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Research Article

A critical review on the drug molecule: Anthraquinone

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Abstract

Background: The world is demanding an increased commercial requirement of various secondary metabolites to cure numerous ailments. Anthraquinones (AQs), is one among them, responsible for the pigmentation of heartwood and bark of many economically valuable plants. It is a natural red dye having an outstanding curative application, used from time immemorial.

Main body of the abstract: AQs have been identified from various plants, animals and even from microbes. In addition to their use in various pharmacopoeias, it is used in the textile industry, cosmetics, food etc. AQs always been a fascinating molecule for chemists to synthesize and access diversely substituted derivatives as therapeutic agents. Its curative efficiency is well utilized in the treatment of various modern diseases and even to Covid 19. Moreover, the AQs exhibit a unique anticancer activity in various cell lines.

Short conclusion: The present work overviews the various effective uses of AQs and highlight its importance in cancer therapy

BACKGROUND

In plants, the production of secondary metabolites (SMs) is a part of their defense mechanism. Of the variety of SMs, phenolics are placed as the major dyestuff group produced either through the shikimate pathway or phenylpropanoid pathway. Plant phenolics including simple phenols, phenolic acids, flavonoids, coumarins, stilbenes, hydrolyzable and condensed tannins, lignans, and lignins are the most abundant secondary metabolites (Kumar and Pruthi, 2014, Li Y, 2009, Li Y and Jiang, 2018). Typically, they are present in a bound form such as amides, esters, or glycosides and rarely in free form (Pereira et al., 2009). Even though phenols do not have hydrogen at their a-carbon atoms, they do undergo oxidation. The most common oxidation products of phenols are quinones, a pervasive biological pigment found in a wide range of organisms. Naturally occurring quininesinclude benzoquinones, naphthoquinones, benzanthreno phenanthrenoquinones, anthraquinones, anthracyclinones, etc (Korulkin and Muzychkin, 2014). AQ (anthracenedione or dioxoanthracene) represents the largest phenolic group, found in their free form (aglycone) or as AQ glycosides (Derksen et al., 2003, Deshkar et al., 2008).AQs are yellow whereas the AQ glycosides are orange-red or brown-red.

Over 200 AQ compounds are identified in flowering plants, bacteria, molds, fungi, lichen, and insects. These pigments are often responsible for the pigmentation of colored heartwood and bark of many economically valuable plants. In intact powdered form, it exhibits different shades of colors (Priya and Siril, 2013, Samatha and Vasudevan 1996, Mishra et al.,) and an array of different colored dyes was also derived (Patel and Patel, 2016) from it. AQs show restricted distributional plant kingdom, found only in families such as *Amaranthaceae, Convolvulaceae, Ericaceae, Euphorbiaceae, Gesneriaceae, Hypericaceae, Leguminosae, Lythraceae, Nyctaginaceae, Polygonaceae, Rhamnaceae, Rubiaceae, Saxifragaceae, Scrophulariaceae, Verbenaceae, Liliaceae* etc (Teuscher and Lindequist, 1994). In fungi, it is represented in Aspergillus, Penicillium, and Trichoderma species (Betina et al., 1986). It is also found in some marine invertebrates (Bandaranayake 2006). Furthermore, a few insect species contain AQ either sequestered (Eisner et al.,

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1994) or not sequestered (Blum and Hilker 2002) from their food plants.

METHODOLOGY

For the present review work the published scientific literature indexed in various databases, peer-reviewed studies were collected and arranged systematically. The central concept is partitioned in various heads each one is discussed and evaluated.

General Uses of Anthraquinones

The tinctorial property of this dye is described in ancient scripts and evidence was gathered from various civilizations. These organic compounds are used to color natural fibers like wool, cotton, and silk with very good fastness to washing and light. Since this is largely employed in textile dyeing, the palatability of this dyestuff was under suspicion. But now it has been used as a food colorant and hair dye (Samantha and Vasudevan, 1996). It is used as a seed dressing or in seed treatments. It can also be employed as a pesticide, to offer bird repellence (Linz and Homan, 2012) also as a gas generator in satellite balloons (Yadav et al., 2019). In addition to the dyeing property, AQ has a significant role in commercial applications. It is used as a catalyst in the production of wood pulp and paper (Sturgeoff and Pitil, 1997). AQs are used in gel preparations of sun protection cream (Dweck, 2002). 2-ethylAQ, an AQ derivative, is utilized in the manufacture of hydrogen peroxide (Goor et al., 2000). The persuasive antioxidant activity of AQ is effectively exploited in the food industry as a chemo-preventive agent. It is a well-documented medical compound and promotes intestinal muscle contraction and speeds up bowel movements (Li 2009). Hydroxy AQs are used as an intermediate in dyes and drug production (Imaki and Fukumoto, 1988). These are stored in plants in the form of glycosides, due to glycosylation (van der Plas et al., 1998), which can improve the solubility of these metabolites and facilitate in better metabolism and distribution (Pandey et al., 2014). Medically, AQs are used as a laxative, which irritate the upper as well as the lower parts of our gastrointestinal tract (Portalatin and Winstead, 2012). AQs also exhibit laxative, diuretic, estrogenic, and immune-modulatory effects. Numerous therapeutic effects like cancer growth inhibition by inducing apoptosis, ease bowel movement, relieve constipation (Khan,2019, Kirtikar and Basu, 1980) and possess antibacterial, antiparasitic, insecticidal, fungicidal, and antiviral properties (Yadav et al., 2019). Reports revealed that the AQ glycosides in plants gradually increase with time. These are mainly absorbed in the intestines and are mostly distributed in blood flow-rich tissues and organs and its transformation produce improved pharmacological and/or toxicological outcomes (Wang et al., 2021). The curative properties of AQs have been successfully practicing to bring about constipation relief through their laxative effects and to stimulate colon contractions (Portalatin and Winstead, 2012). The AQ ring and AQ glycosides have significant anticancer activity and anti-constipation activity, while alizarin has significant antioxidant activity and antibacterial activities (Li and Jiang, 2018).

Uses of AQ in Modern Time

In modern medicine, plant-derived chemicals are offered prime importance and AQ is the secret to the medicinal potency of many medicinal plants. A series of bicyclic peptides (RA-series) has been elucidated from various spectroscopic and chemical methods using various solvent systems in various Rubiaceae members and were noted for its cytotoxic and antitumor competence (Itokawa et al., 1984c, Kato et al., 1987, Hamanaka et al., 1987, Itokawa et al., 1993) and are used against various carcinoma, melanoma, and leukemia. According to Tian et al. (2020), AQ compounds have been considered to have anticancer activity mainly through DNA damage, cycle arrest, and apoptosis and also through paraptosis, autophagy, radio-sensitizing, overcoming chemo-resistance, and other methods. Mechanistically, most of the AQ-based compounds inhibit cancer progression by targeting essential cellular proteins (Malik et al., 2021).

The AQ showed cytotoxicity toward human carcinoma cell lines like colon carcinoma (HT-29), breast carcinoma [(MCF-7), liver carcinoma (HepG2), cervical cancer (Tiwari et al., 2012), MDA-MB-231 (Barlow et al., 2016), human larynx carcinoma and human cervical cancer (Tiwari et al., 2012). It was found to have inhibitions against human cervical cancer cell line (HeLa) and larynx carcinoma (HEp-2) cell lines (Patel et al., 2010). The prominent AQ-based drugs doxorubicin, mitoxantrone as well as more recent epirubicin, idarubicin, and valrubicin are successfully used in chemotherapy of hematological malignancies and solid tumors (Tikhomirov et al., 2018). Nano structured AQ active molecule showed the absence of cytotoxicity and improved cell uptake of photo-sensitizer resulting in increased cell death compared to free AQ (Amantino et al., 2020). The liposomal AQ-based molecule has excellent promise for Triple Negative Breast Cancer therapy (George et al., 2022). Natural anthraquinone (AQ) equivalents extend their antitumor activity on different targets including telomerase, topoisomerases, kinases, matrix metalloproteinases, DNA and different phases of cell lines (Siddamurthi et al., 2020). Moreover, emodin and artinemol may be effective antiviral drugs for the treatment of patients with COVID-19 (Prathiviraj et al., 2021).

Due to the long-term use of AQs the lining of the colon takes on a dark brownish-black hue. This condition in term may, cause short-term side effects but the melanosis of coli can

be reverted when the anthraquinone use was discontinued. However, the presence of the quinone moiety in AQs raises safety concerns, and its laxative has therefore been under critical reassessment (Malik and Müller 2016). Moreover, the transformation of one form of AQ into another may increase the blood concentration of the latter, leading to an increased pharmacological and/or toxicological effect (Wang et al., 2021).

CONCLUSION

Since the world is looking forward to nano-particles for effective drug delivery more attention should be given to those metabolites like AQs and their derivatives, which have proven their potency in controlling many dreadful diseases especially tumor cell lines with minimum drug leakage. There is plenty of opportunity for utilizing AQ-based anticancer drugs in combination therapies with newly approved anticancer drugs targeting different biological receptors, which can be achieved through a detailed understanding of the mechanistic pathways of the intended combination. Recently, Polymer enzyme liposome therapy (PELT), triple block nanocarrier (TBN) platforms and amphiphilic core cross-linked star (CCS) polymers were reported to perform excellent pharmacokinetic profile in in vivo models. Similarly, selective drug delivery, computational techniques like ligand-based drug designing and scaffold hopping, drug repurposing, the in-silico drug designing tools for the diversification of targets and drug repurposing techniques.

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