Quinonoids: A Journey from Natural Pigments to Anticancer Drug Development

Madhushree Das Sarma

Department of Chemistry, Acharya Prafulla Chandra College,
New Barrackpore, North 24 Parganas, Pin - 700131
E-mail : madhushree_dassarma@yahoo.com

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Abstract

Natural products are the repositories for enormous variety of unique organic molecules, among which quinonoid belong to a distinctive category of compounds, ubiquitously found in all respiring plant and animal cells. They play crucial roles in cellular metabolism, mainly involve in photosynthesis and electron transfer reactions in their hosts. Some of them show pronounced cytotoxic and allergenic actions, serving their hosts as weapons for defense against invading pathogens. This observation gave rise to the fruitful utilisation of quinonoid natural products for development of many important therapeutic agents. Again, many quinonoid phytochemicals have been found to serve as the major 'marker' constituents of the medicinal plants used in popular herbal preparations. In another aspect, plant derived quinonoids occurring as chromatic pigments in plants, are notable for their characteristic bright colours. Hence, they are used as dyestuffs in paintings and textiles and a few have also been utilised as colourants in cosmetics and the food - processing industries. Thus, in this article, some important applications of quinonoid secondary metabolites will be discussed.

Key words: Quinonoids, Biocolourants, Anticancer drug

Introduction :

Nature has proved to be a particularly versatile resource, not only for our basic requirements of food, shelter and clothing, but also to make provision for numerous necessities of the people, such as furniture and transportation, tools and tackles, fragrances and spices, and most importantly, medicines and healthcare products[1]. It has been particularly generous in contributing unique chemical entities as secondary metabolites. Most common are alkaloids, terpenenoids, steroids, flavonoids, saponins, etc [2]. Among the various category of natural products characterised so far, quinonoids belong to a special class of compounds with an α,β-bisdienonic ring system in their molecular skeleton[3].

Quinonoids are widely distributed in nature, and hundreds of compounds with amazing diversity of chemical structures have been isolated from animal, plants, fungi and bacteria. For example, ubiquinones and plastoquinones (Figure 1) occur as vital components of the electron transport chain in animal and plant cells performing crucial roles in the biochemistry of energy

production [4]. Coenzyme Q functions as an electron carrier in the mitochondrial respiratory chain in a cellular system, while Vitamin K ((Figure 1) is an indispensable dietary factor with blood-coagulating properties [5]. However, the main focus of the quinonoids would be reflected on their extensive use for imparting various bright colours to cotton and woolen fabrics [6]. On the other hand, plant derived quinonoids are reputed in several traditional medicinal systems [7] and they also exhibit broad spectrum biological activities, particularly as anticancer agents [8]. Here some important members of qunonoid family are chosen to describe their miscellaneous applications.

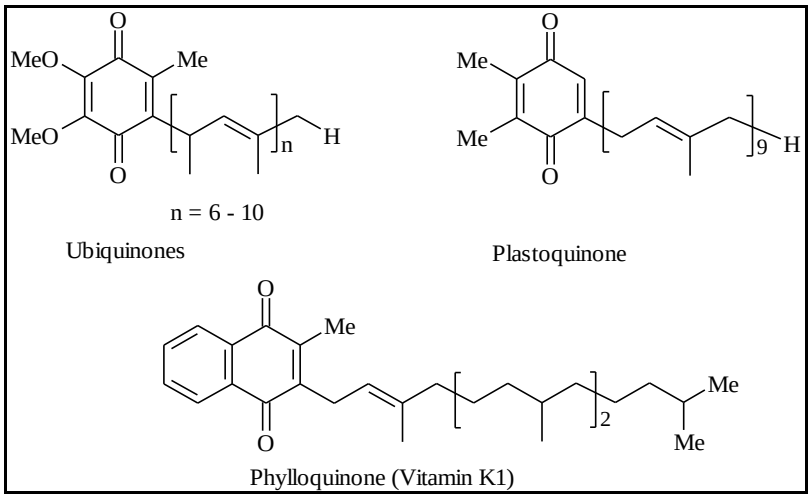

Figure 1 : Structures of some Naturally occurring quinonoid compounds

Various Applications of Quinonoid Compounds:

a) ***Quinonoids as Biocolourants*** :

Economically, quinonoid compounds are important as the source of potential 'biocolourants' (natural dyes). Henna has been used since antiquity by women particularly in India and the Middle East for dying their hair, hands, and feet. Lawsone (2-hydroxynaphthoquinone, Figure 2), a reddish-orange compound, is the main constituent of leaves of the henna plant (*Lawsonia inermis* Linn., Lythraceae) [9]. Even today, the traditional art of henna painting (Mehndi), a form of personal decoration during marriages and festivals, has been used [10]. Lawsone, one of the best wool-colouring agent, reacts with the keratin protein in wool / hair / skin via Michael addition, resulting in a strong permanent stain that lasts for several weeks [11]. Juglone (5-hydroxynaphthoquinone, Figure 2), a close analogue of lawsone, occurs in the roots, leaves and stems of *Juglans spp.* plants of Juglandaceae

family, particularly in walnut hulls [12]. Juglone has been traditionally used as a natural dye for fabrics, particularly wool, and also as ink. Because of its tendency to create dark orange-brown stains, juglone has been used as a coloring agent for foods and cosmetics [12].The roots and rhizomes of Rubiaceae family, such as *Rubia cordifolia* and *Rubia tinctorum* (common madder plant) were known in the past as rich sources of colouring materials, especially for red dyes [13]. Historical reference to the colouring agents from the common madder plant goes back to the findings of stained cloth in the tomb of the Pharaoh Tutankhamen. Alizarin (Figure 2) is the main colouring component identified in madder root, was the first natural pigment synthesized chemically in the early 19th century. Even today, the pigments obtained from various *Rubia* species are used for dyeing fabrics, and also to impart colour to foods (candies, chewing gums, noodles, jams) and cosmetics (hair dyes, shampoos) [14].

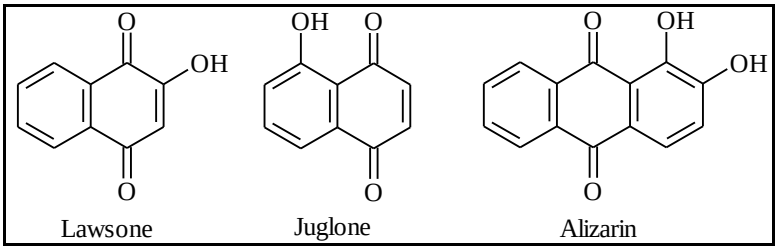

Figure 2 : Structures of some Naturally occurring quinonoid compounds used as dyes

b) ***Quinonoids in Traditional Medicines*** :

An impressive number of modern drugs have been isolated from plants, many based on their use in traditional applications [15]. Several quinonoid phytochemicals and their analogues have been found to serve as the major 'marker' constituents of the medicinal plants frequently used in commercially important herbal formulations prescribed in several traditional Oriental medicines [7]. Some hydroxyanthraquinonoid analogues particularly aloe-emodin, rhein, emodin, chrysophanol and physcion (Figure 3) are the major bioactive constituents of plants belonging to the genera of *Aloe, Rheum, Polygonum, Cassia*, etc. Many traditional Oriental herbal formulations are constituted of the roots/rhizomes/stems/leaves of these species, which continue to be popular even to this day, with a lot of commercial prospect. Most of these herbal preparations have been used all over the world for their laxative and purgative property. In South East Asian countries and India, *Aloe vera* was popular for its abortifacient, uterine stimulant, cathartic, cholerectic, and anthelmintic

properties. *Aloe vera* gel is applied for healing open wounds and soothing damaged tissues [16].The dried roots and rhizomes of *Rheum officinale* Baill, *R. palmatum* Linn. *R. undulatum* Linn and *R. tanguticum* Maxim. et Baill, commonly known as rhubarb (Da-Huang), is one of the best-known herbal medicines used for thousands of years in Chinese pharmacopoeia [17]. Rhubarb is also widely used in Korean and Japanese ethnomedical preparations. It has been traditionally used for the treatment of constipation, fever, hypertension, immunosuppression, inflammation, microbial infection and peptic ulcer [7, 16].

It is assumed that the similarity in the traditional applications of these plants might be correlated to the ubiquitous presence of the quinonoid analogues in all of them. Some recent studies carried out on pharmacological activity of these plant-derived quinonoids support this fact [18, 19] and might explain the popularity of such herbal preparations worldwide.

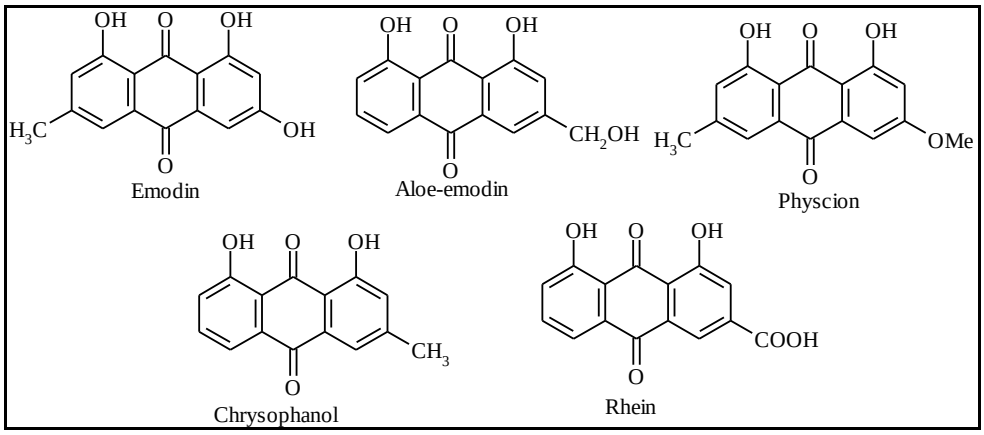

Figure 3 : Structures of major anthraquinonoids present in Rhubarb

c) ***Quinonoids for Anticancer Drug Development*** :

The unique structural feature comprising the cyclohexadienedione ring of the quinonoid skeleton endows them with the versatility to undergo reversible oxidation-reduction reactions *via* facile electron-transfer mechanism [4]. This functional attribute of the naturally occurring quinonoids is the key to their distinctive role as electron carriers in the mitochondrial respiratory chain and photosynthesis, as well as the broad-spectrum pharmacological profile [8]. Furthermore, the extensive research work in this field have ascribed the characteristic redox cycling capability and generation of reactive free radicals to be responsible for the cytotoxicity of many quinonoids, particularly towards tumour cells [20,21]. No wonder that a whole group of quinones are now considered to be an important class of antineoplastic agents

for the treatment of various types of cancerous diseases [18]. In fact, the screening for anticancer drug candidates by National Cancer Institute, USA started in 1955 with a simple benzoquinone derivative (2-Methyl-*p*-benzoquinone, Figure 4) [22]. Later on, a large number of naturally occurring, as well as synthetically derived quinonones have been tested in a panel of human cancer cell lines. To date, anthracycline antibiotics (i.e. anthraquinonoid glycosides) constitute the second largest class of drugs, approved for clinical use against cancer [21]. The most prominent members daunorubicin and its hydroxylated analogue doxorubicin (Figure 4), isolated from various *Streptomyces* strains, are widely used for the treatment of various types of malignancy [23]. Daunorubicin is particularly useful against acute myelocytic and lymphocytic leukemia, whereas doxorubicin is the most effective single agent against soft-tissue sarcomas in adults, and also exhibits a broader spectrum of action in many solid tumours, such as osteosarcoma, non-Hodgkin's lymphoma, and carcinomas of breast, ovary, thyroid and lung [24]. However, the potential clinical utility of anthracyclines, as for the majority of antitumour drugs, is often limited by dose-limiting side effects like bone marrow suppression and cardiotoxicity, and also by the appearance of multi-drug resistance in tumour cells [25, 26].

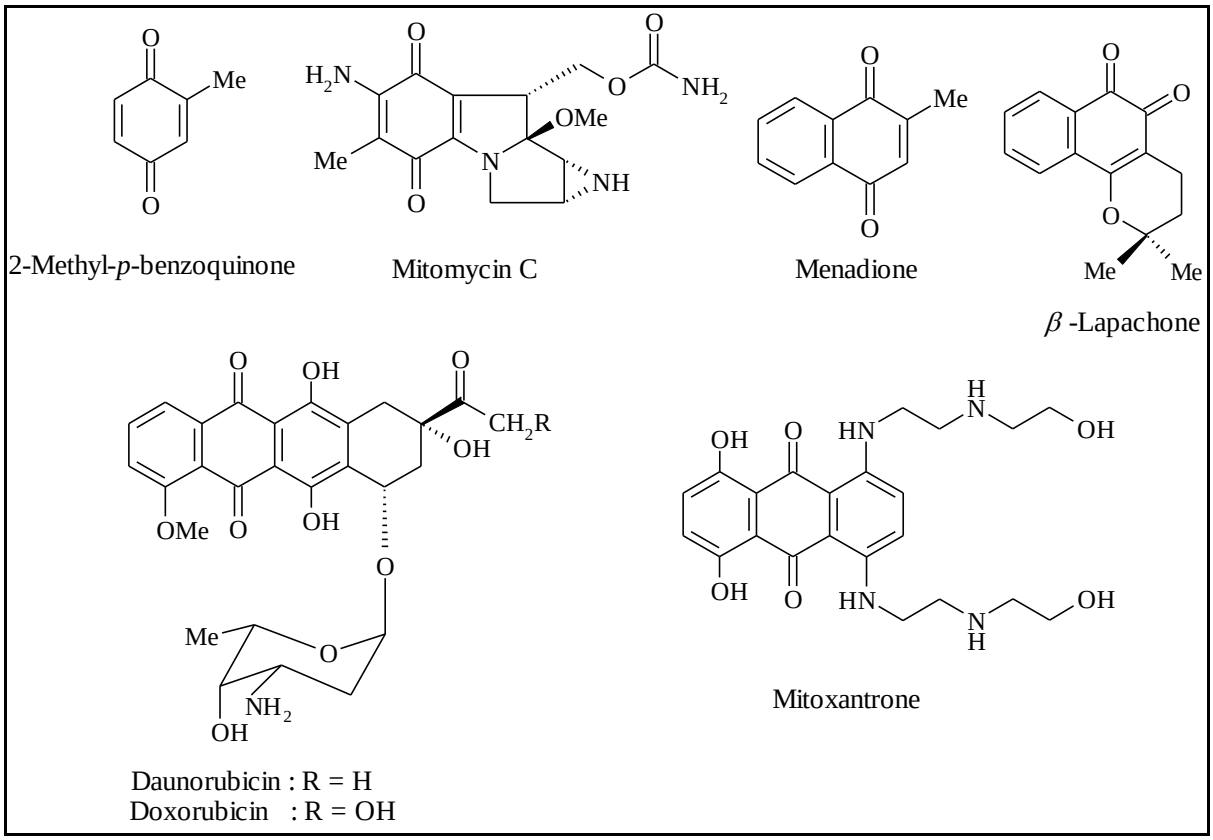

Figure 4 : Structures of quinonoid anticancer agents

Mitoxantrone (Figure 4), a synthetic anthraquinone derivative is clinically approved for the treatment of various cancers, particularly against leukemia, lymphoma and breast cancer [27,28]. Menadione (vitamin K3, Figure 4), a naphthoquinone derivative, exhibited cytotoxicity against several leukemia cell lines and multidrug-resistant tumours, mostly in combination with other drugs or radiation [29]. *β*-lapachone (Figure 4), a pyrano-ortho-naphthoquinone, obtained from the bark of lapacho tree (*Tabebuia avellanedae*) showed significant antitumour and radiosensitising activity [30, 31]. In combination with taxol, it is highly effective against human ovarian and prostate tumours implanted in immunosuppressed mice [21]. In USA, clinical trial on *β*-lapachone against pancreatic cancer has been launched [32]. Among benzoquinonoid, mitomycin C (Figure 4) isolated from *Streptomyces caespitosus*, is a well known clinically approved anticancer drug extensively used for the treatment of several types of solid tumours for more than 35 years. It is called the 'most active single compound' for the treatment of non-small cell lung cancer [33]. A variety of quinonoid analogues have been synthesized and many of them are currently under different stages of clinical and pre-clinical development [34].

Conclusion

Quinonoid natural products have contributed to the human civilisation, mainly as drugs, pigments and cosmetics. However, despite their obvious usefulness as potential pharmacophores and chromophores, they have not so far been exploited as much as compared to other classes of natural products like alkaloids, flavones or terpenoids. So far discoveries of these quinonoid compounds are merely the tip of an iceberg; there are many more potentialities of these compounds which are waiting to be explored.

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