. Synthetically, they can be easily changed into similar structural scaffolds with a wide range of applications. It is well known that they play a crucial function in the biochemistry of living cells [1]. The main structural subtypes of natural quinones are benzoquinone, naphthoquinone, anthraquinone, and phenanthroquinone. Additionally, benzoquinone is further subdivided into o-benzoquinone and p-benzoquinone. However, because of the structural instability of o-benzoquinone, the majority of naturally occurring benzoquinones are derivatives of p-benzoquinone [2]. In addition to these physiological roles, quinones are formed by oxidative metabolism in various xenobiotics. Both a benzoquinoneimine metabolite generated by a cytochrome P450-dependent oxidase reaction and simple p-benzoquinone synthesized from the hydrolysis of

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the benzoquinoneimine metabolite are responsible for the severe hepatotoxicity that can occur from an overdose of the analgetic paracetamol. Quinones are a unique class of naturally occurring secondary metabolites with anticancercharacteristics. A common anthracycline antibiotic used in clinics to treat cancer is doxorubicin. Its 4-membered ring system comprises aminoglycoside, anthraquinone, and chromophore [3]. It is a first-line chemotherapy for breast cancer and is regarded as one of the most potent cancer medications on the market. Even though anthracycline antibiotics are often used in clinical settings, their usage is restricted due to their major adverse effects on healthy tissues and the emergence of drug resistance in cancer cells. The two most significant side effects of anthracycline chemotherapy are neurotoxicity and cardiotoxicity. As quinone derivatives have a structural resemblance to the anthracycline antibiotics that are already utilized in clinical practice, they may be extremely valuable in terms of their potential anticancer characteristics [4]. Additionally, as quinones are found in natural sources and are secondary metabolites, we should take into account the potential that their natural origin makes them relatively safe. For example, several species within several plant groups include structural similarities of naturally occurring quinones. These include the following: Liliaceae (species of Aloe, *etc*.), Hypericaceae (species of Hypericum, *etc*.), Polygonaceae (species of Rheum, Rumex, Polygonum, *etc*.), Rhamnaceae (species of Rhamnus, *etc*.), Rubiaceae (species of Rubia, Galium, *etc*.), Caeselpinaceae (species of Cassia, *etc*.), Boraginaceae (Alkanna, Arnebia spec., *etc*.), and Julienndaceae (species of Juliens, *etc*.) [5]. Plants belonging to the families Polygonaceae, Rubiaceae, and Leguminosae have been identified as containing anthraquinones. Examples of these species include *Rheum palmatum* L., *Rubia cordifolia* L., *Polygoni multiflori*, *Polygonum cuspidatum*, and *Semen cassiae*. Furthermore, 200 of the approximately 700 distinct anthraquinone derivatives that have been identified are found in plants. The general classification of anthraquinones is into anthraquinone monomers, which are further separated into hydroxy anthraquinones, anthranones and anthranols, and bianthraquinones based on the mother nucleus' structure. Studies have shown that the anthracene nucleus serves as the primary structural component of many anticancer medications and that the activity of this nucleus is significantly influenced by a phenolic hydroxyl group. Anthraquinone monomers like emodin, aloe-emodin, rhein, chrysophanol, and physcion receive more attention. But, hypericin, a bianthraquinone variety, is also well-known for its beneficial pharmacological properties, which include anti-depressant, anti-cancer, and anti-viral properties [6].

NATURAL NAPHTHOQUINONES

Natural naphthoquinones, typically in the form of botanical extracts, have been connected to human existence since prehistoric times, far before they were isolated and identified in the present age. Natural quinones, a diverse class of organic compounds found in plants, fungi, and some marine organisms, have gained enormous attention as potential drug candidates due to their various biological activities. Quinones exhibit various pharmacological properties, including antioxidant, anticancer, antimicrobial, anti-inflammatory, and antiparasitic activities [7]. Furthermore, many quinones, such as the naphthoquinones Plumbagin from *Plumbago rosea* and Juglone from *Juglans nigra*, show growth-inhibitory effects on bacteria or fungus and are employed by plants as defensive compounds [8]. Naphthoquinones, such as Shikonin and Plumbagin, are the primary efficacious molecules in some commonly used medical herbals, particularly those that have antibacterial, insecticidal, antiphlogistic, and wound-healing properties [9]. Thymoquinone (2-isopropyl-5-methylbenzo-1,4-quinone) is a benzoquinone molecule widely distributed in the volatile oil portion of *Nigella sativa* seed [10]. Sargaquinoic acid, a hydroquinone acid isolated from *Sargassum siliquastrum,* has anti-inflammatory properties and impedes macrophages' ability to produce nitric oxide by interfering with LPS-induced signaling. Sargaquinoic acid prevented LPS-stimulated RAW264.7 macrophages from producing NO and from expressing the iNOS protein [11]. The adherence of monocytes to TNF-α-induced adhesion was inhibited by sargaquinoic acid. Additionally, by stopping the proteolytic degradation of inhibitor κB-α, SQA prevented TNF-α-induced nuclear factor kappa B (NF-κB) from translocating into the nucleus. Overall, SQA inhibits the NF-κB pathway in HUVECs to prevent vascular inflammation caused by TNF-α [12]. Throughout their lengthy history of use, naphthoquinones have seen a change in use from their early uses as dyes and decorations to their current use as therapeutic compounds [13]. To date, much research has been done to clarify the pharmacological profile of synthetic and natural naphthoquinones. Naphthoquinones are derivatives of naphthalene with two carbonyl oxygen atoms in their structure. Although there are theoretically multiple naphthoquinone isoforms, 1,4-naphthoquinone is the most stable and well-reported one [14]. Many effective analogs, such as simple modified naphthoquinones like Lawsone, Shikonin, Juglone, Plumbagin, and Menadione, have been found based on this scaffold [15]. Additionally, the chemical space renders naphthoquinones stable ligands for a variety of pathologic targets, and in certain circumstances, naphthoquinones may be the preferred chemotype for the development of novel inhibitors.

CHAPTER 8

Understanding Quinones with Reference to Biochemistry

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Abstract: Quinones are a highly flexible group of organic molecules that are naturally present in a diverse range of organisms, such as plants, algae, bacteria, and fungi. These chemicals are also artificially produced in laboratories for diverse purposes. Quinones possess a distinctive chemical structure that allows them to get involved in redox cycling. This means they can easily switch between oxidized and reduced states, a property that underlies many of their biological and pharmacological functions. They have a crucial function in the electron transport chain in both cellular respiration and photosynthesis. They help transmit electrons, which is essential for energy production in cells. Quinones play a crucial role in cellular signaling pathways and defense mechanisms against oxidative stress due to their capacity to perform redox reactions. Quinones possess a diverse array of pharmacological properties, making them highly valuable in the field of medicine. One of the most important uses of these is in the field of anticancer treatments. Quinone-derived chemicals serve as the foundation for some of the most extensive and potent categories of anticancer medications. Their cytotoxic qualities, which allow them to cause cell death in cancer cells, are utilized in treatments for different types of malignancies. Quinones can be classified into several broad categories, including anthraquinones, benzoquinones, phenanthraquinones, and naphthoquinones. These categories consist of a wide range of molecules that have unique chemical structures and biological properties. These classes constitute the fundamental components of numerous natural and synthetic products utilized across multiple industries.

Keywords: Anticancer properties, Novel drug, Oxidative stress, Pharmacological properties, Quinones, Redox reaction.

INTRODUCTION

Quinones are a group of chemical compounds representing a subclass of the quinoid family characterized by conjugated cyclic dione (–CH= groups converted

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to –> –C (=O)– groups) structures and consisting of quinonimines and quinomethanes (Fig. **1**). This chemical group is mostly formed from reactive aromatic compounds like catechols or phenols. Their presence has been determined not only in natural products and biochemicals but also in pharmaceuticals and are requisite compounds having an extensive range of bioactivities [1, 2]. Since quinones represent the group of both naturally existing and synthetically prepared chemicals and are known to exhibit an extensive range of bioactivities such as antitumor, anti-bacterial, anti-cancer, and anticoagulant properties, they are widely applicable for medicinal and industrial purposes [3]. However, DNA is the main target of quinoid antitumor drugs, which contain the structure cyclohexadienedione. It is highly abundant and may be found in endogenous biochemicals, natural products, and environmental pollutants; these agents are alkylating and DNA intercalating agents. Secondly, quinoid chemicals have been demonstrated to target other cellular components, which include heat shock protein (HSP) 90 and telomerase [4, 5]. Examples of some compounds are aziridinylquinones (mitomycin C and Diaziridinyl-benzoquione) [6], naphthoquinones (vitamin K1, phylloquinone) [7], anthracyclines (Daunorubicin, Doxorubicin) [8], aminoquinones (such as streptonigrins), indolequinones (such as mitomycins), and certain vitamins that induce the production of hydrogen peroxide (H_2O_2) in tumor cells *via* redox cycling mechanism and autoxidation reaction to show anticancer activity [9] (Fig. (**2**). The isolation of quinone has been a research topic of global interest in recent times. ^{13}C nuclear magnetic resonance (NMR) spectroscopy is used in the analysis of the intersections of nature-derived quinones. Gathered data from past publications from 2000 to 2022 showed that out of 137 compounds, 70 were newly described [10]. From the biochemistry aspect, the quinones are important reduction-oxidation mediators for numerous electron-transfer chain (ETC) pathways in living systems and, as such, are crucial to countless enzymatic and physiological functional systems such as ubiquinone and plastoquinone and various naturally occurring quinones [11].

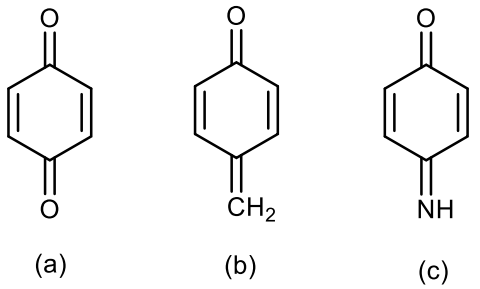

Fig. (1). Simplified structure of quinoids: a) *p*- Benzoquinone b) *p*- Benzoquinone methide c) *p*- Benzoquinone imine.

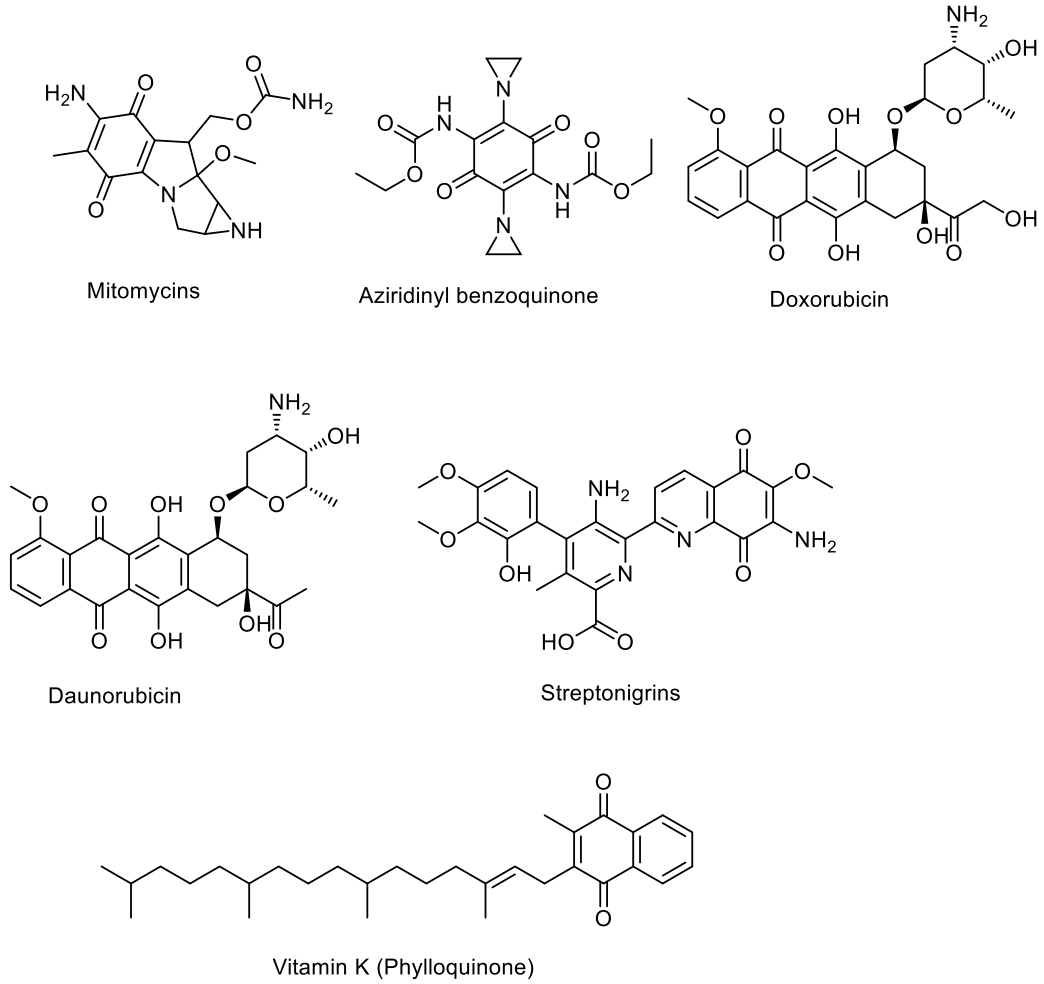

Fig. (2). Diagrammatical illustration of the 2D structure of the different compounds containing quinones moiety.

ISOLATION AND CHARACTERIZATION OF QUINONES

Natural quinones are derived from henna and juglone (walnuts) as well as from various sources such as microorganisms and animals. They are categorized based on the aromatic system in which they are found. The four primary groups of quinones are benzoquinones, naphthoquinones, anthraquinones, and phenanthraquinones, which encompass the majority of known compounds (Table **1**). The subclassification of quinone is shown in Table **2** [10]. Quinone derivatives are often obtained through the process of maceration, percolation, or a mixture of both methods. Before applying these approaches, it is crucial to understand the characteristics of the dissolving solvents (polar or non-polar) to be utilized as they

CHAPTER 9

Quinone Compounds in Medicine: A Biological Perspective

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Abstract: Quinone compounds are versatile molecules with significant biological importance and have therapeutic potential in medicine. This chapter provides a comprehensive overview of quinones, beginning with their definition, historical background, and chemical structure. It explores their diverse roles in biological systems, including their involvement in cellular respiration, enzymatic reactions as co-factors, and their function as endogenous compounds. Mechanistically, quinones employ their effects through redox properties, electron transfer processes, and interactions with cellular components such as proteins, lipids, and DNA. Therapeutically, quinones are pragmatic for their anti-cancer, antimicrobial, anti-inflammatory, and antioxidant properties. Key drugs like doxorubicin and mitomycin C exemplify their efficacy in cancer treatment, while other quinones serve as antimicrobial agents against bacteria, fungi, and viruses. Challenges in drug development, including toxicity and stability issues, are addressed alongside strategies to mitigate these concerns. Case studies and clinical trial data underscore the clinical relevance of quinone-based therapies. Looking forward, future research opportunities include exploring novel quinone derivatives, integrating quinones in combination therapies, and advancing drug delivery systems to enhance their efficacy and safety profiles. The chapter concludes by emphasizing the significant role of quinone compounds in modern medicine and outlining potential breakthroughs that may further expand their therapeutic applications.

Keywords: Anthraquinones, Benzoquinones, Doxorubicin, Mitomycin, Naphthoquinones, Quinones, Reactive oxygen species, Vitamin K, Ubiquinone.

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INTRODUCTION

Quinones are a class of organic compounds characterized by a fully conjugated cyclic di-one structure. The most common quinones include benzoquinones, naphthoquinones, and anthraquinones [1]. Quinones are derived from aromatic compounds through the oxidation of hydroquinones. Their chemical structure typically includes a six-membered aromatic ring with two ketone substitutions, leading to their highly reactive nature due to the presence of electron-deficient carbonyl groups [2].

Quinones possess a basic structure of $C_6H_4O_2$ in the case of benzoquinones, extending to more complex forms such as naphthoquinones ($C_{10}H_6O_2$) and anthraquinones ($C_{14}H_8O_2$). The electron-deficient nature of the carbonyl groups makes quinones highly reactive and capable of participating in various redox reactions [3]. Quinones are typically yellow to red crystalline substances, exhibiting a distinctive coloration due to their conjugated system [4]. They have relatively low melting points and are soluble in organic solvents but exhibit limited solubility in water [5].

Quinones readily undergo reversible redox reactions, cycling between quinone and hydroquinone forms. This redox capability underpins many of their biological activities, including roles in electron transport and enzymatic reactions [6]. The redox properties are influenced by substituents on the aromatic ring, which can either donate or withdraw electrons, thus modifying the quinone's reactivity [7].

Quinones are ubiquitous in nature, playing vital roles in biological processes. For instance, ubiquinones (coenzyme Q) are essential for cellular respiration in the mitochondrial electron transport chain. They act as electron carriers and are involved in the synthesis of ATP, showcasing their importance in energy metabolism [8].

Naturally occurring quinones are found in a variety of plants, fungi, and bacteria. They are involved in pigmentation, such as in the case of lawsone (henna) and juglone (black walnut). Synthetically, quinones can be produced through various chemical reactions, including the oxidation of aromatic precursors and the cyclization of appropriate intermediates. The reactivity of quinones makes them suitable for a variety of applications, including medicinal chemistry. Their derivatives are used in anti-cancer, anti-microbial, and anti-inflammatory drugs due to their ability to generate reactive oxygen species and interact with biological macromolecules [9].

HISTORICAL BACKGROUND AND DISCOVERY IN MEDICINE

Early uses and Discovery

The medicinal use of quinone compounds dates back to ancient times, even before their chemical nature was understood. Natural quinones, especially those found in plants, have been used in traditional medicine for their therapeutic properties. One of the earliest known uses of a quinone compound is henna, derived from the plant Lawsonia inermis, which contains lawsone, a naphthoquinone. Henna has been used for millennia for its dyeing properties and potential medicinal benefits, including antimicrobial and anti-inflammatory effects [10].

19th Century: Isolation and Chemical Characterization

The 19th century marked significant advancements in the chemical isolation and characterization of quinones. In 1838, Pierre Joseph Pelletier and Joseph Bienaimé Caventou isolated the first quinone, quinone itself (benzoquinone), from the oxidation of quinic acid. This discovery laid the groundwork for understanding the chemical structure and reactivity of quinones.

Following this, in the late 1800s, notable chemists such as Friedrich Wöhler and August Kekulé contributed to the elucidation of the structures of various quinones. Wöhler, known for his synthesis of urea, also worked on the synthesis and study of benzoquinone. Kekulé's structural theories further advanced the understanding of aromatic compounds, including quinones [10].

20th Century: Biomedical Discoveries

The 20th century saw significant breakthroughs in the biological and medicinal applications of quinones. In the 1930s, research into the role of quinones in cellular respiration led to the discovery of ubiquinone (coenzyme Q10) by Frederick L. Crane and colleagues in 1957. Ubiquinone's crucial role in the mitochondrial electron transport chain and ATP synthesis underscored the biological importance of quinones [11].

Simultaneously, the anti-cancer properties of quinone compounds began to be explored. The anthracycline antibiotic doxorubicin, derived from the bacterium Streptomyces peucetius, was discovered in the 1960s and became a cornerstone in chemotherapy for various cancers. Its mechanism, involving DNA intercalation and the generation of reactive oxygen species, highlighted the potential of quinones in cancer treatment [12].

CHAPTER 10

Recent Study on Quinone Derivatives and their Applications

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Abstract: Quinone and its derivatives have manifold applications in pharmaceutical industries. In this chapter, we look over the current practices of quinones and their derivatives in several fields. Recent studies have found that quinone-enhanced humification in food waste composting is a strategy for hazard mitigation and nitrogen retention. Quinone derivatives such as diazanthraquinone dimers have been demonstrated as high-capacity organic cathode materials for rechargeable lithium batteries. Their preparation and advantage over conventional batteries have been explained. Quinone-chlorophyll conjugation synthesized by the Diels-alder approach as conformers, called atropisomers, is a recent invention. Currently, in the field of pharmacological practices, quinone and its class of molecules have demonstrated a wide range of therapeutic properties, such as anticancer, anti-inflammatory, and antibiotic.

Keywords: Anticancer agents, Benzoquinone anthraquinone, Diel's alder reaction, Lithium-ion batteries, Naphthoquinone, Pictet Spengler annulation, Quinone.

INTRODUCTION

Quinones are electron carriers that play a role in photosynthesis. As vitamins, they represent a class of molecules preventing and treating several illnesses such as osteoporosis, cardiovascular diseases, cancer [1, 5], bacterial infection, *etc*. They are used in Li-ion batteries [3] and food waste composting [2]. Quinone and chlorin are conjugated *via* the Diels-Alder reaction; the resulting compound can exhibit unique electronic properties due to the new conjugated π-system [4]. One fascinating study observed the synthesis of bis(arylamino) pentiptycenes using pentiptycene quinone in a one-pot process [6]. Quinones exist in nature in many forms, such as benzoquinones, naphthoquinones, anthraquinones, and polycyclic

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quinones [7 - 9]. For example, vitamin K (phylloquinone) include naphthoquinones, emodin, physcion, cascarin, catenarin, and rhein. Anthraquinones and benzoquinones are present in nature and are named carthamins. In this article, we have discussed about recent novelty of work on quinone and its derivative.

CLASSIFICATION OF QUINONES

Benzoquinones

Benzoquinones (Fig. **1**), such as lawsone, plumbagin, and 1,4-benzoquinone (menadione), exhibit various biological activities, including antioxidant, antibacterial, and anticancer effects. Pharmacological targets and pathways include NAD(P)H: quinone oxidoreductase 1 (NQO1), topoisomerases, and the proteasome. Key pathways involve reactive oxygen species (ROS) generation, DNA damage, and inhibition of the proteasome [9, 10].

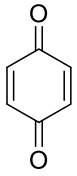

Fig. (1). Structure of benzoquinone.

Naphthoquinones

Naphthoquinones (Fig. **2**) have two carbonyl groups within their naphthalene ring structure. Lawsone, a naphthoquinone, is derived from the henna plant and is a ideal example in this category. The cytotoxic and antitumor properties of naphthoquinones are well-documented, and their potential as anticancer agents has been extensively researched. Pharmacological targets and pathways for naphthoquinones include thioredoxin reductase, topoisomerases, and the mitochondrial electron transport chain. Key biological pathways involve redox regulation, DNA damage, and mitochondrial dysfunction [9, 10].

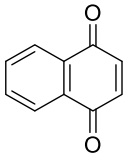

Fig. (2). Structure of naphthoquinones.

ANTHRAQUINONES

The nucleus consists of tricyclic anthracenes featuring two carbonyl groups, which can be readily sourced from plants and fungi. Notable examples include emodin, aloe-emodin, and rhein. Anthraquinones (Fig. **3**) are known for their diverse biological activities, including anti-inflammatory, anticancer, and antibacterial properties. Mode of action as targets includes protein kinase C (PKC), NF-κB, and topoisomerases in cancer and other illnesses. Associated biological pathways encompass the modulation of protein kinases, inflammatory processes, and responses to DNA damage [9 - 11].

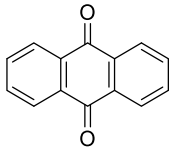

Fig. (3). Structure of anthraquinone.

Heteroquinones

Heteroquinones (Fig. **4**) comprise one or more heteroatoms, such as oxygen, sulfur, or nitrogen, within their ring structure. Examples include menadione bisulfite, a water-soluble form of menadione, and plumbagin, both of which are naturally occurring compounds featuring a quinone-oxygen bridge. These compounds often possess unique chemical and biological properties that make them promising candidates for drug development [9, 10, 12].

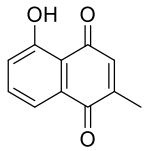

Fig. (4). Structure of heteroquinone.

Pharmacological targets include topoisomerases and DNA methyltransferases, along with reactive oxygen species (ROS) generation. The associated biological pathways involve DNA damage, epigenetic modulation, and oxidative stress responses.

These quinone derivatives have recently been used for emerging sustainable and highly efficient batteries, surpassing traditional lithium-ion battery technology. The development of diazaanthraquinone dimers has led to high-capacity organic cathode materials for rechargeable lithium batteries. 2,2′-bi(1,--diazaanthraquinone) (Li8-BDAAQ) is a recent example. The unique structure of Li8-BDAAQ, with its multiple redox-active sites and the ability to coordinate with lithium ions, makes it a promising candidate for high-performance battery materials. The general process of formulating has been described as follows [3].

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