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The chemical and biological activities of quinones: overview and implications in analytical detection

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Abstract Quinones are a class of natural and synthetic compounds that have several beneficial effects. Quinones are electron carriers playing a role in photosynthesis. As vitamins, they represent a class of molecules preventing and treating several illnesses such as osteoporosis and cardiovascular diseases. Quinones, by their antioxidant activity, improve general health conditions. Many of the drugs clinically approved or still in clinical trials against cancer are quinone related compounds. Quinones have also toxicological effects through their presence as photoproducts from air pollutants. Quinones are fast redox cycling molecules and have the potential to bind to thiol, amine and hydroxyl groups. The aforementioned properties make the analytical detection of quinones problematic. However, recent advances of the available analytical techniques along with the possibility of using labeled compound facilitate their detection hence allowing a better understanding of their action. This review summarizes the current knowledge with respect to the oxido-reductive and electrophilic properties of quinones as well as to the analytical tools used for their analysis. It includes a general introduction about the physiological, and therapeutical functions of quinones. A number of studies are reported to cover the chemical reactivity in an attempt to understand quinones as biologically active compounds. Data ranging from normal analytical methods to study quinones derived from plant or biological matrices to the use of labeled compounds are presented. The examples illustrate how chemical, biological and analytical knowledge can be integrated to have a better understanding of the mode of action of the quinones.

Keywords Quinone · Chemotherapeutic agents · One electron reduction · Two electron reduction · Labeled compounds analysis

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Introduction

Quinones represent a class of quinoid compounds that are widely distributed in nature. So far, more than 1,200 quinones have been described (Dey and Harborne 1989). They are characterized by a

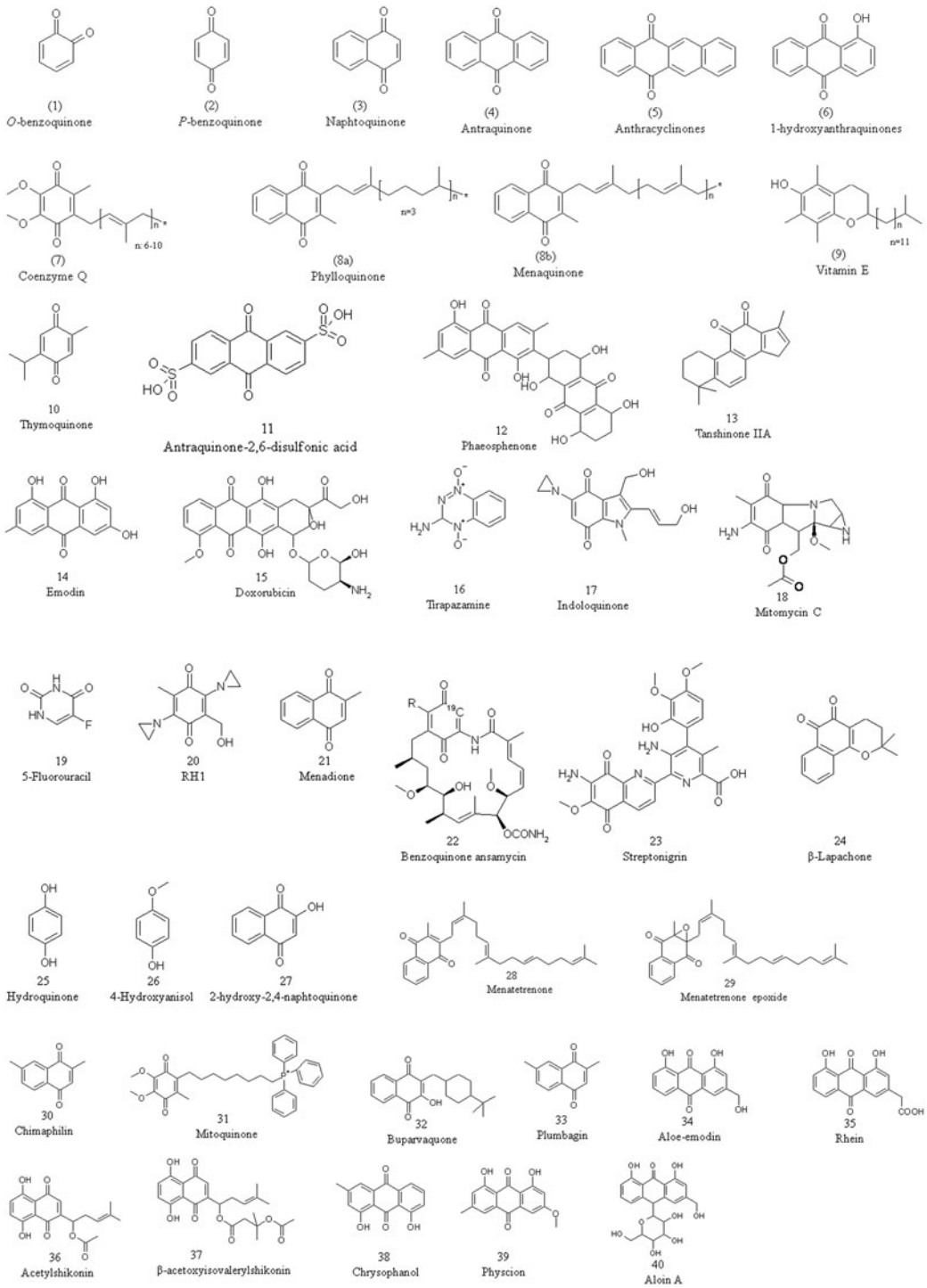


Fig. 1 Chemical structures of quinones numbered in the same order as mentioned in the text

common basic structural pattern: an *ortho* or a *para* substituted dione conjugated either to an aromatic nucleus (benzoquinones) (1, 2) or to a condensed polycyclic aromatic system, such as naphtoquinones (3), anthraquinones (4), anthracyclinones (5) and so on as given in Fig. 1.

Quinones are found in a wide variety of plant families such as Ranunculaceae (Salem 2005), Aphodelaceae (Bringmann et al. 2008), Fabaceae (Bakasso et al. 2008), Ebenaceae (McGaw et al. 2008), and Rhamnaceae (Wei et al. 2008b). They are also present in fungi, bacteria (Carrasco et al. 2008; Kim et al. 2008; Thomson 1991; Wei et al. 2008a; Wijeratne et al. 2008) and in small amounts in animals, specifically in echinoderms (Singh et al. 1967; Thomson 1991). Nevertheless, toxic quinones such as anthraquinone (4) and 1-hydroxyanthraquinones (6) can be formed in the environment by sunlight photo-oxidation of environmental contaminants such as the polycyclic aromatic hydrocarbons (PAHs) (Mallakin et al. 1999; Mallakin et al. 2000). Due to their wide occurrence in nature along with their involvement in a number of essential biological and chemical processes, quinones correspond to a well studied class of compounds. For example, their role in photosynthesis in plants and bacteria is well established (Breton and Nabedryk 1996; Lubitz 2003). In addition Coenzyme Q (7) acts as a powerful antioxidant and membrane stabilizer, prevents cellular damage resulting from normal metabolic processes (Nageswara Rao et al. 2008), and protects against several chronic diseases, including Parkinson's and cardiovascular diseases (Cleren et al. 2008; Pepe et al. 2007). Vitamin K (8a,b) is essential to maintain life by its function in blood coagulation processes (Ahmed et al. 2007; Azharuddin et al. 2007; Benzakour 2008), in preventing cardiovascular disease (Beulens et al. 2008; Wallin et al. 2008), as well as in the prevention and treatment of osteoporosis (Bugel 2008; Lanham-New 2008; Weber 2001). Moreover, many quinones have antioxidant [vitamin E (α-tocopherol) (9)], anti-inflammatory [vitamin E (α-tocopherol) (9)], thymoquinone (10), anthraquinone-2,6-disulfonic acid (11)), antibiotic [phaeosphenone (12)], antimicrobial [anthraquinones (4)], and anticancer [thymoquinone (10), Tanshinone IIA (13), emodin (14), doxorubicin (15)] activities (Alvarez-Cedron et al. 1999; Atasayar et al. 2008; Clarke et al. 2008; Gali-Muhtasib et al. 2008a, b; Halamova et al. 2010; Koka et al. 2010; Lenta et al. 2007; Lu et al. 2008; Mansour and Tornhamre 2004; Mazuel et al. 2003; Rahman et al. 2008; Rizzo et al. 2008; Savarino et al. 2007; Sethi et al. 2008; Sottani et al. 2008; Su et al. 2008; Takahashi et al. 2008; Zhang et al. 2008; Zhu et al. 2007). Moreover, quinones comprise a large class of antitumor quinones that are approved for clinical use against several types of cancer or that are still in different stages of clinical and preclinical development as reviewed in (Asche 2005). Although their precise mechanism of action is not yet fully understood, it is suggested that their major target is DNA. While some interact with DNA by alkylation or intercalation, others induce double strand DNA breaks and both DNA topoisomerase I and II mediated DNA cleavage (Asche 2005; Cai et al. 2007, 2008; Marinho-Filho et al. 2010).

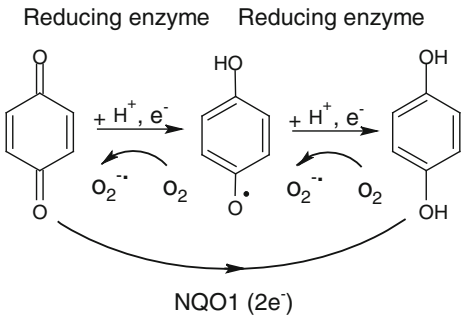
Given that quinones play a role in many physiological and toxicological processes, the knowledge of their mode of action along with their quantification from different matrices represents an interesting research endeavor. This review covers the current knowledge with respect to their chemical and biological activities as well as their implication in their detection by the available analytical methods.

Chemistry of quinones

The knowledge of the inherent chemical reactivity of quinones is relevant to understand their physiological and toxicological properties. Quinones have two properties that are essential for understanding their biological effects. First, quinones can undergo reversible oxido-reduction reactions and, second, many of them can undergo nucleophilic attack due to their electrophilic character. In the section below an overview of the oxido-reductive and electrophilic properties of quinones are presented.

One and two electron reductions of quinones

The mechanism of quinone cytotoxicity is attributed mainly to their ease of reduction and therefore to their ability to act as oxidizing or dehydrogenating agents. In biological systems quinones can undergo one or two electron reduction by cellular reductases leading to the corresponding semiquinones or hydroquinones, respectively (Scheme 1). Although the redox properties of the quinones depend largely on their chemical potential, their interactions with proteins at a specific binding site can further modulate the electronic properties and thus their redox potential in situ (Breton and Nabedryk 1996; Song and Jeon 2003).



Scheme 1 Illustration, using benzoquinone as an example, of one and two electron reduction yielding semiquinone and hydroquinone, respectively. NQO1: NAD(P)H: quinone acceptor oxidoreductase

The one-electron reduction of quinones can be catalyzed by a number of enzymes, including microsomal NADPH cytochrome P450 reductase (P450R), microsomal NADH cytochrome b5 reductase (b5R), and mitochondrial NADH ubiquinone oxidoreductase (Holtz et al. 2003; Monks and Jones 2002; Wang et al. 2010; Yan et al. 2008). The semiquinone radical, formed by one electron reduction, gets oxidized under aerobic conditions to the initial quinone with the generation of superoxide anion radicals. In aqueous solutions the former radicals interact with molecular oxygen to give rise to hydrogen peroxide which, in the presence of iron, forms toxic hydroxyl radicals to which the toxicity of quinones is attributed (Asche 2005; Kappus 1986). Due to their activity in enhancing drug toxicity, the one electron reducing enzymes might be used in the design of bioreductive chemotherapeutic agents (Celik and Arinç 2008; Pan et al. 1984; Yan et al. 2008). A panel of anticancer drugs has attracted the attention for use as bioreductive drugs. Ample evidence proves that bioreductive activation of the antitumor drugs: doxorubicin (15), tirapazamine (16), and indoloquinone (EO9) (17) by the cellular oxidoreductases P450R leads to significant increases in their covalent binding to DNA and cytotoxic activity against tumour cells (Bailey et al. 2001; Bartoszek and Wolf 1992; Chinje et al. 1999; Cowen et al. 2003; Cullinane et al. 1994; Kostrzewa-Nowak et al. 2005; Patterson et al. 1995, 1997; Skladanowski and Konopa 1994). The bioreduction of mitomycin C(MMC) (18) by P450R leads to the formation of free radicals which cause lipid peroxidation, protein and DNA damage, and, ultimately cell death (Belcourt et al. 1998; Joseph et al. 1996; Kappus 1986; Wang et al. 2007). Similarly, the toxicity of 5-fluorouracil (19) is enhanced by P450R through reactive oxygen species (ROS) production and NADPH depletion in P450R-overexpressing cells (Martinez et al. 2008). The P450R enzyme is therefore an attractive target for the enhancement of the chemotherapeutic efficacy of 5-fluorouracil (19) (Martinez et al. 2008). Despite the fact that the one electron reducing enzymes play a role in the bioreductive activation of several antitumor agents, this effect seems to be dependent on both the enzymatic activity level and the concentration of the drug. This can be illustrated by the example on 2,5-Diaziridinyl-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone (RH1) (20), a substrate for P450R and b5R (Nemeikaite-Ceniene et al. 2003). Although RH1 reduction causes ROS production and both DNA strand breaks and DNA crosslinks (Begleiter et al. 2007; Hasinoff and Begleiter 2006), its toxicity is only observed in tumor cells at high enzyme activity levels and high drug doses (Begleiter et al. 2007; Hasinoff and Begleiter 2006; Nemeikaite-Ceniene et al. 2003; Yan et al. 2008). Consequently, the contribution of b5R and P450R in the bioactivation and cytotoxicity of RH1 (20) is expected to be minor in cancer cells harboring normal activity levels of these enzymes (Yan et al. 2008).

In addition to the one-electron reduction, quinones can undergo a two-electron reduction process which is catalysed by the cytosolic flavoenzymes NAD(P)H: quinone acceptor oxidoreductases (NQO). NQO1, also known as DT-diaphorase, is a well studied NQO, while its iso-enzyme, NRH:quinone oxidoreductase 2 (NQO2), is studied to a lesser extent.

Although both NQO1 and NQO2 can use NAD(P)H as a source of reducing equivalents, the former uses this cofactor more efficiently (Wu et al. 1997; Zhao et al. 1997). NQO2 catalyzes the same reactions as DT-diaphorase but at significantly lower rates (Jaiswal et al. 1990; Jaiswal 1994). Compared to DT-diaphorase, NQO2 is a less effective two-electron transfer oxidoreductase and a more effective four-electron transfer oxidoreductase (Wu et al. 1997). In fact, DT-diaphorase is a distinctive flavoenzyme for three reasons. First, it displays a nonspecific reactivity towards NADH and NADPH and shows a broad electron acceptor specificity, catalyzing the reduction of quinones and structurally related compounds.

DT-diaphorase can catalyze the reduction of a variety of both ortho- and para-quinones (Gaikwad et al. 2007). Second, it is strongly inhibited by the NAD(P)H competitive inhibitor dicumarol and other oral anticoagulants. Third, the most striking feature is its ability to catalyze the so-called "obligatory" two-electron transfers (Bianchet et al. 2004; Cadenas 1995). This obligatory 2-electron reduction competes with the one-electron reduction of quinones by enzymes such as P450R and protects cells against oxidative stress (Gong et al. 2008). This protection results from the conversion of quinones to hydroquinones rather than semiquinones and ROS which is generated by redox cycling of semiquinones in the presence of molecular oxygen (Bianchet et al. 2004; Kappus and Sies 1981; Tampo and Yonaha 1996).

Three types of hydroquinones are formed by DT-diaphorase action, 1) redox-stable hydroquinones, 2) redox-labile hydroquinones that subsequently autoxidize with formation of ROS and 3) hydroquinones that readily rearrange to potent electrophiles participating in bioalkylation reactions (Cadenas 1995). The properties of the hydroquinone generated by DT-diaphorase determine whether this reduction leads to the activation or deactivation of quinones. The detoxification property of DT-Diaphorase and its role in cellular protection have been supported by many studies (Joseph and Jaiswal 1994; Tampo and Yonaha 1996). The efficient detoxification of quinones by DT-diaphorase stems from the generation, via two electron reduction, of the more water soluble and relatively more stable hydroquinones which are easily excreted following glucuronide or sulfate conjugation (Lind 1985). The detoxification mechanism for menadione (21) is due to its two electron reduction by DT-diaphorase followed by UGT-glucuronidation (Nishiyama et al. 2008). The same mechanism of DT-diaphorase reduction and subsequent glucuronidation has been documented for the anticancer compound Tanshinone IIA (13) (Hao et al. 2007). In addition, a decrease in the beneficial antioxidant effect of short chain CoQ derivatives has resulted from the formation of CoQ1 sulfate conjugate which is DT-diaphorase and sulfotransferase dependent (Chan and O'Brien 2003).

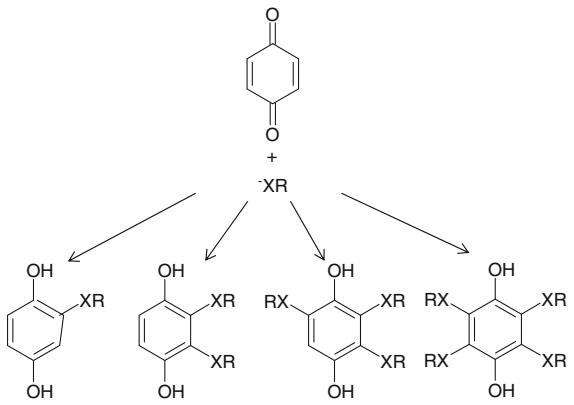
The use of dicumarol, the DT-diaphorase inhibitor, has been found to enhance the toxicity of quinones (Thor et al. 1982), and its induction protected cultured cells against quinone toxicity (Lim et al. 2008). In vivo, the detoxification of quinones by DT-diaphorase has been confirmed in DT-diaphorase knockout mice (Radjendirane et al. 1998). Increased menadione (21) toxicity has been observed in the null mice as compared to wild-type mice whereby 70% of null mice have died after exposure to 10 mg menadione/kg body weight (Radjendirane et al. 1998). These results suggest a protective role of DT-diaphorase against quinone toxicity through detoxification.

In addition to its possible role in the detoxification of dietary quinones, the enzyme has been shown to catalyze the reductive activation of quinolic chemotherapeutic compounds, such as E09 (17), MMC (18), RH1 (20), benzoquinone ansamycin (BA) (22), streptonigrin (23) and β-lapachone (24) (Begleiter et al. 2007; Bianchet et al. 2004; Cai et al. 2008; Cummings et al. 2003; Danson et al. 2011; Guo et al. 2008; Vainchtein et al. 2008; Yan et al. 2008). In this case the bioactivation results in the formation of more toxic metabolites (Cadenas 1995; Danson et al. 2011; Workman 1994). This can be explained by the fact that some hydroquinones as mentioned earlier can either autoxidize to generate ROS or undergo rearrangement to produce a reactive alkylating species (Cadenas 1995). This bioactivation property of DT-diaphorase along with the fact that it is highly expressed in certain tumors types has been used in the development of bioreductive chemotherapeutic agents for the therapy of tumors rich in DT-diaphorase (Bianchet et al. 2008; Danson et al. 2011; Malkinson et al. 1992; Mikami et al. 1998; Siegel et al. 1998; Siegel and Ross 2000; Winski et al. 1998; Workman 1994).

Nucleophilic addition of quinones

Quinones's electrophilic character enables them to undergo nucleophilic attack which may lead to either detoxification or enhanced toxicity (Scheme 2).

Quinone's facile adduction with electron-rich nucleophilic species such as activated amino, hydroxyl and thiol groups occurs in the classical Michael addition (Land et al. 2004; Li et al. 2005; Song and Buettner 2010). In a biological system, such nucleophiles may be found as reactive side-groups of lysine, serine and cysteine (Magee 2000). However, the thiol group of glutathione (GSH) represents the first to be involved in the nucleophilic addition with quinones. In fact, the first line of cellular defense is



Scheme 2 Illustration, using benzoquinone as an example, of the nucleophilic addition with formation of mono-,di-,tri, and tetra-susbtitution

controlled by GSH which is an active ROS scavenger and the most abundant non-protein antioxidant present in the cell. Many quinones can be conjugated to the sulfhydryl group of GSH, and this reductive addition represents their major route of elimination. Quinone-GSH conjugation is a detoxification reaction because of the more hydrophilic character of the formed adduct as compared to the parent quinone. This conjugation either can occur spontaneously via a reductive addition or is catalyzed by glutathione-*S*-transferases leading to hydroquinone-glutathionyl conjugates (Buffinton et al. 1989; Jakoby and Ziegler 1990). PAH *o*-quinones can be detoxified by the non-enzymatic or enzymatic conjugation with cellular thiols (Murty and Penning 1992). The conjugation of quinones-GSH by the detoxification enzyme glutathione-*S*-transferase represents the defense mechanism of melanocytes against the melanocytotoxic chemicals hydroquinone (25) and 4-hydroxyanisole (26), compounds that after oxidation lead to skin depigmentation (Bolognia et al. 1995; Kasraee et al. 2003).

Although it has been shown in the above section that nucleophilic addition leads to quinones's detoxification, yet, in some cases it might lead to enhanced toxicity. For instance, quinone-GSH conjugation can also contribute to compound toxicity. This is caused in some cases by the faster redox cycling of the glutathionyl conjugates compared to that of the parent quinone (Buffinton et al. 1989; Jakoby and Ziegler 1990; van Ommen et al. 1992). Recent studies have shown that thiol conjugation in position 19 of the quinone ring of the four anticancer compounds BAs derivatives (22) may play a role in their mechanism of liver toxicity (Cysyk et al. 2006; Guo et al. 2008). Another mechanism of toxicity stems from the significant depletion of the reduced thiol form of glutathione by alkylation in the presence of high concentrations of quinones. Once the detoxification system is saturated by GSH depletion, cellular SH-dependent proteins can be alkylated, thereby causing irreversible changes and cell death (Buffinton et al. 1989; Jakoby and Ziegler 1990). The propensity of quinones to bind to nucleophilic functional groups, commonly found on many cellular components, represents the most popular mechanistic theory underlying their toxicity. The intrinsic chemical reactivity of quinones controls the speed and type of the quinone-protein conjugation reactions (Ito and Wakamatsu 2008). Mutation and/or protein dysfunction can result from the conjugation of quinones to proteins or DNA. The binding of quinones to proteins can also lead, through the recognition of quinone-bound epitopes from degraded protein, to immunological damage. For instance, quinone-protein conjugation has been implicated in playing a causative role in the incidence of certain allergic or idiosyncratic drug reactions (Lepoittevin and Benezra 1991; Parrish et al. 1997; Petersen 2002). Contact allergic reactions have been linked to 2-hydroxy-2,4-naphthoquinone (henna) (27), a principal ingredient in many types of body dyes (Bolhaar et al. 2001; Calogiuri et al. 2010). Menadione (21) has been also found to react non-enzymatically with protein thiols that are present in rat plasma and generate ROS that potentiate cellular injury to platelets (Chung et al. 1999).

Analytical methods for the detection of quinones

A wide range of analytical methods has been reported for the determination of quinones in plants, pharmaceutical preparations, as well as in biological samples. Gas chromatography (GC) (Raspotnig et al. 2010; Zuo et al. 2008), Raman microscopy (Beattie et al. 2007), high-performance liquid chromatography (HPLC) (Sakunphueak and Panichayupakaranant 2010; Xue et al. 2008), and mass spectrometry (MS) (Zhao et al. 2010) have been used for the

identification and quantification of quinones. An extensive literature search showed that among the methods, HPLC or HPLC/MS are the most often used methods. Despite the fact that many methods have been used, the identification and quantification of quinones is still challenging. Efforts to establish efficient, accurate and precise procedures for their quantification are ongoing.

Sample cleanup procedures for quinones are usually performed using solid phase extraction (SPE), liquid–liquid extraction (LLE) or protein precipitation. Protein precipitation using methanol, ethanol, and acetonitrile has been usually used to disrupt protein binding and remove interferences from biological samples. SPE, in addition to its use as a cleanup method, is performed to concentrate the samples. C18 and Oasis HLB cartridges are the most commonly used during sample preparations (Azharuddin et al. 2007; Karpinska et al. 2006; Vainchtein et al. 2008).

Detection methods such as UV (Fahmy et al. 2004; Ojha et al. 2009; Qian et al. 2008; Song et al. 2010; Xue et al. 2008), chemiluminescence (CL) (Ahmed et al. 2007; Ahmed et al. 2009), and fluorescence (Azharuddin et al. 2007), have been combined to HPLC methods. Several quinones can be detected by chemiluminescence due to their ability to generate hydrogen peroxide and a fluorophore when subjected to UV irradiation, a property that allows their determination by mixing with aryloxalate through peroxyoxalate chemiluminescence (PO-CL) reaction (Ahmed et al. 2007). Also post column chemical reduction for the detection of the reduced form of the quinone using a catalyst reduced column and a methanol-ethanol mobile phase as reductant have been used (Azharuddin et al. 2007).

Gas chromatography can also be used for the detection of various quinones. Samples require often derivatization with *N,O* –Bis (trimethylsilyl) trifluoroacetamide) +1% TMCS (trimethylchlorosilane) (El Sohly et al. 2004); they are often separated using dimethylpolysiloxane and silica based columns (El Sohly et al. 2004; Zuo et al. 2008).

Mass spectrometry, in negative or positive ionisation mode, is often coupled to GC or HPLC for the identification of the quinones. Different mass analysers are used, depending on the structures of the studied compounds, especially electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI) instruments such as triple-quadrupole and ion trap instruments which enable tandem mass spectrometry (MS/MS) measurements.

There is a large variation in the limits of quantification (LOQ) reported for various quinones, as the LOQs range from 0.067 to 6,070 ng/ml with HPLC methods, while they can range from 0.5 to 600 ng/ml with GC methods. This data show that, while all compounds are quinones, their actual nature and chemical properties vary, and their analytical detectability is dependent on the chemical structure of the compound but also on the analytical method used.

Although seldom used, Raman microscopy has been applied for the identification and localization of vitamin E (9) and related lipophilic compounds in complex biological samples. This non-destructive analysis may allow the discrimination between different tocopherols and oxidation specimens as well as the visualization of lipid-protein interactions. As an imaging technique, Raman microscopy may help to identify biological functions of alpha tocopherol especially, with regards to intracellular distributions and metabolic fate (Beattie et al. 2007).

A summary of different analytical methods used for the detection of quinones in different matrices is presented in Table 1. For each method a summary of the followings is presented: compound analysed, matrix, sample cleanup, separation, detection, and minimum quantification limits.

Detection of labeled quinones in biological samples

Wherever the conventional analytical methods for studying quinones in biological samples have failed in their detection, other approaches such as the use of radiolabeled or isotopically labeled compounds have been adopted.

Tracer compounds whether isotopic or radioactive are useful tools for measuring and understanding the metabolism and disposition of both endogenous molecules and drugs. This is true in the case of compounds that are unstable or require to be detected at low concentrations.

Studying quinones is challenging due to their high reactivity as fast redox cycling molecules as well as their potential of binding to hydroxyl, thiol, and amine groups. Therefore, designing radiolabeled or

Table 1 Summary of selected analytical methods used for the detection of quinones

Compound (s)	Matrix	Sample preparation	Separation	Detection	LOQ (ng/ml)	Ref
Coenzyme Q (7) and its impurities	Bulk drug formulations	Coenzyme Q Capsule formulation dissolved in H_2O and extracted by hexane	C_8 column Mobile phase: ACN-isopropanol (84:16, v/v)	NARP-HPLC- PDA: 210 nm The impurities identified by APCI-MS in positive ionization mode	290	Nageswara Rao et al. (2008)
Vitamin K1 (8a)	Human plasma	Protein precipitation with EtOH followed by SPE using C_{18} column	C_{18} column A post column reactor was connected between the C_{18} column and the detector. Mobile phase: MeOH - EtOH (80:20, v/v)	HPLC-fluorometric detection after reduction with platinium reactor. Excitation wavelength: 244 nm Emission wavelength: 420 nm	0.067	Azharuddin et al. (2007)
Vitamin K1 (8a), Vitamin K2 (8b)	Human plasma	Protein precipitation with EtOH followed by extraction with hexane	C_{18} column Mobile phase: imidazol-HNO3 buffer (600 mM, pH 9)-ACN (5:95, v/v) and 0.6 mM TDPO in ACN as post column CL reagent	HPLC-PO-CL following on line-UV irradiation	14.4 (vitamin K1), 16.9 (vitamin K2 ($n - 1 = 4$)), 55.16 (vitamin K2 ($n - 1 = 7$))	Ahmed et al. (2007)
Indoloquinone (17)	Human/dog plasma	Extraction with ethyl acetate	C_{18} column Mobile phase: gradient elution with 1 mM ammonium hydroxide in H_2O/MeOH	HPLC/MS/MS using ESI in positive ionization mode	0.5	Vainchtein et al. (2008)
Emodin (14), Aloe-emodin (34), Rhein (35), chrysophanol (38), physcion (39)	Plant (radix *Polygoni multifori*)	Extraction with MeOH followed by derivatization with BSTFA* + 1% TMCS	EC^{TM}- 5 capillary column	Capillary GC-FID/MS	220 (Emodin), 600 (Rhein),260 (chrysophanol), 520 (Aloe-emodin), 540 (physcion)	Zuo et al. (2008)
Coenzyme Q_{10} (7), vitamin E (9)	Human plasma	Protein precipitation with MeOH followed by extraction with hexane	C_{18} column Mobile phase: MeOH - hexane (72:28, v/v)	HPLC–UV 276 nm (coenzyme Q (7)) 292 nm (vitamin E (9)	0.71 (coenzyme Q_{10}), 0.33 (vitamin E)	Karpinska et al. (2006)
Emodin (14), Rhein (35), chrysophanol (38), physcion (39)	Plant (rhisoma et radix polygoni cuspidate)	Extraction with MeOH	C_{18} column Mobile phase: gradient elution with H_2O (0.4% formic acid)-ACN	HPLC–UV (290 nm)	620 (Rhein, chrysophanol), 544 (physcion), 330 (Emodin)	Qian et al. (2008)
Doxorubicin (15), 5-Fluorouracil (19)	Human plasma	Protein precipitation with MeOH	C_{18} column Mobile phase:0.05 M disodium hydrogenphosphate in 0.1% (w/v) laurylsulfate (pH 3.7)-ACN (50:50, v/v)	HPLC–UV (260 nm)	6070 (Doxorubicin), 1620 (5-Fluorouracil)	Fahmy et al. (2004)

Table 1 continued

Compound (s)	Matrix	Sample preparation	Separation	Detection	LOQ (ng/ml)	Ref
Aloe-emodin (34), aloin A (40)	Commercials Aloe-based products (liquids, gels and solids)	Extraction with ethylacetate/MeOH followed by derivatization with BSTFA*	DB-1 GC column	GS/MS	5 (aloe-emodin), 50 (aloin A)	ElSohly et al. (2004)
Menatetrenone (28), Menatetrenone epoxide (29)	Human plasma	Protein precipitation with MeOH	C_{18} column Mobile phase: MeOH	LC/MS/MS with APCI in positive ionization mode	2.5	Kang et al. (2007)
Vitamin K1 (8a)	Human plasma	Protein precipitation with EtOH followed by SPE	C_{18} column Mobile phase: MeOH-EtOH (95:5, v/v)	HPLC-fluorometric detection after post column reduction with zinc. Excitation wavelength:244 nm Emission wavelength:430 nm	0.09	Paroni et al. (2009)
Chimaphilin (30)	Rat plasma	Extraction with diethylether	C_{18} column Mobile phase: MeOH–H_2O (75:25, v/v)	HPLC-APCI in negative ionization mode	10	Zhang et al. (2006)
Mitoquinone (31) and its metabolites	Rat plasma	Protein precipitation with ACN	C_{18} column Mobile phase:0.1% formic acid in H_2O -0.1% formic acid in ACN	HPLC/MS/MS using ESI in positive ionization mode	0.5	Li et al. (2007)
Buparvaquone (32)	Rat perfusion solution	Centrifugation	C_4 column Mobile phase: ammonium acetate (0.02 M)-ACN (30:70, v/v)	HPLC–UV (251 nm)	200	Venkatesh et al. (2007)
Buparvaquone (32)	Human and rabbit plasma	Protein precipitation with ACN followed with SPE	C_{18} column Mobile phase: ammonium acetate (0.02 M)-ACN (18:82, v/v)	HPLC–UV (251 nm)	50	Venkatesh et al. (2008)
Naphtoquinones (3)	Plant material (E. Americana bulbs)	Extraction with MeOH	C_{12} column Mobile phase: gradient elution with H_2O (0.01%formic acid)-CAN	HPLC–UV (254 nm)/MS using ESI in alternating ionization mode	1300–2800	Paramapojn et al. (2008)
Plumbagin (33)	Rat plasma	Extraction with ethylacetate	C_{18} column Mobile phase: H_2O/ACN (40:60,v/v)	LC–MS/MS using ESI in negative ionization mode	10	Hsieh et al. (2006)
Emodin (14), Aloe-emodin (34), Rhein (35)	Rat plasma	Protein precipitation with MeOH	C_{18} column Mobile phase: H_2O (0.1% formic acid)- MeOH (30:70, v/v)	LC–MS/MS using ESI in negative ionization mode	0.5 (Emodin), 0.2 (Aloe-emodin), 2 (Rhein)	Xu et al. (2008)

Table 1 continued

Compound (s)	Matrix	Sample preparation	Separation	Detection	LOQ (ng/ml)	Ref
Acetylshikonin (36), B-acetoxyisovaleryls-hikonin (37)	Cell culture suspension of A. *euchroma*	Extraction with chloroform	C_{18} column Mobile phase: ACN- MeOH (95:5, v/v)	Prep-HPLC (520 nm)	209 (Acetylshikoni), 487 (B-acetoxyisovaleryl-shikonin)	Sharma et al. (2008)
17AAG (22,-R:$NHCH_2CHCH_2$), 17AG (25,-R:$NHCH_2CH_2NC_4H_8$)	Human plasma	Protein precipitation with ice cold ACN	SB-phenyl column Mobile phase: gradient elution with H_2O (0.1% acetic acid)-ACN (0.1% acetic acid)	HPLC/MS using APCI in negative ionization mode	0.5	Johnston et al. (2008)
17DMAG (22-R: $NHCH_2CH_2N(CH_3)_2$)	Human plasma	Extraction with ethylacetate	C_{18} column Mobile phase: H_2O (0.2% formic acid)- MeOH (45:55, v/v)	HPLC/MS using ESI in positive ionization mode	1	Chen et al. (2007)
17DMAG (22-R: $NHCH_2CH_2N(CH_3)_2$)	Human plasma	Extraction with ethylacetate	Synergy polar-RP (ether-linked phenyl phase) = phenyl column Mobile phase: gradient elution with H_2O (0.1% formic acid)- MeOH	LC–MS/MS using ESI in positive ionization mode	1.1	Moreno-Farre et al. (2006)
Emodin (14), ALoe-emodin (34), Rhein (35), chrysophanol (38), physcion (39)	Plant (rhubarb)	Extraction of the MeOH plant extract with chloroform	C_{18} column Mobile phase: H_2O (0.1% phosphoric acid)-MeOH (31:69, v/v)	UPLC (254 nm)	200 (Emodin, Rhein, chrysophanol), 120 (Aloe-emodin), 400 (physcion)	Wang et al. (2008)
β-lapachone (24)	Mouse plasma, tumor homogenate	Protein precipitation with ACN	SB-C_8 column Mobile phase: gradient elution with H_2O (0.1% formic acid)-ACN (0.1% formic acid)	HPLC/MS/MS using ESI in positive ionization mode	3	Savage et al. (2008)
Vitamin E (9), Menadione (21)	Animal feed	Samples treated with Savinase proteinases followed with extraction with EtOH and SPE	C_{18} column Mobile phase:MeOH- H_2O (98:2, v/v)	HPLC–UV 230 nm Vitamin E (9), 265 nm Menadione (21)	250–4200	Xue et al. (2008)

**MeOH* methanol, *EtOH* ethanol, *ACN* acetonitrile, *H_2O* water, *BSTFA N,O* -Bis(trimethylsilyl)trifluoroacetamide, *TMCS* trimethylchlorosilane, *NARP* non-aqueous reversed phase, *FID* flame ionization detection

isotopically labeled quinone molecules could improve their detection. Several studies using labeled quinones have been conducted so far and were very instrumental in clarifying their metabolic fate and/or mode of action. Safety concerns especially, for in vivo applications limit the use of radioactive tracers; Consequently, efforts are directed onto the use of stable isotopes which are non-radioactive forms of elements that naturally occur within the environment and are safe for human studies. These isotopes can be separated and quantified by mass spectrometry which allows also determining simultaneously the tracer and tracing molar ratios.

A thorough literature search showed that extensive efforts have been made to study Vitamin K1 (8a). Specific challenges for vitamin K1 (8a) analysis in plasma result from its low concentration, interfering plasma lipid components, and the sensitivity of the molecule to degradation by light and strong alkalines. Therefore, in vivo studies using labeled vitamin K1 (8a) quinones have been conducted. Extensive efforts for studying labeled vitamin K1 (8a) have been made over the last 30 years for better understanding its metabolic turnover as well as its absorption and disposition. Between 1972 and 1979, three attempts to measure vitamin K1 (8a) turnover in human subjects have been made by using [1′, 2′-$^{3}H_2$] vitamin K1 (8a). However, none of these studies has allowed the calculation of the body pool of vitamin K1 (8a) due to the absence of a suitable method for measuring vitamin K1 (8a) in plasma (Bjornsson et al. 1979; Shearer et al. 1972, 1974). Nearly 20 years later, Olson et al., succeeded to determine the total body vitamin K1 (8a) and its turnover in human subjects at two levels of vitamin K intake using tritiated vitamin K1 (8a) (Olson et al. 2002). A GC/MS method has been validated for the measurement of isotope ratios of vitamin K1 (methyl-^{13}C or ring deuterated) obtained from human volunteers. The method involves liquid–liquid extraction, enzyme hydrolysis, solid phase extraction and subsequent derivatisation with pentafluoropropionic anhydride before the analysis. The major advantage of derivatisation is the increase in molecular weight of vitamin K1 to a region of the mass spectrum where there is less interference from other biological compounds (Jones et al. 2006).

In a human study the use of an HPLC method for the assessment of vitamin K transport during the ingestion of collard greens containing physiological dose of vitamin K1 (8a) that has been endogenously labeled with deuterium has been reported. The intrinsic labeling and delivery method has allowed tracking of the exogenous vitamin K1 (8a) derived from the test meal that included collard greens. The method has shown that deuterated-vitamin K1 (8a) is rapidly cleared from plasma and the triglyceride rich lipoprotein fraction is its major carrier, whereas LDL and HDL fractions carry small amounts. The percent recovery of vitamin K1 (8a) from the subfractions is less than 50%, suggesting that detection is limited by the assay sensitivity (Erkkila et al. 2004).

Absorption and clearance of deuterated-vitamin K extracted from broccoli has been also studied in human serum by HPLC and GC/MS (Dolnikowski et al. 2002). The bioavailability of ^{13}C-vitamin K has been determined following feeding carbon-13 labeled kale (*Brassica oleracea* var. acephala) to an adult volunteer. The LC-APCI-MS method has allowed simultaneous selective detection of labeled and unlabeled molecule as well as defining their kinetic curve (Kurilich et al. 2003).

The use of deuterium-labeled form of vitamin K1 (8a) along with structural assignments by NMR spectrometry and liquid chromatography-tandem mass spectrometry (LC–MS/MS) has offered unequivocal evidence of the origin of vitamin K2 in the cerebra of mice when given vitamin K1 as the sole source of vitamin K (Okano et al. 2008). Two forms of vitamin K occur naturally. Vitamin K1 (8a) is produced by plant and algae while vitamin K2 (8b) is derived from bacteria and animals (Kamao et al. 2007). Over 90% of dietary vitamin K is vitamin K1 (8a) but its concentration in animal tissues is considerably low compared with vitamin K2 (8b) that corresponds to more than 90% of vitamin K in tissues (Okano et al. 2008). It has been reported that the livers of chicks, fed with vitamin K1 (8a) as a sole source of vitamin K, contain as much vitamin K2 as vitamin K1 (Will et al. 1992). It is claimed that vitamin K2 in tissues originate from the conversion of vitamin K1 (8a) (Davidson et al. 1998; Ronden et al. 1998). The use of D-labeled compound has shown that cerebral vitamin K2 originates via two potential mechanisms, 1) from systemic conversion comprising the release of menadione from vitamin K1 in the intestine and the prenylation of menadione into vitamin K2 in the cerebra and 2) the in-cell

conversion of vitamin K1 into vitamin K2 in cerebra (Okano et al. 2008).

Although safety concerns limit the use of radiolabeled compounds in vivo, this method is still in use in vitro. Miao et al. (Miao et al. 2008) have shown in an in vitro study that β-lapachone (24), a promising anticancer compound, is metabolized by red blood cells (RBCs). While studying its in vitro metabolism in plasma and whole blood, the compound could not be detected with conventional LC–MS. The use of ^{14}C β-lapachone (24) has allowed studying the metabolic profiling, and determined the reason for the failure of its detection in blood using the conventional analytical methods. Using LC–MS coupled to a radioisotope counting system it has been shown that β-lapachone (24) is extensively metabolized in whole blood under in vitro conditions and that the enzymatic activity is located in the RBC. By determining the percent of radioactivity present in protein pellet prepared from whole blood spiked with ^{14}C β-lapachone, it has been proven that covalent protein binding of β-lapachone and/or its metabolites is a minor contributor in the failure of its detection in blood (Miao et al. 2008).

^{14}C labeling has been also used for the study of Coenzyme Q (7) biosynthesis in HepG2 cells. Therefore, the labeled compound could be useful for diagnosis of patients with deficiency in Coenzyme Q (7) biosynthesis. The method has involved incubation of the cells with the radioactive precursor 4-hydroxy-[U-^{14}C] benzoate for 24 h followed by different extraction procedures including: 1) alcohol-hexane lipid extraction, 2) alcoholic-hexane lipid extraction from trichloroacetic acid (TCA)-insoluble materials, and 3) NaOH solubilisation from (TCA)-insoluble materials. HPLC analysis along with quantification of radioactivity by scintillation counter has shown 1) total conversion of 4-hydroxy-[U-^{14}C] benzoate to CoQ, and 2) high radioactivity observed by direct alkali solubilisation of TCA-insoluble materials without the necessity for lipid extraction (Cordoba-Pedregosa Mdel et al. 2005).

In addition to their importance in giving a better understanding of compound disposition, radiolabeling methods can also be used with the aim of finding a promising radiopharmaceutical in nuclear medicine. The potential use of iodine-labeled 17AAG (22,R:$NHCH_2CHCH_2$), [^{131}I] Iodo-17-AAG, as a target for tumor imaging or as treatment agent has been investigated (Daozhen et al. 2007).The study shows that the distribution of the labeled molecule in mice is consistent with the biologic distribution of the unlabeled one.

Conclusion and future prospects

Quinones are an important class of molecules harbouring physiological and therapeutical effects. They have two properties that define their biological activities; The first is their ability to undergo one or two electron reduction and the second is their ability to undergo nucleophilic attack. In many cases quinones's activity/metabolic fate determination is difficult for their isolation and detection from biological matrices is problematic. Fortunately, these problems may be overcome and a better understanding of quinones' activity and potential use will be more readily available with the ongoing advances in the available analytical methods along with the possibility of using labeled compounds.

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