



Review

Analytical techniques for the determination of biologically active quinones in biological and environmental samples



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ABSTRACT

Quinones are compounds that have various characteristics such as biological electron transporter, therapeutic agent and harmful environmental pollutant. Therefore, an effective analytical method for quinones is useful in many fields including biomedical, clinical and toxicological studies. This review describes the principle and feature of analytical techniques for quinones including high-performance liquid chromatography with ultraviolet, fluorescence, chemiluminescence, electrochemical detection and mass spectrometry, gas chromatography with mass spectrometry and capillary electrophoresis. Furthermore, the sensitivity and the sample preparation method for the determination of several quinones such as vitamin K, ubiquinone, doxorubicin and polycyclic aromatic hydrocarbon quinone in biological and environmental samples are summarized.

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1. Introduction

Quinones are interesting compounds which have unique characteristics and several important roles. Quinones are widely distributed in the nature including plant and animal tissues.

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Quinones have an important role in the electron transport chain to maintain biological functions of plants and animals. It is well known that plastoquinone is involved in the light-dependent photosynthetic reactions in plants. In the animal system, ubiquinone (UQ, other name for coenzyme Q₁₀(CoQ₁₀)) acts as an electron carrier in the mitochondrial electron transport chain and participates in aerobic cellular respiration and energy production [1,2]. Also, quinone structures are related to some vitamins. Vitamin K is a structurally related group of 2-methyl-1,4-naphthoquinone derivatives having either a phytyl side chain (phylloquinone (PK), vitamin K₁), or a side chain with repeated isoprenoid units (menaquinones (MKs), vitamin K₂). It was known that vitamin K has a beneficial role in blood coagulation, bone metabolism and growth [3–5]. α -Tocopherol, known as vitamin E, is oxidized to tocopherylquinone during the process of antioxidation [6]. It is conceivable that tocopherylquinone concentrations may be increased under pathological conditions. Recently, it has been reported that pyrroloquinoline quinone is nutritionally important as a vitamin in mammals [7].

In addition to these biological roles, quinones have been used in a wide variety of clinical practice and industrial application. For example, doxorubicin (DXR) is an anthraquinone (AQ) antibiotic that has been used clinically in the treatment of malignant tumors [8]. AQ derivatives such as rhein, the principle active constituents of traditional Chinese herb rhubarb, have immunosuppressive and anti-inflammatory effects [9]. The structures of these AQ drug are shown in Fig. 1. Vitamin K is clinically applied for the treatment of several diseases including osteoporosis and vitamin K deficiency symptoms [5]. In addition, AQ derivatives are used as a large class of dyes and pigments [10].

While quinones have several beneficial effects mentioned above, they are regarded as a class of toxins which can cause a variety of hazardous effects on living cells. For example, quinones act as a generator of reactive oxygen species (ROS) through the redox cycle in biological system and ROS can induce several types of oxidative damage such as lipid peroxidation [11,12]. Additionally, some quinones such as 9,10-phenanthrenequinone (PQ) serve as an inhibitor of certain enzymes, for example, nitric oxide synthase or glyceraldehyde-3-phosphate dehydrogenase, by the covalent binding to the active site of enzymes [13,14]. In the atmospheric environment, the presence of polycyclic aromatic hydrocarbon quinone (PAHQ) including PQ was confirmed [15]. It was thought that PAHQs are formed by photo-oxidation of polycyclic aromatic hydrocarbons (PAHs) that are mainly released from motor vehicle engines in atmosphere (Fig. 2). PAHQ in atmospheric environment is considered to be involved in the pathogenesis of respiratory diseases [16].

From these aspects, the determination method of quinones in biological and environmental samples should be important in various fields including the investigation of physiological properties of quinone, therapeutic monitoring of quinone drugs and the estimation of risk of toxic quinones on human health. In this review, the principle and the feature of analytical techniques for biologically active quinones especially vitamin K, UQ, DXR and PAHQ are described according mainly to the recent reports. Furthermore, the sensitivity and the sample preparation procedure for the determination of these quinones in biological and environmental samples are summarized in tables.

2. Analytical techniques for quinones

Until now, various analytical methodologies have been developed for the determination of quinones. In the following section, the principle and the feature of analytical techniques for quinones are described.

2.1. High-performance liquid chromatography (HPLC)

Chromatographic separation is one of the techniques of choice for the analysis of various compounds in complicated matrices. Thus, HPLC is one of the most frequently used tools for the analysis of quinones in biological and environmental samples. Several detection techniques including ultraviolet (UV), fluorescence (FL), chemiluminescence (CL), electrochemical detection (ECD) and mass spectrometry (MS) have been coupled with HPLC analysis.

2.1.1. HPLC-UV

HPLC with UV detection method is most common and widespread due to its easy handling nature. Various HPLC-UV methods for quinones have been developed because most of quinones have absorbance at UV region [17–20]. However, the sensitivity of UV detection is insufficient to determine trace amount of quinones. Also, the selectivity of UV detection is generally low because co-existing UV-absorbing compounds can interfere with the detection of quinones. Even though the low sensitivity and selectivity, HPLC-UV has been frequently utilized for the simultaneous determination of quinones and other types of compounds owing to its universality. For example, vitamin K and UQ were determined with other fat soluble vitamins such as retinol (vitamin A) and α -tocopherol in biological fluids [17,18]. Also, simultaneous determination method for co-administered anticancer drugs including DXR and 5-fluorouracil was developed by HPLC-UV in order to explore the synergistic effects between these drugs [19].

2.1.2. HPLC-FL

Since FL detection is usually sensitive and selective than UV detection, a large number of chemicals were measured by HPLC with FL detection technique. Among quinones, AQ derivatives such as DXR and rhein have strong FL itself, thus these compounds were determined directly by HPLC-FL [21,22]. However, most of quinones do not have intrinsic FL. Therefore, several FL derivatization reactions were developed for the conversion of non- or weakly fluorescent quinone to strongly fluorescent derivative.

The most simple derivatization reaction is the reduction of quinone to fluorescent hydroquinone and this reaction has frequently been applied to determine vitamin K in biological samples by HPLC-FL. Vitamin K (NQ derivative) was reduced to corresponding hydronaphthoquinone and it was detected at excitation and emission wavelengths of 240 or 320 and 430 nm, respectively. Several chemical reductants such as sodium borohydride, zinc and platinum were used for the FL derivatization of vitamin K. Sodium borohydride solution was used as a post column derivatization reagent [23]. Zinc was usually packed in a stainless steel column and it was incorporated as an on-line reactor between an analytical column and a fluorescence detector [24]. A platinum catalyst reduction column was also used as an on-line reactor for the reduction of vitamin K [25] and it was known that the durability of platinum was higher than that of zinc. In addition to chemical reduction, electrochemical or photochemical reduction was also employed for the FL derivatization of vitamin K. In an HPLC system coupled with an on-line electrochemical reactor, vitamin K was reduced prior to fluorescence measurements by applying a negative voltage [26,27]. A photochemical reactor constructed of PTFE tubing coiled around a low-pressure mercury lamp could reduce vitamin K to hydronaphthoquinone in the presence of sodium dodecyl sulfate (SDS) and methanol [28]. The direct reductive derivatization reaction was also applied for quinones other than vitamin K. Pollok and Melchert developed an HPLC-FL system with on-line photoreactor for the determination of tocopherylquinones in human serum [29]. In this HPLC system, tocopherylquinones were reduced to corresponding tocopherylhydroquinone under UV irradiation and they were detected at 331 nm with an excitation at 294 nm. Also,

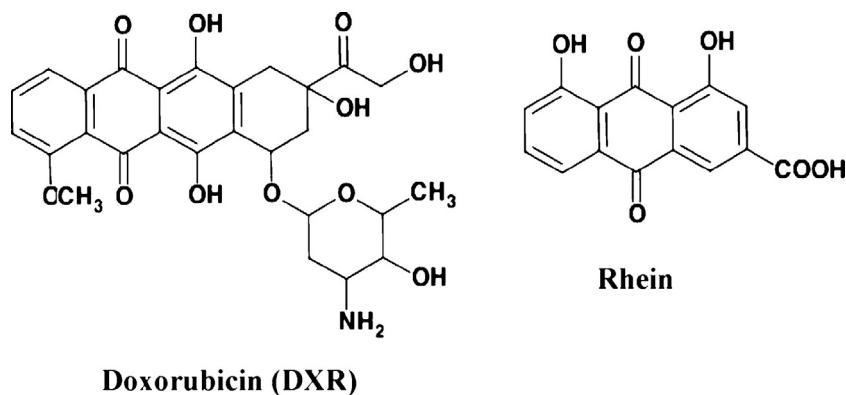


Fig. 1. Structures of anthraquinone (AQ) derivative drug, doxorubicin and rhein.

the performance of the photochemical reactor was compared with that of a zinc catalyst reduction column as the reduction system for tocopherylquinone, and it was concluded that the reducing ability of zinc was deteriorated within short time. Kameda et al. used a platinum–rhodium catalyst column for the conversion of benz[*a*]anthracene-7,12-quinone (BaAQ), one of PAHQ detected in airborne particulates, to dihydroxybenz[*a*]anthracene which show fluorescence at 465 nm with an excitation at 285 nm [30]. On the other hand, a reduction of UQ to ubiquinol for the FL determination of UQ was not practical because the sensitivity of HPLC-FL detection of ubiquinol reduced from UQ was inferior to that of HPLC-UV detection of UQ [31].

Other than reductive derivatization reaction, several reagents were developed for the FL derivatization of quinones. It was found that PQ could be converted to strongly fluorescent lophine derivative by the reaction with benzaldehyde in the presence of ammonium acetate (Fig. 3) [32]. Based on this reaction, an HPLC method for the determination of PQ in airborne particulates was developed using pre-column derivatization and FL detection. Furthermore, 4-carbomethoxybenzaldehyde was discovered as the most suitable derivatization reagent for PQ compared to other aldehyde because the derivative shows stronger fluorescence at longer wavelength region [33]. Additionally, a simple and rapid determination method for PQ was developed by HPLC with post-column

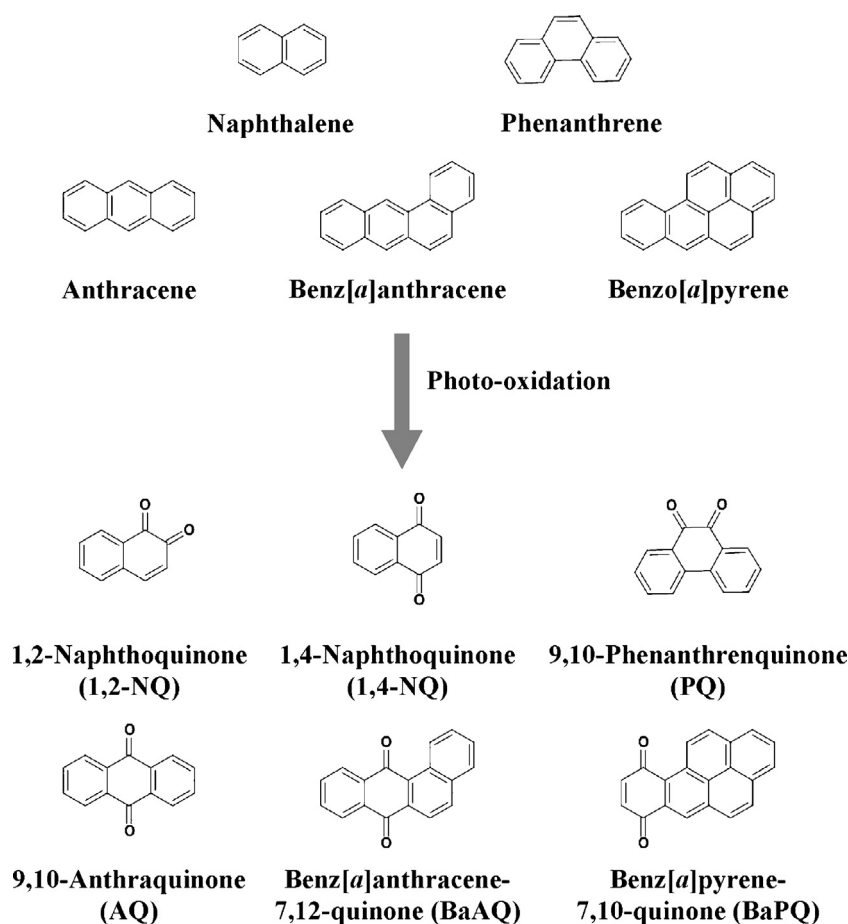


Fig. 2. The formation of polycyclic aromatic hydrocarbon quinones (PAHQs) by photo-oxidation of polycyclic aromatic hydrocarbons (PAHs).

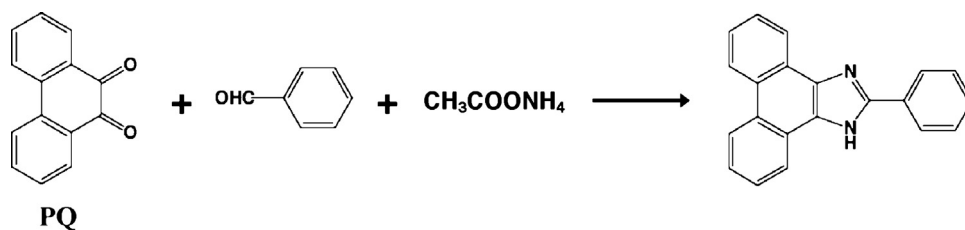


Fig. 3. Fluorogenic derivatization of phenanthrenequinone (PQ) with benzaldehyde and ammonium acetate.

derivatization and FL detection. This method was based on the reaction of PQ with 2-aminothiophenol under acidic condition to form fluorescent derivative, which emits green fluorescence at 510 nm [34]. On the other hand, Nohara et al. developed an HPLC with post-column FL derivatization method for the determination of UQ in plasma using 2-cyanoacetoamide as a reagent. They reported that 2-cyanoacetoamide reacted with UQ under alkaline conditions through Craven's reaction to form fluorescent derivative, which emits fluorescence at 549 nm with an excitation at 442 nm [35].

2.1.3. HPLC-CL

Among several detection methodologies, it is well known that CL detection has numerous advantages owing to its high sensitivity, selectivity and wide linear working ranges. However, since quinone cannot react with CL reagents such as luminol and diaryl oxalate, it is difficult to detect directly by CL. Therefore, a redox or photochemical reaction was applied to convert quinone to ROS, which can be sensitively detected by CL [36].

A unique CL assay for quinones including UQ based on their redox reaction cycle was developed [37]. In this assay, quinones were reduced to semiquinone radicals by dithiothreitol (DTT) as a reductant. Successively, semiquinone radicals convert dissolved oxygen to superoxide anion, which reacts with luminol to generate CL (Fig. 4). An HPLC-CL method based on this CL reaction system was developed for the determination of UQ in plasma samples [38].

An HPLC method was developed for the determination of quinones with peroxyoxalate chemiluminescence (PO-CL) detection following on-line UV irradiation. This method was based on simultaneous formation of hydrogen peroxide and a fluorescent photoproduct, 3,6-dihydroxyphthalic acid (DHPA) under UV irradiation to quinone, and the liberated hydrogen peroxide and fluorophore were mixed with only diaryl oxalate to produce PO-CL [39]. The proposed HPLC-PO-CL system was applied for the determination of vitamin K [40] and DXR [41] in plasma samples. Additionally, it was noticed that DHPA has an enhancing effect on luminol CL [42]. The photogeneration of the enhancer (DHPA) in association with the ROS in that photochemical reaction greatly increases the light output of luminol CL. This phenomenon allowed the development of a highly sensitive and selective HPLC-CL method for the determination of quinones. The developed HPLC-luminol CL method was successfully applied to determine PAHQs such as NQ, PQ and AQ in airborne particulates or to determine vitamin K in plasma sample obtained from rheumatoid arthritis patients [43].

On the other hand, Li et al. reported an HPLC-CL method for the determination of benzo[*a*]pyrene-7,10-quinone (BaPQ) in airborne particulates [44]. The method is based on the enhancing effect of BaPQ on the CL generated from the reaction between sodium hydro-sulfite and hydrogen peroxide.

2.1.4. HPLC-ECD

HPLC-ECD is a sensitive and suitable method for the determination of compounds having electrochemical activity. Since quinones are electroactive species, HPLC-ECD should be an effective analytical method for quinones. However, quinone has to be detected

with ECD in the reductive mode. In the reductive mode, complicated degassing instruments are required in order to remove the influence of dissolved oxygen in mobile phase. Thus, quinone is usually reduced to hydroquinone prior to measurement with ECD in the oxidative mode. Where, the signal response was achieved with the re-oxidation of hydroquinone to quinone.

The HPLC-ECD methods after quinones reduction were frequently used for the determination of UQ in biological samples. Chemical reductants such as sodium borohydride, zinc and platinum could be used for the reduction of UQ in a similar way to the reductive FL derivatization of quinone. Sodium borohydride was added to UQ solution as a pre-column reductant and then the mixture was injected into an HPLC-ECD system [45,46]. Leray et al. reported an HPLC-ECD system that was equipped with a column packed with zinc for the post-column reduction of UQ, and the HPLC system was applied to the simultaneous determination of UQ and tocopherylquinone [47]. HPLC-ECD systems having a platinum catalytic reduction column placed downstream of an analytical column were also developed [48–50]. An on-line electrochemical reactor was also used to convert UQ to ubiquinol for an HPLC-ECD analysis. UQ was reduced by applying a negative voltage after the separation, and the formed ubiquinol was re-oxidized by applying positive voltage to measure UQ (Fig. 5) [51–53]. Additionally, HPLC-ECD methods with a platinum catalyst reduction column and with an on-line electrochemical reactor were applied to the determination of vitamin K [54] and DXR [55] in blood sample, respectively.

2.1.5. LC-MS

LC-MS is a sensitive and selective method, and provides not only quantitative information but also qualitative information. Even though the instruments for MS are expensive and not widespread, the application of LC-MS or LC-MS/MS for the determination of a variety of quinones has been increasing.

Since ionization efficiency of analyte influences on the sensitivity in LC-MS analysis, the selection of appropriate ionization mode should be important. Usually, four types of ionization mode are available, namely, atmospheric pressure chemical ionization (APCI) in the positive ion mode (APCI(+)), APCI in the negative ion mode (APCI(-)), electrospray ionization (ESI) in the positive ion mode (ESI(+)) and ESI in the negative ion mode (ESI(-)).

The ionization of vitamin K for LC-MS was usually performed using APCI (+). Ducros et al. compared the performance between APCI(+) and ESI(+) in the analysis of PK by LC-MS/MS, it was reported that the APCI gave a 5-fold higher signal-to-noise ratio than ESI [56]. Sano et al. concluded that ESI was not suitable for the ionization of MK because several adduct ions were formed by ESI [57]. Likewise, Suhara et al. employed an LC-MS/MS with APCI(+) for the simultaneous determination of PK and MKs [58]. The ionization of tocopherylquinone for LC-MS/MS analysis was also performed using APCI(+) like vitamin K [59].

Hansen et al. compared the chromatograms of UQ in serum extract obtained by LC-MS with four ionization modes [60]. They concluded that the APCI(-) was most convenient by considering the peak intensity of UQ against the intensities of interfering peaks derived from serum components. While, Li et al. employed

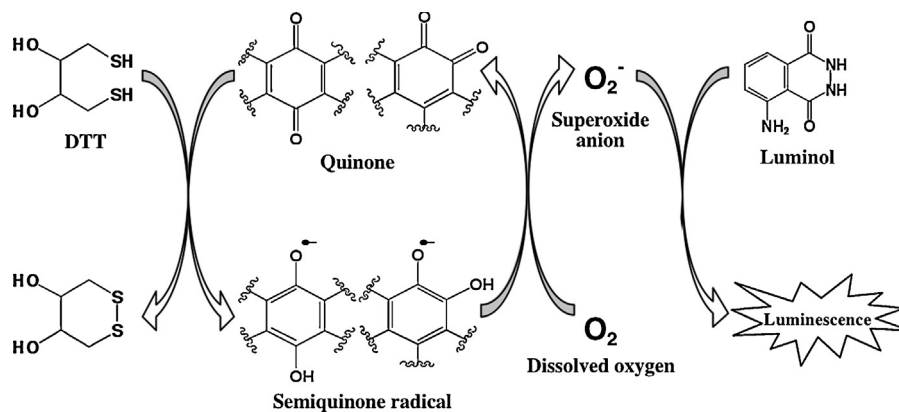


Fig. 4. Chemiluminescence assay for quinones based on generation of reactive oxygen species through the redox cycle of quinone.

an LC–MS with APCI(+) for the determination of UQ in rat plasma [61]. In addition, an LC–MS/MS with ESI(+) was used to determine UQ in human serum [62]. In this way, it seems to be no consensus on the ionization mode for UQ. Teshima and Kondo mentioned that the ionization efficiency of UQ was poor. In order to improve the ionization efficiency of UQ, they added methylamine as an ionization-supporting agent to the mobile phase of LC–MS/MS with APCI(+) system [63].

The ionization of AQ derivative was usually performed using ESI interface. Arnold et al. mentioned that ESI provided greater sensitivity than APCI for the detection of DXR by LC–MS/MS [64]. DiFrancesco also used an LC–MS/MS with ESI(+) for the simultaneous determination of DXR and their hydroxylated metabolites, doxorubicinol (DXR-ol) in biological samples [65]. In contrast, Rhein that has only carboxylic and hydroxyl group was determined by an LC–MS/MS with ESI(–) [66,67].

The ionization of PAHQ detected in atmospheric environment was performed using APCI interface. Both the positive and negative ion modes have been used for LC–MS analysis of PAHQ. Lintelmann et al. employed APCI(+) for the LC–MS/MS analysis of PAHQ [68,69]. On the other hand, Mirivel et al. employed APCI(–) considering the electrophilic nature of PAHQ [70]. Delhomme et al. compared the sensitivity of PAHQ between APCI(+) and APCI(–) [71]. As a result, limit of detections (LODs) obtained by APCI(–) (0.19–1.20 $\mu\text{g/L}$) were more sensitive than those (1.28–7.00 $\mu\text{g/L}$) obtained by APCI(+). Jakober et al. reported the derivatization method of PAHQ with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine (PFBHA) in order to improve the ionization efficiency in LC–MS/MS with APCI interface [72]. The application of PFBHA enhanced the sensitivity of PAHQ both in positive and negative ion modes. Although the negative ion mode gave better sensitivity for PAHQ without derivatization, the better sensitivity was obtained in the positive ion mode after derivatization.

2.2. Gas chromatography with mass spectrometry (GC–MS)

Since GC–MS is sensitive and offers higher resolution than LC, it is also widely used in biomedical and environmental analysis. However, due to low vapor pressure and ionization efficiency of

quinone, derivatization to improve volatility is necessary before GC–MS analysis. Several GC–MS methods have been developed for the determination of PK and PAHQ in biological and environmental samples. PK was firstly reduced by zinc to form chromanol and remaining hydroxyl group was esterified with perfluoroacetyl anhydride such as heptafluorobutyric anhydride (HFBA, Fig. 6) [73,74]. Fauler et al. compared the potential of three perfluoroacetyl anhydrides including trifluoroacetic anhydride, pentafluoropropanoic anhydride and HFBA for GC–MS analysis of PK in plasma, and reported that HFBA derivative showed the least interference from plasma components owing to its high molecular mass. In a similar way, PAHQ including NQ was reduced to hydroquinone by zinc and hydroxyl groups were esterified with acetic anhydride [75]. It was reported that the derivatization with zinc and acetic anhydride could improve the sensitivity of 1,2-NQ by approximately 100 times. On the other hand, Jakober et al. used PFBHA as a derivatization reagent for GC–MS analysis of PAHQ to form oxime derivative [76]. They reported that GC–MS was 4 times more sensitive for PFBHA derivative of benzoquinone compared to LC–APCI–MS.

2.3. Capillary electrophoresis (CE)

CE methods were developed for rapid analysis of quinone in blood samples. UQ in human plasma extract was separated from plasma components by microemulsion electrokinetic chromatography (MEEKC), which allows separation of neutral compounds, and UQ was detected at 275 nm of absorbance [77]. DXR in human plasma was also determined by CE with UV detection [78]. Furthermore, CE with laser-induced FL detection was developed for the sensitive determination of DXR in human serum. In this method, DXR was detected at a wavelength of 560 nm with an excitation at 488 nm by argon-ion laser [79].

2.4. Other analytical techniques

A voltammetric determination method for DXR in human plasma was reported. The method was based on measurement of the current originating from the reduction of DXR at nanoTiO₂-modified electrode [80]. An immunosensor for DXR was developed

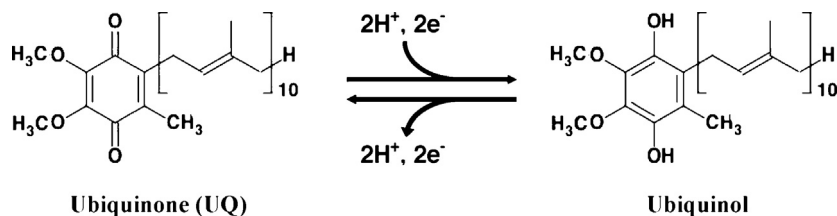


Fig. 5. Reduction of ubiquinone (UQ) to ubiquinol, and re-oxidation of ubiquinol to UQ.

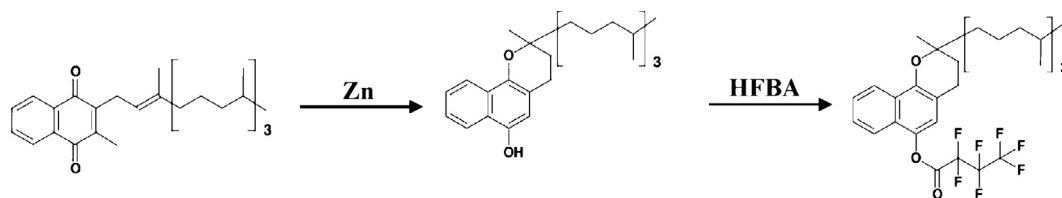


Fig. 6. Derivatization of phyloquinone (PK) with heptafluorobutyric anhydride (HFBA) after reduction with zinc.

by immobilization of a DXR-specific antibody on to the gold nanoparticles modified electrode [81]. The immunosensor could determine DXR in human serum without interference from biological components. An indirect competitive enzyme linked immunosorbent assay (ELISA) was developed for the specific determination of menadione (2-methyl-1,4-naphthoquinone) [82]. The monoclonal antibody used in the assay was prepared by ovalbumin modified with plumbagin (2-hydroxy-1,4-naphthoquinone) as a hapten protein. Due to the specificity of antigen-antibody interaction, the ELISA could determine menadione in fetal calf serum without any pre-treatment procedure. Recently, a microplate based CL assay was developed for the rapid determination of quinone using a time resolved fluorescence microplate reader [83]. In this assay, quinone was pulse UV irradiated to form ROS that react with luminol analog, L-012, and the generated CL was monitored during 1500 μ s. The microplate assay allowed the rapid determination of menadione in human serum within short time.

2.5. Advantages and drawbacks of each analytical technique for quinone

Analytical techniques mentioned above have several advantages and drawbacks. Although HPLC-UV system is easy handling and spread widely, HPLC-UV methods lack sensitivity and suffer from interferences from co-existing compounds. Therefore, complex and laborious enrichment and clean-up procedure is often required to determine quinone in biological and environmental samples. HPLC-FL methods have sufficient sensitivity and selectivity to determine trace amount of quinone. However, the derivatization reaction procedure is necessary for the conversion of quinone to fluorescent derivative, and total analysis time may be extended. In spite of excellent sensitivity of HPLC-CL, only a few methods were developed for the determination of quinone in biological and environmental samples. This might be due to the scarcity of conversion reaction of quinone to ROS. Although HPLC-ECD methods are sensitive, HPLC system is tend to be complicated because quinone should be converted to hydroquinone with reduction column or on-line electrochemical reactor just before the detector. While, HPLC-ECD system is useful for the simultaneous determination of quinone and hydroquinone. LC-MS and GC-MS may be an ideal analytical tool for quinone in biological and environmental samples considering to their sensitivity and specificity. However, the high cost of the mass spectrometer limits the widespread use. Moreover, GC-MS methods require the conversion reaction of quinone to volatile derivative. CE based methods are suitable for the rapid analysis of quinone, but the concentration sensitivity of CE is inherently low.

3. Measurement of quinones in biological and environmental samples

In the following sections, the applications of analytical techniques for the measurement of quinones including vitamin K, UQ, DXR and PAHQ in blood and atmospheric samples are described.

The applications are also summarized in tables with sample amount, preparation procedure and sensitivity (LOD/LOQ).

3.1. Vitamin K in blood samples

Vitamin K is an essential cofactor in the activation of specific proteins involved in blood clotting and bone mineralization such as prothrombin and osteocalcin. In Japan, PK is often prescribed to treat and prevent for vitamin K deficient syndromes and MK is used orally to treat osteoporosis and steroid-induced bone loss. In order to evaluate the clinical and nutritional status, the monitoring of vitamin K levels should be important. Analytical applications for vitamin K in blood samples are summarized in Table 1.

After the protein precipitation with alcohol, the extraction of vitamin K from blood samples was almost accomplished with a hydrophobic organic solvent such as *n*-hexane owing to lipophilic character of vitamin K. In addition, solid-phase extraction (SPE) with ODS or silica was sometimes used to remove interfering components from blood samples. Among the analytical methods for vitamin K, HPLC-FL with a platinum catalyst reduction column [25] and LC-APCI(+)-MS/MS [56] provided efficient sensitivity.

3.2. UQ in blood samples

UQ in blood protects circulating lipoproteins against oxidative damage due to their antioxidant capacity, and therefore the blood concentration of UQ may reflect the redox status in the human body. Furthermore, it has been reported that the plasma levels of UQ in patients with certain diseases including hyperthyroidism, melanoma, cystic fibrosis, and phenylketonuria and mevalonic aciduria are significantly lower than those in healthy subjects. Therefore, the determination of UQ in blood can also be useful for diagnosis of these diseases. Analytical applications for UQ in blood samples are summarized in Table 2.

Since UQ is lipophilic compound like vitamin K, the extraction is also accomplished with a hydrophobic organic solvent. While, some methods based on LC-APCI(+)-MS employed a simple protein precipitation for the sample preparation. In human body, it was reported that almost of UQ is presented as ubiquinol, and ubiquinol is converted to UQ during the sample preparation procedure such as evaporation of solvent [50]. Therefore, an antioxidant such as butylated hydroxytoluene (BHT) was sometimes added in order to prevent the oxidation of ubiquinol [51,52]. Also, in some methods, the extract was injected immediately and directly for HPLC analysis without evaporation [49,50]. This procedure was helpful to investigate the UQ to ubiquinol ratio in blood that could be used as a marker of oxidative stress [84]. In contrast, some methods added an oxidant such as hydrogen peroxide [38] or 1,4-benzoquinone [60] in order to oxidize ubiquinol completely. HPLC-ECD with a platinum catalyst reduction column [50] should be suitable for the determination of UQ in blood samples considering to its excellent sensitivity.

Table 1
Analytical methods for the determination of vitamin K in blood samples.

Sample (volume)	Sample preparation	Analytical technique	LOD/LOQ	Ref.
Human serum (0.1 mL)	Protein precipitation with acetonitrile, then the supernatant was cleaned by Bakerbond cyclohexyl cartridge	HPLC-UV (abs: 280 nm)	0.6 ng (PK), 6.6 ng (MK-4)	[17]
Rat plasma (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with isopropanol	HPLC-FL after post-column reduction with NaBH ₄ (ex: 320 nm, em: 430 nm)	0.4 ng (PK), 0.4 ng (MK-4)	[23]
Human plasma (0.1–0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Sep-Pak silica cartridge	HPLC-FL with a zinc catalyst reduction column (ex: 240 nm, em: 430 nm)	2.0 pg (PK)	[24]
Human serum and plasma (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Sep-Pak silica cartridge	HPLC-FL with a platinum catalyst reduction column (ex: 240 or 320 nm, em: 430 nm)	2 pg (PK), 4 pg (MK-4), 4 pg (MK-7)	[25]
Human plasma (1.0 mL)	Extraction with <i>n</i> -hexane after protein precipitation with isopropanol	HPLC-FL with an on-line electrochemical reactor (ex: 320 nm, em: 430 nm)	25 pg (PK)	[26]
Rat plasma (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with isopropanol	HPLC-FL with an on-line electrochemical reactor (ex: 330 nm, em: 430 nm)	1 ng (PK), 1 ng (MK-4)	[27]
Human plasma (1 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Sep-Pak silica cartridge.	HPLC-peroxyoxlate CL with an on-line photo-reactor	14 pg (PK), 17 pg (MK-4), 55 pg (MK-7)	[40]
Human plasma (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Sep-Pak silica cartridge	HPLC-luminol CL with an on-line photoreactor	6 pg (PK), 8 pg (MK-4), 20 pg (MK-7)	[43]
Human serum (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Accubond ODS cartridge	HPLC-ECD with a platinum catalyst reduction column	2–10 pg	[54]
Human plasma (0.1–0.5 mL)	Extraction with cyclohexane after protein precipitation with ethanol	LC-APCI(+)-MS/MS	14 ng/L (PK)	[56]
Human plasma (0.5 mL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol, then the extract was cleaned by Sep-Pak silica cartridge	LC-APCI(+)-MS/MS	40 pg/mL (PK), 50 pg/mL (MK-4), 80 pg/mL (MK-7)	[58]
Human plasma (1 mL)	Extraction with <i>n</i> -hexane after protein precipitation with methanol, then PK in the extract was derivatized with heptafluorobutyric anhydride after reduction with zinc	GC-MS	1.0 pg (PK)	[73]

Table 2
Analytical methods for the determination of UQ in blood samples.

Sample (volume)	Sample preparation	Analytical technique	LOD/LOQ	Ref.
Human plasma (250 μL)	Extraction with <i>n</i> -hexane after protein precipitation with methanol	HPLC-UV (abs: 276 nm)	14 ng	[18]
Human plasma (20 μL)	Extraction with 1-propanol after addition of potassium formate	HPLC-FL after post-column fluorescent derivatization with 2-cyanoacetamide (ex: 460 nm, em: 550 nm)	0.16 ng	[35]
Human plasma (50 μL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol and oxidation by H ₂ O ₂	HPLC-CL after reaction with luminol and DTT	130 pg	[38]
Human plasma (50 μL)	Protein precipitation with ethanol, then UQ in the supernatant was reduced by NaBH ₄	HPLC-ECD	50 fmol	[46]
Human serum (100 μL)	Extraction with <i>n</i> -hexane after protein precipitation with ethanol	HPLC-ECD with a platinum catalyst reduction column	100 pg	[48]
Human plasma (100 μL)	Protein precipitation with isopropanol	HPLC-ECD with a platinum catalyst reduction column and an on-line solid phase extraction system.	1 ng/L	[49]
Human plasma (50 μL)	Extraction with <i>n</i> -hexane after protein precipitation with methanol	HPLC-ECD with a platinum catalyst reduction column	2 fmol	[50]
Human plasma (10 μL)	Extraction with <i>n</i> -hexane after addition of ethanol containing butylated hydroxytoluene	HPLC-ECD with an on-line electrochemical reactor	60 fmol	[51]
Human plasma (10 μL)	Extraction with <i>n</i> -hexane after addition of ethanol containing butylated hydroxytoluene	HPLC-ECD with an on-line electrochemical reactor	28 fmol	[52]
Human plasma (100 μL)	Protein precipitation with 1-propanol	HPLC-ECD with an on-line electrochemical reactor	5 μg/L	[53]
Human serum (50 μL)	Protein precipitation with 1-propanol after oxidation by 1,4-benzoquinone	LC-APCI(-)-MS/MS	10 pg	[60]
Rat serum (50 μL)	Protein precipitation with 2-propanol	LC-APCI(+)-MS	50 ng/mL	[61]
Human serum (100 μL)	Extraction with <i>n</i> -hexane after protein precipitation with 1-propanol	LC-ESI(+)-MS/MS	1.69 ng/mL	[62]
Human plasma (600 μL)	Extraction with <i>n</i> -hexane after protein precipitation with 1-propanol	CE-UV (abs: 214 nm)	1 μg/mL	[77]

Table 3
Analytical methods for the determination of DXR in blood samples.

Sample (volume)	Sample preparation	Analytical technique	LOD/LOQ	Ref.
Human plasma (2.0 mL)	Protein precipitation with methanol	HPLC-UV (abs: 260 nm)	1.82 µg/mL (DXR)	[19]
Human plasma (1.0 mL)	Protein precipitation with acetone and zinc sulfate	HPLC-FL (ex: 480 nm, em: 560 nm)	1.0 ng/mL (DXR), 0.5 ng/mL (DXR-ol)	[21]
Human plasma (50 µL)	Protein precipitation with methanol	HPLC-peroxyoxalate CL with an on-line photo-reactor	0.90 nM (DXR), 0.76 nM (DXR-ol)	[41]
Human plasma (200 µL)	Extraction with Oasis HLB SPE column	HPLC-ECD with an on-line electrochemical reactor	1 ng/mL	[55]
Rat plasma (100 µL)	Protein precipitation with acetonitrile and ammonium acetate	LC-ESI(+)-MS/MS	0.343 nM (DXR), 1.89 nM (DXR-ol)	[64]
Human plasma (0.4 mL)	Extraction with Oasis HLB SPE column	LC-ESI(+)-MS/MS	7.2 ng/mL (DXR), 3.6 ng/mL (DXR-ol)	[65]
Human plasma (100 µL)	Extraction with chloroform	CE-UV (abs: 234 nm)	1 nM	[78]
Human serum (50 µL)	Protein precipitation with acetonitrile	CE-laser induced FL (ex: 488 nm, em: 566 nm)	0.9 ng/mL	[79]
Human plasma (1 mL)	Protein precipitation with acetone	Voltammetry	1 nM	[80]

3.3. DXR in blood samples

Although DXR has been used in the treatment of a wide range of malignant tumors, the clinical use of DXR is limited by a cumulative dose-dependent irreversible chronic cardiomyopathy. An administration schedule that produces low peak plasma drug concentrations can prevent DXR-induced cardiotoxicity. Additionally, DXR is rapidly metabolized in liver to DXR-ol, which also causes cardiotoxicity. Taking these aspects into account, it is clinically

important to determine blood concentrations of DXR and DXR-ol. Analytical applications for DXR and DXR-ol in blood samples are summarized in Table 3.

Only simple protein precipitation with an organic solvent was used for the pre-treatment of DXR in blood sample. Some methods employed a SPE with Oasis HLB column after dilution with water. HPLC-CL should have significant advantage considering to the sensitivity against the required sample amounts [41].

Table 4
Analytical methods for the determination of PAHQ in airborne particulates.

Sample preparation	Analytical technique	LOD/LOQ	Ref.
Extraction with dichloromethane by ultrasonication	HPLC-UV (abs: 254 nm)	15 ng (1,2-NQ), 15 ng (1,4-NQ), 3 ng (PQ), 3 ng (AQ)	[20]
Extraction with ethanol by ultrasonication	HPLC-FL with a platinum-rhodium catalyst reduction column and an on-line solid phase extraction system (ex: 285 nm, em: 465 nm)	97 fmol (BaAQ)	[30]
Extraction with methanol by ultrasonication, then PQ in the extract was derivatized with benzaldehyde and ammonium acetate	HPLC-FL (ex: 265 nm, em: 390 nm)	5 fmol (PQ)	[32]
Extraction with methanol by ultrasonication, then PQ in the extract was derivatized with 4-carbomethoxybenzaldehyde and ammonium acetate	HPLC-FL (ex: 370 nm, em: 465 nm)	1.2 fmol (PQ)	[33]
Extraction with methanol by ultrasonication	HPLC-FL after post-column fluorescent derivatization with 2-aminothiophenol (ex: 390 nm, em: 510 nm)	70 fmol (PQ)	[34]
Extraction with mixture of dichloromethane and methanol by ultrasonication	HPLC-luminol CL with an on-line photoreactor	24 fmol (1,2-NQ), 16 fmol (1,4-NQ), 7 fmol (PQ), 1.5 fmol (AQ)	[42]
Extraction with mixture of benzene and ethanol, then the extract was cleaned by Sep-Pak silica cartridge	HPLC-CL after reaction with H ₂ O ₂ and NaHSO ₃	30 fmol (BaPQ)	[44]
Extraction with ethyl acetate by ultrasonication	LC-APCI(+)-MS/MS	0.1–5.8 pg/µL	[68]
Extraction with methanol at high temperature and high pressure in an accelerated solvent extractor	LC-APCI(-)-MS	215 pg (BaAQ), 20 pg (PQ), 10 pg (AQ)	[70]
Extraction with dichloromethane by ultrasonication	LC-APCI(-)-MS/MS	0.20 µg/L (BaAQ), 0.40 µg/L (1,4-NQ), 1.15 µg/L (PQ), 0.92 µg/L (AQ)	[71]
Extraction with mixture of dichloromethane and <i>n</i> -hexane, and methanol by ultrasonication, then PAHQ in the extract was derivatized with PFBHA	LC-APCI(+)-MS/MS	26 pg (1,4-NQ) and 180 pg (AQ)	[72]
Extraction with dichloromethane by ultrasonication, then PAHQ in the extract was derivatized with acetic anhydride after reduction with zinc	GC-MS	0.3 ng (1,2-NQ), 0.4 ng (1,4-NQ), 0.2 ng (PQ) and 4.8 ng (AQ)	[75]

3.4. PAHQ in airborne particulates

PAHQs are regarded as harmful pollutants which have been detected in environmental samples including airborne particulates. It was proven that PAHQ has significant toxicity on living cell. Thus, it has been reported that several respiratory diseases, such as asthma and inflammation, can be caused by inhalation of PAHQ in the air. Therefore, it is necessary to measure the concentration of PAHQ in the atmospheric environment in order to estimate the potential adverse effects of PAHQ on human health. Analytical applications for PAHQs in airborne particulates are summarized in Table 4.

Solvent extraction by ultrasonication is most frequently used for the extraction of PAHQ from airborne particulates. Also, in order to avoid degradation of PAHQ during the ultrasonic extraction, accelerated solvent extraction techniques under high pressure are often used [69]. HPLC-FL methods after pre-column derivatization with benzaldehyde provided [32,33] a good sensitivity even though the analytical instruments are very simple. This technique was successfully applied to evaluate the seasonal and weekly variations of PQ in atmospheric environment [85].

4. Summary

This review described various analytical techniques for quinones and their application in biological and environmental samples. Although the detection of quinones in complicated matrices is seemed to be difficult, various techniques make it possible to analyze quinones with high sensitivity and selectivity. Each technique has various characteristics in regard to sensitivity, specificity and simplicity. It is important to choose the appropriate techniques according to the characteristics of target quinones and analytical situations.

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