

QUINONE TOXICITY: INVOLVEMENT OF REACTIVE OXYGEN SPECIES.

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1. Introduction.

Quinones have been detected in interstellar dust, and are thus among the oldest organic chemicals in the universe (Song and Buettner 2010). Quinones and their reduction products, hydroquinones, are also widely distributed on earth, as metabolites of fungi, bacteria, lichen, plants, insects, worms, spiders and mammals (Thomson 1987). Ubiquinones are components of the electron transport chain, and vitamin K₁, which is essential for the synthesis of blood clotting factors, is a naphthoquinone derivative. Quinones are found in tea, coffee, fruit, wine, vegetables, wheat-based cereals, bread and drinking water (Deisinger, Hill, and English 1996; Zhao et al. 2012). Henna, which has been used since antiquity as a dye for the hair and skin, owes its activity to the presence of 2-hydroxy-1,4-naphthoquinone (Semwal et al. 2014) and the anthraquinone derivative, carminic acid, is the major component of cochineal, which is widely used as a dye for food and lipstick. Creams containing hydroquinone are used as cosmetics in many parts of the world, particularly in the Middle East, sub-Saharan Africa and Asia, where fair skin is considered beautiful and an indicator of high socio-economic class (AlGhamdi 2010). 2,3-Dichloro-1,4-naphthoquinone has been used for many years as a fungicide and the anthraquinone derivatives emodin and chrysazin are, or have been, used as laxatives. Quinones are also produced during combustion, and are important environmental pollutants. Plant-derived quinones have been widely used in traditional medicine, and quinones comprise one of the largest classes of anti-cancer drugs (Asche 2005) and are in use for therapy of malaria (Schuck et al. 2013). Other quinones are under investigation for possible use in the treatment of schistosomiasis and trypanosomiasis.

We are thus exposed to a wide range of quinones and hydroquinones, which may have beneficial or adverse effects upon our health. In this review, the focus will be on natural and synthetic

derivatives of 1,2-benzoquinone (**1**), 1,4 benzoquinone (**2**), 1,2-naphthoquinone (**3**) and 1,4-naphthoquinone (**4**), 9,10-phenanthrenequinone (**5**) and 9,10-anthraquinone (**6**), including the azirindylquinones, such as diaziquone (2,5-diaziridinyl-3,6-bis(carboethoxyamino)-1,4-benzoquinone (**7**), mitomycin c (**8**), β -lapachone (**9**) streptonigrin (**10**), anthracyclines, such as doxorubicin (**11**, R = CH₂OH) and daunorubicin (**11**, R = CH₃), 17-(allylamino)-17-demethoxygeldanamycin (**12**), deoxynyboquinone (**13**), gossypol (**14**), mitoxantrone (**15**) and chrysazin (**16**). The effects of certain derivatives of hydroquinone and catechol, the reduction products of 1,4- and 1,2-benzoquinone respectively, are also discussed.

Insert structures 1-16 (in that order) here

2. Reduction of quinones.

Quinones and hydroquinones constitute a 2-electron redox system, with intermediacy of the one-electron reduction/oxidation product, the semiquinone (Reaction 1).

Insert Reaction 1 here

The reduction of quinones is mediated by several enzyme systems. Reduction may be a one-electron reaction, yielding the semiquinone, as mediated by NADPH-cytochrome P450 reductase, cytochrome *b*₅ reductase, mitochondrial NADH:ubiquinone oxidoreductase (Complex I) (Siegel, Reigan, and Ross 2008), sepiapterin reductase (Yang et al. 2013) and neuronal nitric

oxide synthase (Matsuda, Kimura, and Iyanagi 2000). Alternatively, reduction may be a two-electron reaction, yielding the hydroquinone, as catalysed by NAD(P)H:quinone acceptor oxidoreductase (NQO1) (Ernster, Danielson, and Ljunggren 1962) and other carbonyl reductases (Oppermann 2007) or may proceed via both one- and two-electron reactions, as seen with xanthine oxidase (Siegel, Reigan, and Ross 2008), glutathione reductase (Čénas, Rakauskienė, and Kulys 1989), thioredoxin reductase (Čénas et al. 2004), trypanothione-disulphide reductase (Belorgey, Lanfranchi, and Davioud-Charvet 2013) and lipoamide dehydrogenase (Vienožinskis et al. 1990).

Quinones with relatively high reduction potentials, such as benzoquinone, methylbenzoquinone and halogenated benzoquinones, are reduced non-enzymatically by NAD(P)H (Carlson and Miller 1985) and by GSH (Wilson et al. 1987). Quinones are reduced by ascorbate in two one-electron steps, forming the semiquinone and hydroquinone (Isaacs and van Eldik 1997). They are also reduced to the semiquinone by reaction with oxyhaemoglobin ($\text{Hb}^{\text{II}}\text{O}_2$), with concomitant formation of methaemoglobin (Hb^{III}) (Winterbourn, French, and Claridge 1979) (Reaction 2).

Insert Reaction 2 here

The ease of reduction of a particular quinone is related to its reduction potential. The more positive the reduction potential, the more easily the quinone or semiquinone is reduced.

Conversely, the more negative the potential of a quinone, the more difficult it is to reduce (Song and Buettner 2010).

3. Autoxidation of hydroquinones.

Hydroquinones undergo autoxidation. Reaction of the mono-anion of a hydroquinone with molecular oxygen produces the semiquinone and superoxide radical (Reaction 3).

Insert Reaction 3 here

The same products are formed by reaction of the mono-anion of a hydroquinone with a transition metal in its higher oxidation state (Reaction 4), followed by autoxidation of the reduced metal (Reaction 5).

Insert Reactions 4 and 5 here

The semiquinone reacts with molecular oxygen to form the quinone and superoxide radical (Reaction 6). This reaction is reversible:

Insert Reaction 6 here

More semiquinone is formed by comproportionation between the quinone and hydroquinone, a reaction that is in equilibrium with disproportionation of the semiquinone (Reaction 7), and by oxidation of the hydroquinone by superoxide (Reaction 8).

Insert Reactions 7 and 8 here.

The rate of autoxidation of a hydroquinone depends upon its reduction potential. The more

negative the reduction potential, the more easily the hydroquinone is oxidised (Song and Buettner 2010). Substitution with electron-donating groups in the aromatic ring decreases reduction potentials, thereby increasing autoxidation rates (Monks et al. 1992). Conversely, compounds substituted with electron-withdrawing groups have more positive reduction potentials, and a lower rate of oxidation would be expected (Monks et al. 1992). Since the initial step of oxidation involves the hydroquinone anion, autoxidation rates will also be dependent upon ionisation potentials. This is again influenced by substituent groups, with electron-donating groups leading to a decrease in the degree of ionisation, while electron-withdrawing groups increase it (Song and Buettner 2010). The effect of these parameters is shown by the rapid autoxidation of hydroquinones (Gao et al. 1998; Lewis, Stewart, and Adams 1988; Varela and Tien 2003) and naphthohydroquinones (Munday 1997, 2000) containing electron-donating groups. Halogenated hydroquinones (Song and Buettner 2010), halogenated 1,4-naphthohydroquinones (Munday 2000) and 5-hydroxy-1,4-naphthohydroquinone (juglone) (Munday 2000) also undergo rapid autoxidation at neutral pH. These compounds have very high reduction potentials, and for this reason low oxidation rates would be expected. However, they are highly ionised at neutral pH, and the high concentration of the anion in solution compensates for the effect of the reduction potential.

The position of the equilibrium in the reaction between the semiquinone and oxygen and the reaction between the quinone and superoxide radical (Reaction 6) is also of crucial importance, since the forward reaction initiates a radical chain reaction for oxidation of the hydroquinone via reaction 8. If the reduction potential of a quinone is lower than the one-electron reduction potential of oxygen (i.e. < -180 mV), the equilibrium position for Reaction 6 will lie to the right, favouring formation of superoxide. For quinones with a potential greater than -180 mV,

however, the generation of superoxide will not be thermodynamically favourable (Song and Buettner 2010). In this case, a lag phase in the autoxidation reaction will be observed, with the rate increasing as the level of quinone increases, facilitating semiquinone formation via Reaction 7. The lag phase would be abolished by addition of catalytic amounts of quinone. Such effects have been observed with hydroquinone (Eyer 1991), phenylhydroquinone (Kwok and Eastmond 1997) and 1,4-naphthohydroquinone (Munday 2004).

This reaction will also determine the effect of superoxide dismutase on the rate of autoxidation. If the equilibrium lies to the left, superoxide dismutase, by destroying superoxide radical, will shift the equilibrium to the right, increasing the formation of the quinone, which can then participate in the comproportionation reaction (Reaction 7). In this way, the rate of autoxidation will be increased. Such an effect has been seen with hydroquinone (Eyer 1991), phenylhydroquinone (Tayama and Nakagawa 1994), chlorophenylhydroquinones (Amaro et al. 1996) and 1,2-naphthohydroquinone (Cadenas et al. 1988). Conversely, if the equilibrium lies to the right, superoxide dismutase will decrease the rate of autoxidation by eliminating the superoxide-driven radical chain reaction, as seen with 1,2,3- trihydroxybenzene (pyrogallol) and 1,2,4-trihydroxybenzene (Hiramoto, Mochizuki, and Kikugawa 2001; Marklund and Marklund 1974), 1,2-dihydroxy-4-(1-hydroxy-2-(methylamino)ethyl)benzene (epinephrine) (Misra and Fridovich 1972), 1,2,4-trihydroxy-5-(2-aminoethyl)benzene (6-hydroxydopamine) (Heikkila and Cabbat 1976) and alkyl-, alkoxy-, hydroxy- and amino-1,4-naphthohydroquinones (Munday 1997, 2000).

4. Redox cycling of quinones

The reaction of quinones by cellular reducing agents and the autoxidation of the hydroquinones

and semiquinones leads to redox cycling, in which a single molecule of the quinone may generate many molecules of ROS. Redox cycling of quinones has been observed in mitochondria (Frei, Winterhalter, and Richter 1986; Pritsos et al. 1982) and in microsomes (Bergmann, Dohrmann, and Kahl 1992; Kumagai et al. 1997), and when these compounds are incubated with NAD(P)H (Cone et al. 1976; McLean, Twaroski, and Robertson 2000), ascorbate (Kwiecinski et al. 2012; Shang et al. 2012), NQO1 (Munday 2001) or with monothiol (Ross et al. 1985) or dithiols (Molina Portela and Stoppani 1996).

Thiols are nucleophiles as well as reducing agents, and thiolated hydroquinones as well as unsubstituted hydroquinones have been observed as products of the reaction between thiols and quinones (Wilson et al. 1987). Since the thiol moiety is electron donating, the redox potential of the hydroquinone thiol conjugates will be lower than that of the parent hydroquinone, and will therefore undergo more rapid autoxidation (Monks & Lau 1992). The reaction with thiols may therefore constitute an activation reaction, and redox cycling of quinones has been observed in the presence of thiols, with generation of ROS. This may occur not only with low molecular weight thiols (Sun et al. 2006), but also with protein thiols (Chung et al., 2001). It has been suggested, however, that conjugation of quinones with *N*-acetylcysteine could constitute a detoxification reaction (Mlejnek and Dolezel 2014).

5. Cytotoxicity and ROS production by quinones and hydroquinones *in vitro*.

The toxicity of quinones and hydroquinones to cell lines *in vitro* has been extensively studied. Cancer cell lines have been most extensively used, mainly with a view to identifying compounds that could possibly be useful in the therapy of cancer *in vivo*. More than a thousand compounds have been tested, in a wide range of cell lines. In general, cell death by quinones involves

apoptosis via the intrinsic pathway, although necrosis is sometimes seen in cells exposed to very high levels of these substances.

In many cases, increased intracellular levels of ROS have been reported, generally attributed to redox cycling of the test material after uptake by the cells, and such species have been suggested to be responsible for the observed toxic effects. In most instances, fluorescent probes have been used to detect ROS in cells, although there are significant problems with the specificity of such probes and the interpretation of the results derived from their use (Winterbourn 2014). Another problem arises in studies on hydroquinones due to the possibility that they may undergo autoxidation in the culture medium (Passi, Picardo, and Nazzaro-Porro 1987; Saito et al. 2007), generating ROS extracellularly. Superoxide radical is unable to cross cell membranes, but its decomposition to hydrogen peroxide, which is able to enter cells, could lead to increased intracellular levels of this substance, as detected by the fluorescent dyes. Extracellular SOD was shown to protect against the cytotoxicity of gallic acid (Nose et al. 1998), 6-hydroxydopamine (Tiffany-Castiglioni et al. 1982), gossypol (Grankvist 1989) and 4-allylcatechol (Jeng et al. 2004), the autoxidation of which is inhibited by this enzyme. In contrast, the cytotoxicity of phenylhydroquinone was increased by addition of SOD to the culture medium (Tayama and Nakagawa 1994), consistent with the fact that the rate of autoxidation of this substance is increased by SOD (Inoue, Yamamoto, and Kawanishi 1990; Tayama and Nakagawa 1994). It is possible that extracellular autoxidation and generation of ROS contributes to the cytotoxic activity of these compounds.

The cytotoxicity of 2-methyl-1,4-naphthoquinone (menadione) (Abe and Saito 1996; Sun et al. 1997), 2,3-dimethoxy-1,4-naphthoquinone (Tan and Berridge 2010) and β -lapachone (Bey et al. 2013) was also decreased by addition of SOD to the culture medium, again suggesting

extracellular production of ROS. With these compounds, such an effect could reflect intracellular formation of the hydroquinone with subsequent release into the culture medium, although in view of the instability of naphthohydroquinones, this appears unlikely. Alternatively, the quinone may be reduced by membranal quinone reductase (Tan and Berridge 2010) or by components of the culture medium, such as the thiol groups of proteins. Ascorbate has been shown to increase the cytotoxicity of menadione (McGuire et al. 2013), juglone and 2,3-dichloro-1,4-naphthoquinone (Verrax et al. 2005) and 2-(4-hydroxyanilino)- and 2-(4-methoxyanilino)-1,4-naphthoquinone (Felipe et al. 2013), again most likely due to extracellular redox cycling.

While high levels of ROS may kill cancer cells *in vitro*, low concentrations of such species stimulate cancer cell growth (Burdon 1995; Halliwell 2007), and such an effect has been observed with several quinones (Kimura et al. 2012; Matsunaga et al. 2014).

ROS production and oxidative damage by quinones in erythrocytes has been extensively studied. In these cells, generation of hydrogen peroxide has been investigated by the rather old-fashioned, but apparently specific, technique involving inhibition of cellular catalase activity in the presence of 3-aminotriazole (Margoliash and Novogrodsky 1958). Oxidative damage to erythrocytes, occurring via Reaction 2, is indicated by methaemoglobin formation and by further irreversible oxidation of haemoglobin leading to the formation of intracellular precipitates (Heinz bodies). Such changes have been observed in erythrocytes incubated with benzoquinones (Cohen and Hochstein 1964), catechols (Kusumoto and Nakajima 1964), 1,2- and 1,4-naphthoquinone (Harley and Robin 1963), alkyl-1,4-naphthoquinones (Munday et al. 1994), dialkyl-1,4-naphthoquinones (Munday, Smith, and Munday 1995), alkoxy-1,4-naphthoquinones (Munday, Smith, and Munday 2007), chloro-1,4-naphthoquinones (Sikka et al. 1974), juglone ('t Hart et al. 1989), β -lapachone (Lopes et al. 1978) and daunorubicin (Pedersen et al. 1988). No effects were

observed in rodent erythrocytes incubated with 2-hydroxy-1,4-naphthoquinone ('t Hart et al. 1989) or in erythrocytes from normal individuals. Oxidative damage was seen, however, in erythrocytes from individuals deficient in glucose-6-phosphate dehydrogenase (Zinkham and Oski 1996), an enzyme of the pentose phosphate pathway, which is the sole route for NADPH generation in erythrocytes. Low levels of this enzyme compromise the ability of erythrocytes to withstand oxidative stress and such cells are particularly susceptible to oxidative damage induced by quinones (Bashan et al. 1980).

6. Effect of quinones on chemically-induced cancer in animals.

Protection against chemically-induced cancer has been observed in animals dosed with a number of quinones. With 2,6-dimethoxy-1,4-benzoquinone (Zalatnai et al. 2001), plumbagin and juglone (Sugie et al. 1998), 5,8-dihydroxy-2-(1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone (shikonin) (Yoshimi et al. 1992) and β -lapachone (Higa et al. 2011), protection was given when the quinone was given before, during and after the carcinogen. In comparative studies, 2-isopropyl-5-methyl-benzoquinone (thymoquinone) (Raghunandhakumar et al. 2013) and gallic acid (Jagan et al. 2008) were much more effective when given before, rather than after, the carcinogen. 3,4-Dihydroxybenzoic acid was equally effective in either situation (Tanaka et al. 1995; Tanaka et al. 1993).

7. Effect of quinones and hydroquinones on tumour growth *in vivo*

Thymoquinone (Zhu et al. 2016), mitomycin c (Phillips et al. 2000), gossypol (Ko et al. 2007), juglone (Aithal et al. 2011), plumbagin (Hafeez et al. 2013; Niu et al. 2015), shikonin (Wang et al. 2014), doxorubicin (Giuliani, Zirvi, and Kaplan 1981) and β -lapachone (Li et al. 2011) have

been shown to decrease the growth of cancer cell transplants in immunocompromised mice or in syngeneic mouse models.

8. Antiparasitic action of quinones.

Protozoans of the genus *Plasmodium* are responsible for malaria, a major problem in countries within a broad band around the equator. Organisms of the genera *Trypanosoma* and *Leishmania* are responsible for African trypanosomiasis (sleeping sickness), American trypanosomiasis (Chagas' disease) and leishmaniasis, which are major health problems found almost exclusively in low-income populations of developing countries in tropical and subtropical areas of the world (Fidalgo and Gille 2011). Drugs to treat these diseases are available, but they are expensive and are associated with severe side effects. Furthermore, resistance is growing to such drugs. New, preferably cheap, drugs are needed, but development of such drugs is of little interest to pharmaceutical companies (de Castro 1993). Research is being undertaken in academic institutions, however, particularly in South America. The main focus of this research has been on naphthoquinones, in view of the traditional use of lapachol (2-hydroxy-3-[3-methylbut-2-enyl]-1,4-naphthoquinone) in South America, which was originally isolated from the Brazilian tree *Tabebuia avellanedae*. Many naturally-occurring and synthetic naphthoquinone derivatives have been tested and some have shown high activity against various stages of the life cycle of *Trypanosoma* (Diogo et al. 2013) and of *Plasmodium* (Ehrhardt et al. 2016) *in vitro*.

9. Induction of Phase 2 enzymes by quinones and hydroquinones in animals.

t-Butylhydroquinone increased the activities of NQO1 and glutathione *S*-transferase in the liver, lungs, kidneys, forestomach, glandular stomach and upper small intestine of mice (De Long,

Prochaska, and Talalay 1985) while 3,4-dihydroxybenzoic acid increased hepatic glutathione *S*-transferase activity in rats (Hung et al. 2006). 2-Amino-, 2-methylamino-, 2-dimethylamino-, 2-amino-3-methyl-, 2-amino-3-hydroxy-, 2,3-dichloro-, 2-bromo- and 2-amino-3-chloro-1,4-naphthoquinone increased NQO1 activity in the livers and kidneys of rats (Munday, Smith, and Munday 2007). Juglone and 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin) increased the activity of NQO1 and glutathione *S*-transferase and NQO1 in the forestomach, glandular stomach, duodenum, jejunum, caecum and colon of rats, but they had no significant effect on the activities of these enzymes in the liver, spleen, heart, lungs or urinary bladder of these animals (Munday and Munday 2000).

10. Toxicity of quinones and hydroquinones to animals.

10.1. Haemolytic anaemia.

Oxidative damage to erythrocytes *in vivo* is reflected by methaemoglobinaemia and by the presence of Heinz bodies within the cells. Such damaged erythrocytes are removed from the circulation by phagocytic cells. In rodents, the primary site of erythrocyte destruction is the spleen, although in severe cases, hepatic Kupffer cells are also involved (Azen and Schilling 1964; Rifkind and Danon 1965). The spleen plays a major role in erythrocyte regeneration following haemolysis (Jenkins et al. 1972), and splenic erythropoiesis is associated with engorgement of red pulp sinusoids, recognised macroscopically as splenic enlargement and darkening. Iron released from phagocytised cells is stored as haemosiderin, predominantly in the spleen, with lesser amounts in the liver and kidneys. When the rate of erythroclasis exceeds that of compensatory erythropoiesis, blood packed cell volumes and haemoglobin levels decline. In severe haemolytic anaemia, immature erythrocytes are released into the circulation, recognised

as reticulocytosis. The haematological, histological and organ weight changes associated with oxidative haemolysis are thus quite characteristic, and easily distinguished from other forms of anaemia.

Many quinones have been shown to induce oxidative haemolysis in animals. Among monocyclic compounds, benzoquinone, hydroquinone and *t*-butylhydroquinone are relatively weak haemolytic agents in animals. The addition of a third hydroxy group increases activity, and 1,2,4-trihydroxybenzene, gallic acid and pyrogallol are potent haemolytic agents *in vivo* (Jung and Witt 1947; Niho et al. 2001). The last-named compound, which is found in acorns and oak leaves, has caused severe toxicity in farm animals grazing in fields containing oak trees.

Thousands of animals are poisoned each year (Plumlee, Johnson, and Galey 1998). Severe, and sometimes fatal, methaemoglobinaemia, Heinz body formation and haemolytic anaemia have been recorded in horses eating the leaves of red maple (*Acer rubrum*), and poisoning by this plant is a serious problem for horse owners in the eastern United States and Canada (Tennant et al. 1981). Again, pyrogallol is held responsible for these toxic effects (Agrawal et al. 2012).

Mitomycin c (Adikesavan, Barrios, and Jaiswal 2007) and 17-(allylamino)-17-demethoxygeldanamycin (Solit et al. 2002) are also haemolytic agents in animals.

Similarly, 1,2-naphthoquinone (Harley and Robin 1963) and its alkyl, alkoxy and amino derivatives (Munday, Smith, and Munday 2007) induce oxidative haemolysis in rats, as does β -lapachone (Noh et al. 2010). 1,4-Naphthoquinone is also a haemolytic agent in animals, as are 2-monoalkyl- (Munday et al. 1994), 2,3- dialkyl- (Munday, Smith, and Munday 2001), 2-amino- and 2-alkylamino- (Munday, Smith, and Munday 2007), 2,3-dichloro- (Ivanov and Makovskaya 1970) and 2-hydroxy-1,4-naphthoquinone (Munday, Smith, and Fowke 1991). 9,10-Anthraquinone (National Toxicology Program 2005) and its 2-amino- (Baker et al. 1975) and 1-

amino-2,4-dibromo derivatives (Fleischman et al. 1986) are also haemolytic agents in rodents. The toxic effects of a series of 2-hydroxy-3-alkyl-4-naphthoquinones, with alkyl substitution from methyl to pentyl, has been examined in rats. Haemolytic activity decreased with increasing size of the alkyl group, possibly reflecting a steric effect of the substituent (Munday, Smith, and Munday 1995). Steric effects cannot be the whole answer, however, since substitution at the 3-position with relatively small groups (chloro or amino) also decreased the severity of haemolysis. Similar effects were observed with 2-amino-1,4-naphthoquinones substituted at the 3-position (Munday, Smith, and Munday 2007).

When fed at excessive levels, gossypol-containing cottonseed causes haemolysis in farm animals (Rogers, Poore, and Paschal 2002), and at times, gossypol poisoning has caused major problems in agricultural production, such as the death of 1,600 calves in a single incident (Morgan 1997).

10.2. Hepatotoxicity.

Centrilobular hepatic necrosis was induced in mice after intraperitoneal injection of tetrachloro-1,4-benzoquinone (Xu et al. 2014) and there is evidence for gossypol-induced hepatotoxicity in rats (Wang and Lei 1987). Liver damage was also observed in animals after acute or chronic administration of anthracyclines (Hiona et al. 2011; Park et al. 2003). Hepatic necrosis was observed in rats injected with 17-[(dimethylaminoethyl)amino]-17-demethoxygeldanamycin (Glaze et al. 2005), and liver damage, in addition to haemolytic anaemia, has been observed in farm animals eating cottonseed or acorns and oak leaves (Basden and Dalvi 1987; Rogers, Poore, and Paschal 2002).

10.3. Nephrotoxicity.

Oral administration of hydroquinone induces renal tubular necrosis in male F344 rats, but not in

female F344 rats, Sprague-Dawley rats or male or female mice (Kari et al. 1992). F344 rats, particularly males, are known to be very susceptible to renal damage, and the relevance of this strain of rat in the evaluation of nephrotoxic agents is questionable (English et al. 1994).

Unlike the mono-alkyl derivatives, 2,3-dimethyl-1,4-naphthoquinone not only caused haemolysis in Sprague-Dawley rats but also renal tubular necrosis in the distal segment of the proximal convoluted tubules (Munday, Smith, and Munday 2001). Mitoxantrone (Alderton, Gross, and Green 1992) and aminoanthraquinones (Murthy et al. 1979) have also been shown to be nephrotoxic in mice.

2-Hydroxy-1,4-naphthoquinone is a potent nephrotoxin in rats (Munday, Smith, and Fowke 1991) and both haemolytic anaemia and nephrotoxicity were reported in a dog that ate a large amount of a hair dye containing henna (Jardes, Ross, and Markovich 2013).

In none of these cases was nephrotoxicity due to urinary excretion of haemoglobin or methaemoglobin, since there was no evidence of intravascular haemolysis in the animals.

10.4. Cardiotoxicity.

Although effective broad-spectrum anticancer drugs, the clinical use of doxorubicin, daunorubicin and other anthracyclines is restricted by their toxicity, particularly irreversible cardiomyopathy. Acute effects on the heart are rare with currently-employed doses of anthracyclines, but cumulative toxicity, resembling congestive heart failure, occurs in a significant proportion of patients, with occurrence proportional to dose. Myocytic vacuolation, accompanied by areas of interstitial fibrosis, are seen in patients, although necrosis is rarely seen (Takemura and Fujiwara 2007). Mitoxantrone, another anthraquinone anticancer drug, has been shown to be cardiotoxic in mice, although the severity of the cardiac effects induced by this

compound was lower than those induced by doxorubicin (Alderton, Gross, and Green 1992). Replacement of one of the quinone groups of doxorubicin with an imine function, to yield 5-iminodaunorubicin, diminishes the rate of redox cycling in mitochondria and cardiotoxic activity (Tong, Henry, and Acton 1979, Doroshow & Davies 1986).

10.5. Effects on reproduction

Oral administration of plumbagin decreased spermatogenesis in male rats (Bhargava 1985), and in dogs dosed with this compound by intraperitoneal injection. In the latter animals, testicular atrophy and damage to seminiferous tubules were also observed (Bhargava 1984). In female rats, plumbagin prolonged the duration of the oestrus cycle, inhibited foetal implantation and induced abortion (Premakumari, Rathinam, and Santhakumari 1977). Decreased spermatogenesis was observed in rodents after acute (Park et al. 2003) or chronic (Desai et al. 2013) administration of anthracyclines, and gossypol decreased spermatogenesis and decreased spermatozoal motility in rats (Gadelha et al. 2014).

10.6. Carcinogenicity.

In a 2-year feeding study with hydroquinone in F344 rats and B6C3F₁ mice, an increase in the incidence of renal tubular adenomas were seen in male rats, but not in female rats or in either sex of mice, and it was concluded that this compound is a carcinogen (Kari et al. 1992). The interpretation of the results of the above study has been criticised, however, on the basis of the association between the spontaneous nephropathy seen in F344 rats (mainly in males) and the observed increase in the incidence of renal adenomas (O'Donoghue and English 1994). In short-term studies, hydroquinone administered by gavage induced degeneration and increased cell

proliferation in the renal tubules of male F344 rats, but not in female F344 rats or in male Sprague-Dawley rats. It was concluded that chemically-induced cell proliferation secondary to toxicity may be important in the pathogenesis of the benign renal tumours observed in male F344 rats dosed with hydroquinone, which may be associated with chronic regenerative activity (Hard et al. 1997).

In long-term feeding studies in rats, catechol induced adenocarcinoma formation and adenomatous hyperplasia in the glandular stomach of rats and mice. Papillomas and squamous cell carcinomas were occasionally observed in the forestomachs of these rats (Tanaka et al. 1995). Similar studies with 9,10-anthraquinone showed an increased incidence of hepatic, renal and bladder cancer (National Toxicology Program. 2005), while 1-amino-2,4-dibromoanthraquinone induced cancer at various sites in both mice and rats (National Toxicology Program 1996). 1-Hydroxy-9,10-anthraquinone (Mori, 1990 #171), 1-amino-2-methylanthraquinone (Murthy et al. 1979), and chrysazin (Mori et al. 1986) were shown to be carcinogenic in the large intestine and liver of animals, and formation of 1,2-quinones is possibly involved in the carcinogenic action of polycyclic hydrocarbons (Xue and Warshawsky 2005).

10.7. Cataract formation.

1,2- and 1,4-naphthoquinone (Wells, Wilson, and Lubek 1989), and doxorubicin (Bayer et al. 2005) are cataractogenic in rats.

11. Toxicity of quinones and hydroquinones to humans.

Hydroquinone appears to be of low oral toxicity in humans, and there is no evidence for adverse effects in individuals employed in the manufacture or use of this compound (Pifer et al. 1995)

and oral administration of hydroquinone at 300-500 mg/day, in 3 divided doses, to volunteers for 3 months showed no adverse effects (Carlson and Brewer 1953). 17-(Allylamino)-17-demethoxygeldanamycin causes anaemia in humans. It is also hepatotoxic (Sausville, Tomaszewski, and Ivy 2003). Azirinidylquinones have also been shown to induce anaemia in cancer patients, together with myelosuppression and renal damage (Danson et al. 2011).

Hykinone (menadione sodium bisulphite) and Synkavit (menadiol sodium phosphate) are drugs that were once routinely administered to babies in order to prevent haemorrhagic disease of the newborn, an uncommon, but very serious, event. These compounds are rapidly metabolised to menadione *in vivo*, and it was first noticed in 1953 that some infants treated with these drugs suffered oxidative haemolysis (Gasser 1953). The association between the use of these drugs and haemolytic anaemia was later confirmed, with some deaths being reported (Laurance 1955). A decrease in recommended dose levels, and the use of Vitamin K₁ rather than menadione or its derivatives, appears to have resolved this problem. A Phase 1 trial of Synkavit in patients with advanced cancer showed a high incidence of haemolytic anaemia (Lim et al. 2005) and trials in cancer patients with menadione in addition to other cancer chemotherapeutics revealed rate-limiting haemolytic anaemia (Tetef et al. 1995). 1,4-Naphthoquinone is a metabolite of naphthalene, which may contribute to the haemolytic anaemia seen in humans after ingestion of this substance, which is a common household item used as a moth deterrent (Zuelzer and Apt 1949).

Application of henna extract to the skin of new-born babies is a traditional practice in some cultures. In individuals with glucose-6-phosphate dehydrogenase deficiency, such application may be associated with haemolytic anaemia and even death (Raupp et al. 2001). Fatal haemolytic anaemia and renal failure also occurred in a 27-day old boy treated with henna for nappy rash

(Devecioğlu et al. 2000). Acute renal failure and haemolysis occurred after accidental ingestion of henna (Rund et al. 2007) and in an individual who consumed a large amount of henna as a presumed therapeutic (Qurashi, Qumqumji, and Zacharia 2013). Severe haemolytic anaemia occurred in a young woman who ingested a henna decoction as an abortifacient (Perinet et al. 2011). A complex of β -lapachone with hydroxypropyl- β -cyclodextrin, code-named ARQ 501, underwent unsuccessful clinical trials as a therapeutic for a variety of cancers. The reasons for failure included dose-limiting toxicity in the form of haemolytic anaemia (Blanco et al. 2010). The cardiotoxicity and myelosuppression of anthracyclines are important factors in the use of these compounds in cancer therapy.

In the 1930's and 1940's, the culinary use of unrefined cottonseed oil, containing high levels of gossypol, in certain areas of China was associated with a pronounced decrease in birth rate and purified gossypol has been evaluated as a male contraceptive (Wang et al. 2009).

No information on the chronic oral or inhalation toxicity of phenanthrene-9,10-quinone is available. Since this substance is a common atmospheric pollutant, and in view of the observation that individuals exposed to diesel exhaust fumes, of which phenanthrene-9,10-quinone is a major component (Schuetzle 1983) (10820, Schuetzle 1983), show oxidative DNA damage, such studies would be of considerable value.

12. The role of NQO1 in quinone toxicity

The enzyme NQO1 (then named "DT-diaphorase") was first reported by Ernster et al. in 1962 (Ernster, Danielson, and Ljunggren 1962). They showed that NQO1 reduced a number of quinones to the corresponding hydroquinones with either NADH or NADPH as cofactor, and that the enzyme was strongly inhibited by dicoumarol. In later publications by Ernster and

colleagues, it was suggested that NQO1 could protect against the toxic effect of quinones by producing “relatively stable” hydroquinones, thus avoiding one-electron reduction of the quinones to the highly unstable semiquinones, which can react with molecular oxygen to produce ROS ((Lind, Hochstein, and Ernster 1982). The concept that NQO1 protected against quinone toxicity became dogma (Cadenas 1995), even though later publications indicated that two-electron reduction of quinones does not necessarily lead to detoxification (Lind et al. 1989; Ross et al. 2000), and it is still regularly stated in the literature that NQO1 detoxifies quinones.

In fact, NQO1 may either detoxify or activate quinones, and which process occurs depends upon the rate of reduction of the quinone, the rate and mechanism of autoxidation of the hydroquinone and the concentration of NQO1 employed. These factors are clearly shown in studies with quinones and purified NQO1. With menadione, redox cycling occurred at low levels of NQO1, indicating activation. As the level of NQO1 was increased, however, redox cycling was progressively inhibited, indicating detoxication. Menadione is rapidly reduced by NQO1. At low levels, only a proportion of the quinone will be reduced to the hydroquinone, so that semiquinone formation via the comproportionation reaction (Reaction 7) will proceed, leading to redox cycling and ROS production. Furthermore, with menadione, the equilibrium position of reaction 6 lies to the right, so superoxide radical will be available for further semiquinone formation via Reaction 8. As the level of NQO1 is increased, the concentration of quinone will decrease, and oxidation via the comproportionation reaction will be inhibited, thereby leading to a decrease in oxidation rate and ROS production. Similar effects were seen with 2,3-dimethyl and 2,3-dimethoxy-1,4-naphthohydroquinone, although with these compounds, a higher concentration of NQO1 was required for inhibition than that for menadione, possible reflecting the relatively low rates of reduction of these compounds by NQO1 (Munday 2001).

In contrast, the rates of redox cycling of 2-hydroxy- and 2-amino-1,4-naphthoquinone and streptonigrin increased with increasing levels of NQO1, and no inhibition was seen even at high levels of this enzyme. These compounds are but slowly reduced by NQO1, so that it is likely that levels of the hydroquinone were never low enough to inhibit Reaction 7 (Munday 2001, 2004). Redox cycling with juglone in the presence of NQO1 was very fast, and again no inhibition was observed in the presence of high levels of this enzyme (Munday 2001). Juglone is reduced relatively rapidly by NQO1, and in this case it is likely that the failure of inhibition is due not to slow reduction but to the fact that the comproportionation reaction is unimportant in the mechanism of oxidation of this compound (Munday 2001). Similar results are to be expected with 2,3-dichloro- and 2-bromo-1,4-naphthoquinone, since the comproportionation reaction likewise plays little part in the autoxidation of the hydroquinones derived from these substances.

13. Conclusions.

It has been concluded in many cases that the ability of quinones to undergo redox cycling, with generation of ROS, is responsible for the biological effects of the compounds. Certainly, redox cycling occurs during the interaction of these compounds with biological reducing agents at physiological pH, making such a conclusion feasible.

With regard to effects in cells *in vitro*, several criteria for the involvement of ROS in toxicity may be considered:

1. The demonstration of ROS within the cells incubated with the test compounds.
2. The demonstration of a protective effect of scavengers of ROS.
3. The demonstration that factors that increase or decrease the production of ROS by quinones *in vitro* increase or decrease the cytotoxicity of these substances.

ROS formation has consistently been reported in cells incubated with quinones and hydroquinones. There is a question with regard to the site at which ROS production occurs, particularly with hydroquinones, which may undergo autoxidation in the culture medium, thereby generating ROS extracellularly.

N-Acetylcysteine has regularly been described as scavenger of ROS, and addition of this substance to the culture medium has been shown to protect against the cytotoxicity of benzoquinones (Dong et al. 2014), 6-hydroxydopamine (Wanpen et al. 2004), naphthoquinones (Gaascht et al. 2014; Xu et al. 2012), anthraquinones (Bair, Palchaudhuri, and Hergenrother 2010) and phenanthrene-9,10-quinone (Shang et al. 2014). The rate of reaction of *N*-acetylcysteine with superoxide radical and hydrogen peroxide is low, however, (Aruoma et al. 1989; Winterbourn and Metodiewa 1999), and it has been suggested that protection is given not by direct scavenging of ROS but by the ability of this thiol to increase intracellular levels of NADPH, thereby maintaining intracellular antioxidant defences (Rushworth and Megson 2014). As discussed above, ROS production by menadione and 2,3-dimethoxy-1,4-naphthoquinone was inhibited by high levels of NQO1. It would be expected that cytotoxicity would be decreased by increasing cellular levels of NQO1, while it would be increased by inhibiting this enzyme. In accord with these expectations, the toxic effects of menadione (Chiou, Wang, and Tzeng 1999) and 2,3-dimethoxy-1,4-naphthoquinone (Karczewski, Peters, and Noordhoek 1999) in cells *in vitro* have been shown to be inversely proportional to cellular NQO1 levels and the cytotoxicity of these substances was increased by inhibition of NQO1 (Helinska, Belej, and O'Brien 1996; Thor et al. 1982). Similar effects have been observed with benzoquinone (Rubio et al. 2011), doxorubicin (Wang et al. 2008), 2,6-dimethoxy-1,4-benzoquinone (Helinska, Belej, and O'Brien

1996) and mitoxantrone (Duthie and Grant 1989).

In contrast, high levels of NQO1 stimulated ROS production by streptonigrin, and it would therefore be expected that the cytotoxicity of this compound would be increased by increasing cellular levels of this enzyme and protection would be afforded by its inhibition. Again, such expectation has been fulfilled (Beall et al. 1996). Similar effects have been recorded in cells exposed to 17-(allylamino)-17-demethoxygeldanamycin (Siegel et al. 2011), 2,3-dimethoxy-1,4-naphthoquinone (Karczewski, Peters, and Noordhoek 1999) and β -lapachone (Li et al. 2011). Overall, there is good evidence for the involvement of ROS in quinone toxicity to cells *in vitro*.

For consideration of the involvement of ROS in the *in vivo* toxicity of quinones and hydroquinones, one may consider the following criteria:

1. Demonstration of ROS production, or of the products of oxidation by ROS, *in vivo* at the sites at which toxicity has been observed.
2. Demonstration of ROS production in the target cells *in vivo*
3. Proportionality between the efficacy of derivatives in generating ROS *in vitro* and the severity of the toxic effects that they induce.
4. Demonstration of a protective effect of scavengers of ROS
5. Effects of modulators of ROS production on toxicity *in vivo*.
6. The induction of toxic effects similar to those observed with the test compound by other ROS generators.

Some of these criteria have been met with regard to the haemolytic activity of quinones and hydroquinones. ROS production was observed with several of the haemolytic quinones *in vitro*, and hydrogen peroxide was detected in erythrocytes of mice injected with menadione (Cohen &

Hochstein, 1965). Haemolysis by quinones and hydroquinones was of the oxidative type, as indicated by methaemoglobinaemia and Heinz body formation, in erythrocytes *in vivo*.

Erythrocytes are particularly susceptible to oxidative damage, and oxidative haemolysis is seen with other compounds that are known to generate ROS, such as polysulphides (Munday 2012) and aromatic amines (Khan et al. 1997). In the case of mono-alkyl-1,4-naphthoquinones, haemolytic activity in rats was correlated with their ability to generate superoxide radical through reaction with oxyhaemoglobin, and with their ability to generate hydrogen peroxide and induce oxidative damage in erythrocytes *in vitro*, indicating that no extra-erythrocytic activation is needed for their *in vivo* haemolytic action (Munday et al. 1994).

Pre-administration of compounds that increase the activity of Phase 2 enzymes, including NQO1, would be expected to decrease the toxicity of compounds that are detoxified by this enzyme while toxicity would be increased by concurrent administration of an NQO1 inhibitor. The severity of haemolytic anaemia induced in rats by menadione was indeed decreased by increasing tissue levels of Phase 2 enzymes, and the degree of protection was correlated with the extent of NQO1 induction in the livers of the animals. Inhibition of NQO1 increased the severity of haemolysis (Munday, Smith, and Munday 1999). Similarly, the haemolytic action of 2,3-dimethyl-1,4-naphthoquinone was decreased in rats by induction of Phase 2 enzymes (Munday, Smith, and Munday 2001). Conversely, pre-treatment of rats with the Phase 2 enzyme inducers butylated hydroxyanisole, butylated hydroxytoluene, dimethyl fumarate or disulfiram increased the severity of the haemolytic anaemia induced by 2-hydroxy- and 2-amino-1,4-naphthoquinone, for which high levels of NQO1 were shown to increase ROS production. The nephrotoxicity of the latter compound was also decreased by all the inducers, but that of 2-hydroxy-1,4-naphthoquinone was decreased only by dimethyl fumarate or disulfiram (Munday, Smith, and

Munday 1998, 1999). The reason for this disparity is unknown.

The increased susceptibility of individuals with glucose-6-phosphate dehydrogenase deficiency, in which the inability of erythrocytes to maintain intracellular levels of GSH makes them particularly susceptible to oxidative damage, is also consistent with the involvement of ROS in quinone-induced haemolysis. Although high levels of doxorubicin were shown to generate ROS in erythrocytes *in vitro*, accompanied by methaemoglobin formation (Pedersen et al. 1988), no haemolysis has been reported in animals dosed with these compounds. In view of the susceptibility of erythrocytes from glucose-6-phosphate dehydrogenase deficient individuals to oxidative damage it was suggested in 1980 that these drugs should be used with caution in patients with this disorder (Shinohara and Tanaka 1980). Three years later, severe oxidative haemolysis was reported in such an individual following administration of doxorubicin (Doll 1983).

Thus there is evidence for the involvement of ROS in the haemolytic activity of quinones *in vivo*.

The involvement of ROS in the nephrotoxicity of quinones is not established. The nephrotoxic action of 2,3-dimethyl-1,4-naphthoquinone, which is detoxified by high levels of NQO1, was abolished by induction of Phase 2 enzymes, while inhibition of NQO1 caused a massive increase in the severity of the renal tubular necrosis induced by this compound (Munday, Smith, and Munday 2001). The nephrotoxicity of 2-amino-1,4-naphthoquinone was decreased by butylated hydroxyanisole, butylated hydroxytoluene, dimethyl fumarate or disulfiram, but that of 2-hydroxy-1,4-naphthoquinone was decreased only by dimethyl fumarate or disulfiram (Munday, Smith, and Munday 1999){Munday, 1998 #45. The reason for this disparity is unknown. It is therefore not possible to generalise with regard to the effects of modulators of Phase 2 enzyme

induction on the nephrotoxicity of naphthoquinones *in vivo*. Structure-activity relationships indicate the importance of electron-donating groups for nephrotoxic activity. Compounds with a relatively weak electron-donating effect, such as an alkyl group, or with an electron withdrawing group, are not nephrotoxic. Dialkyl-1,4-naphthoquinones contain two electron-donating groups, and these are nephrotoxic. 2-Hydroxy- and 2-amino-1,4-naphthoquinone are potent nephrotoxins, and both these substituents are strongly electron-donating. Furthermore, methylation of the amino group, which produces a greater electron-donating effect increases the nephrotoxic activity of 2-aminonaphthoquinones. However, substitution with either electron-donating or electron-withdrawing groups at the 3-position of 2-hydroxy- or 2-amino-naphthoquinones decreases nephrotoxic activity. It must be concluded that a free 3-position in hydroxy and amino-1,4-naphthoquinones is important for renal toxicity, although the role that this may play in the nephrotoxic action is unclear, and further work on the mechanism of the renal damage induced by these compounds is required.

Although several other ROS-generating compounds, such as diquat (Clark and Hurst 1970), paracetamol (Lubek, Basu, and Wells 1988) and sodium selenite (Huang et al. 1992) have been shown to be cataractogenic in animals, there is no direct evidence that the cataract formation by quinones is attributable to ROS production. Similarly, testicular damage and decreased spermatogenesis have been observed not only with quinones, but also with other ROS producers, including arsenic trioxide (da Silva et al. 2016), aromatic nitro compounds (Matsumoto, Hirose, and Ema 2008), sodium selenite (Cabaj et al. 2012), quinacrine (Siegel and Mushett 1944), 1,4-diaminobenzene (Bharali and Dutta 2012) and paraquat (Clark, McElligott, and Hurst 1966) but again there is no direct evidence for the involvement of ROS in the induction of such lesions by quinones.

Innumerable studies on the toxicity of quinones to cells *in vitro* have been conducted, and the results of experiments on new compounds and on the effects of previously-studied compounds on different cell lines continue to be published. Detailed investigations on the mechanisms of cytotoxicity of quinones and the signalling pathways involved have been conducted, but no clear structure-activity relationships have been identified. Although many reports on the *in vitro* effects of quinones end with a statement along the lines of “this compound is a promising drug for the therapy of such-and-such cancer”, few studies have progressed to the next steps of the evaluation process, *viz.* demonstration of growth inhibition effects in xenografts and assessment of toxicity.

There has been much interest in the use of quinones in cancer therapy, and the use of anthracyclines is an outstanding example of the value of such compounds. Results with other quinones have, however, generally been rather disappointing. In a Phase I clinical trial in cancer patients, administration of 17-(allylamino)-17-demethoxygeldanamycin was associated with dose-limiting hepatotoxicity and anaemia (Sausville, Tomaszewski, and Ivy 2003). A small Phase II trial involving administration of this compound to cancer patients showed no beneficial effects, but good effects in the intra-vesicle therapy of non-muscle invasive bladder cancer were observed (Anastasiadis and de Reijke 2012). Clinical development of other geldanamycin derivatives is continuing (Fukuyo, Hunt, and Horikoshi 2010). Several azirinidylquinones have been used clinically as anti-cancer drugs, although further development of some compounds of this class was discontinued because of toxicity issues (Miliukienė, Nivinskas, and Čėnas 2014). Mitomycin c has been used as a cancer therapeutic agent in Japan since the early 1960's, although it was not approved for use in North America until 1974. It is effective in the treatment of a variety of solid tumours, although its toxicity has restricted its use. Menadione and

derivatives were tested in clinical trials, but no beneficial effects were seen, and haemolytic anaemia was a serious side-effect. In the 1960's and 1970's, there was considerable interest in the potential use of streptonigrin for cancer chemotherapy. In early studies in patients with advanced cancer at various sites (Harris et al. 1965; Sullivan et al. 1963), streptonigrin was administered at various doses and by different routes of administration. A positive response in terms of objective tumour regression and clinical benefit was claimed in some cases. These findings were not substantiated in later studies, however, and streptonigrin was found to cause severe bone marrow depression in patients (Smith et al. 1967), and human trials were discontinued. A complex of β -lapachone with hydroxypropyl- β -cyclodextrin, code-named ARQ 501, underwent unsuccessful clinical trials as a therapeutic for a variety of cancers. The reasons for failure included dose-limiting toxicity in the form of haemolytic anaemia (Blanco et al. 2010; Wilson, Labra, and Barrist 1961). Research on derivatives of β -lapachone are continuing.

Many cancer cells contain high levels of NQO1, and it was suggested that this property could be exploited by anti-cancer drugs that redox cycle with this enzyme with generation of ROS (Leinonen et al. 2014). However, this conclusion does not take into account the fact that while many quinones undergo redox cycling with NQO1 at relatively low concentrations, redox cycling and ROS production by some such compounds are inhibited at high levels of the enzyme. Such compounds may therefore be ineffective in cancer cells with high activities of NQO1. In this situation, compounds with which redox cycling with NQO1 is not inhibited at high levels of the enzyme may be the agents of choice. This property is seen with some dihydroxy-1,4-naphthoquinones and dihydroxyanthraquinones, with halogenated 1,4-naphthoquinones and with many 1,2-naphthoquinones.

The situation with regard to the use of quinones in the therapy of malaria, schistosomiasis and

trypanosomiasis is in some respects similar to that regarding their use as anti-cancer agents. Atovaquone (*trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone) in combination with proguanil hydrochloride is used in the prophylaxis and therapy of malaria under the trade name “Malarone” (Schuck et al. 2013) and many new hydroxynaphthoquinones have been tested for their effects on the parasites *in vitro*, and some have been shown to be effective in mouse models (de Rezende et al. 2013), while others, while highly effective *in vitro*, showed no benefit in such models (Docampo 1990). A mixture of menadione and ascorbate was shown to be highly toxic to the epimastigote, trypomastigote and amastigote forms of *Trypanosoma cruzi* (Desoti et al. 2015), suggesting that further work with this preparation would be worthwhile, although the possibility of haemolytic anaemia as a side effect must be considered.

Several quinones have been shown to protect against chemically-induced cancer, and such effects may reflect intervention at either the initiation or subsequent phases of carcinogenesis. Quinones have been shown to increase tissue activities of Phase 2 enzymes in animal tissues, and since these enzymes are known to facilitate the detoxification of carcinogens by conversion to water-soluble metabolites that can be excreted in urine (Slocum and Kensler 2011; Talalay, Dinkova-Kostova, and Holtzclaw 2003), it is possible that enzyme induction could be responsible for the observed protection against chemically-induced carcinogenesis. In this situation, the test material would have to be given before exposure to the carcinogen. Alternatively, the toxic effects of quinones and hydroquinones on cancer cells, as demonstrated *in vitro*, could, if translated to the *in vivo* situation, lead to a decrease in the promotion and/or progression of chemically-induced tumours. In this case, the test compounds would be effective when administered after of the carcinogen. These possibilities have not been sufficiently

explored, with the test compounds in most experiments being administered before, during and after the carcinogen. In the few comparative studies that have been conducted, some compounds were shown to be more effective when given before the carcinogen, suggesting an effect at the initiation phase, while one compound, 3,4-dihydroxybenzoic acid was effective when given either before or after the carcinogen. How such effects could be translated into the human situation for protection against cancer is unclear.

There is evidence for the involvement of reactive oxygen species in the toxicity of quinones *in vitro* and *in vivo*, and their ability to generate such species may be exploited for protection against cancer, and for therapy of cancer and of parasitic diseases. Substantial progress has been made on the possibility of such use via *in vitro* experiments and studies in animals, and it is to be hoped that some of the more active compounds identified in these studies will progress toward clinical use.

Abbreviations: ROS: reactive oxygen species; GSH, reduced glutathione; SOD, superoxide dismutase; NQO1, NAD(P)H:quinone acceptor oxidoreductase.

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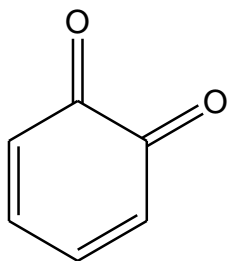
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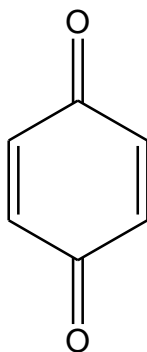
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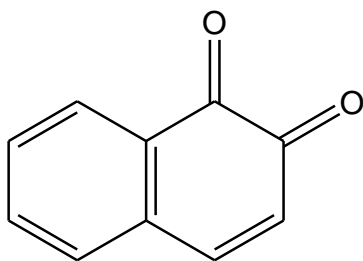
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Structures 1-16**1**

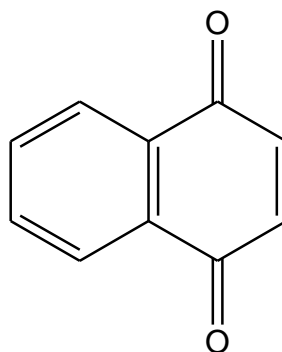
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**2**

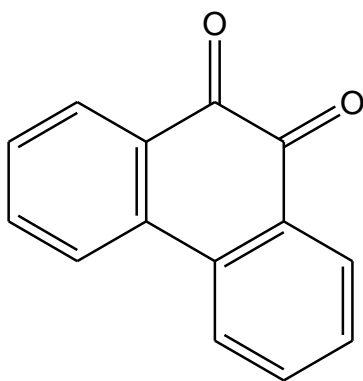
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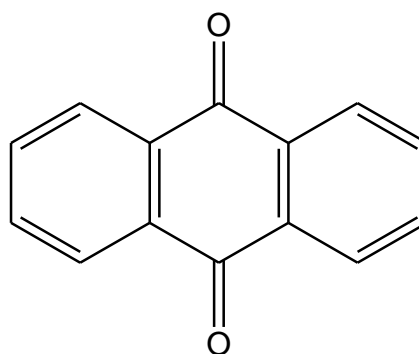
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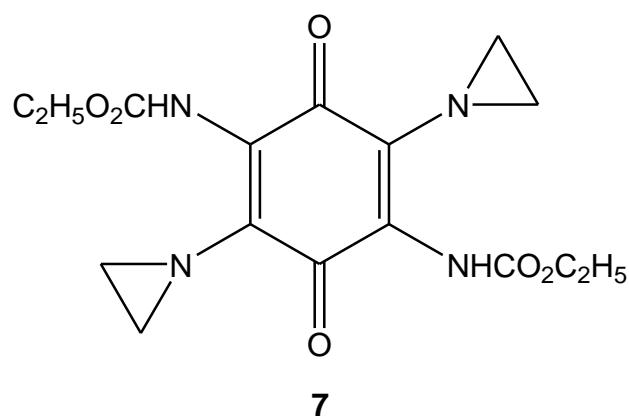
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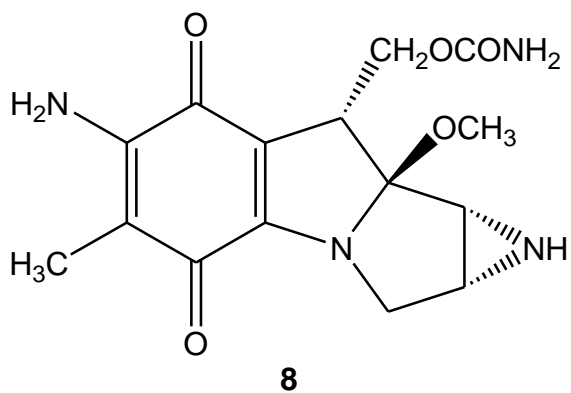
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**6**

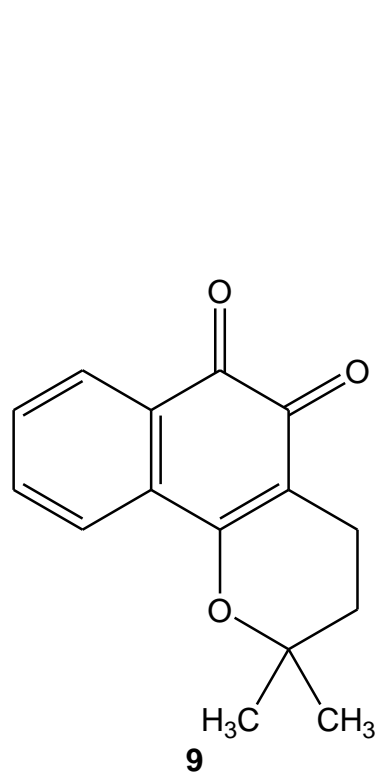
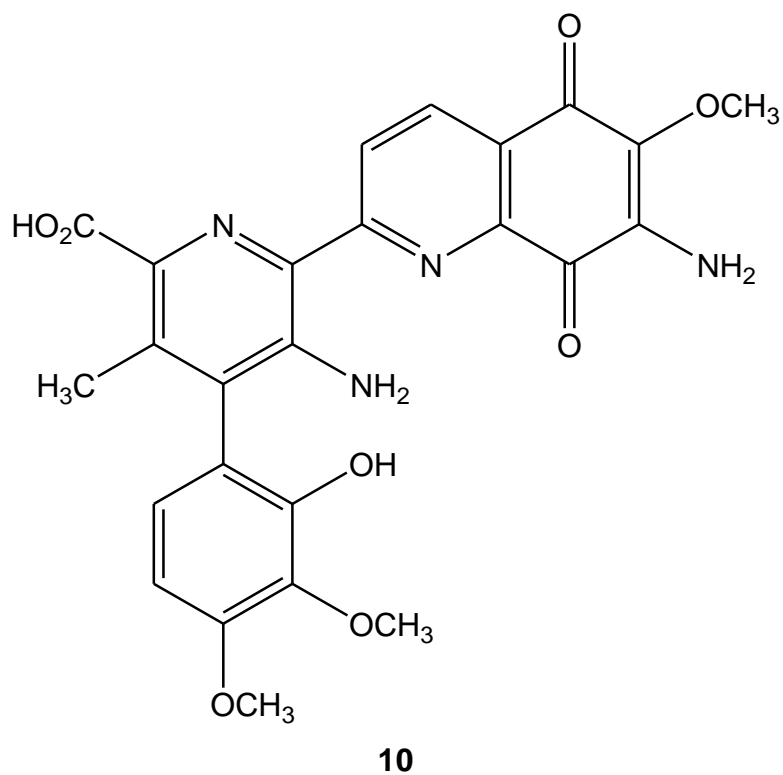
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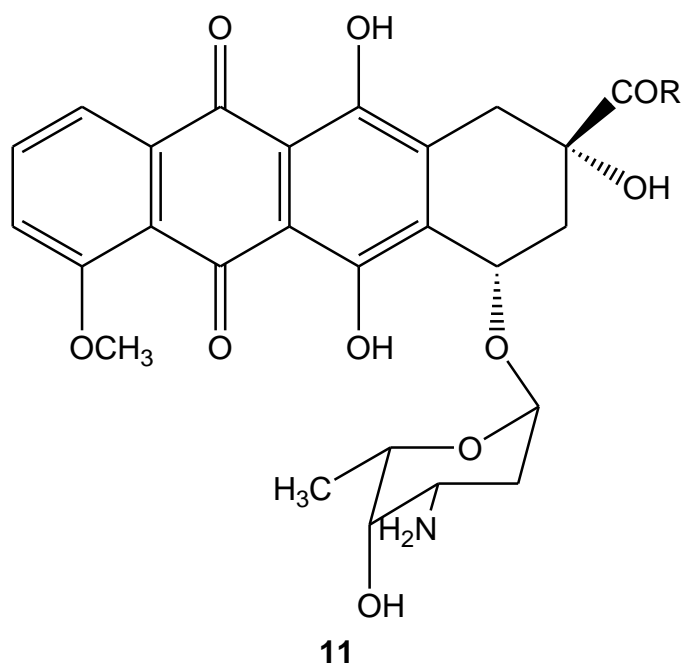
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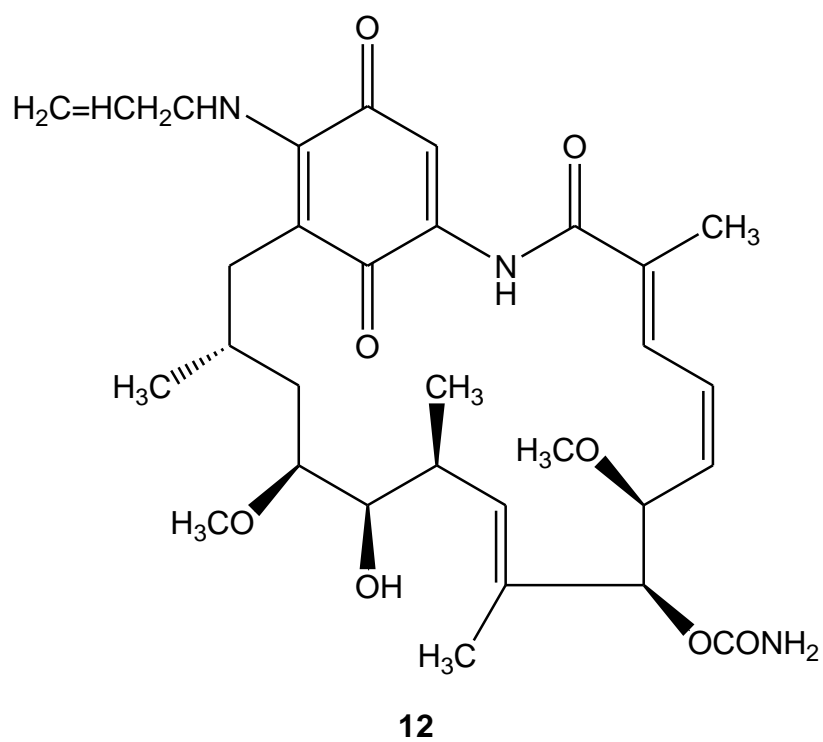
Mitomycin c

 β -Lapachone

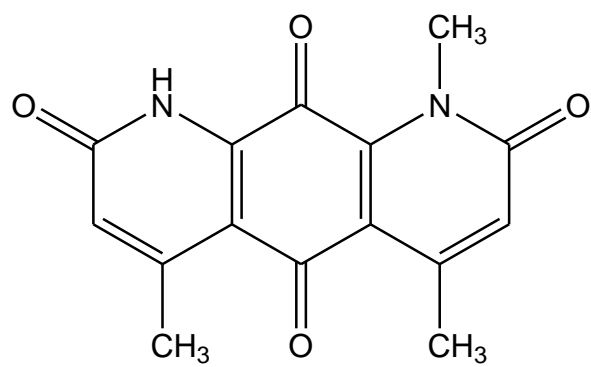
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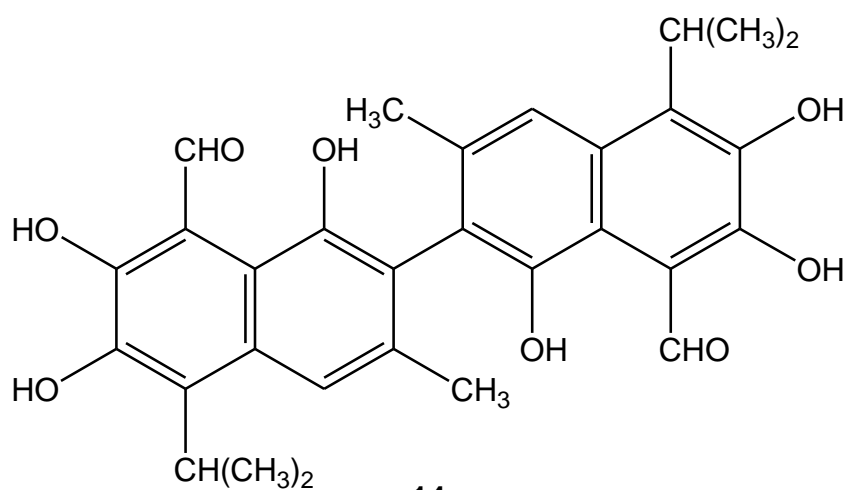
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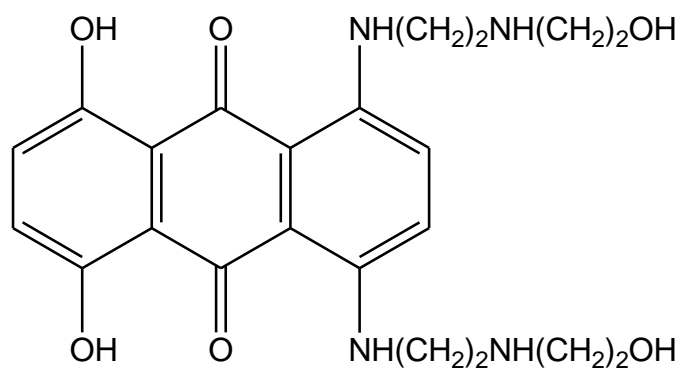
17-(allylamino)-17-demethoxygeldanamycin

**13**

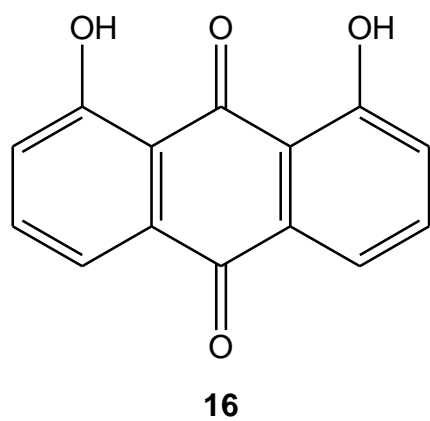
Deoxynyboquinone

**14**

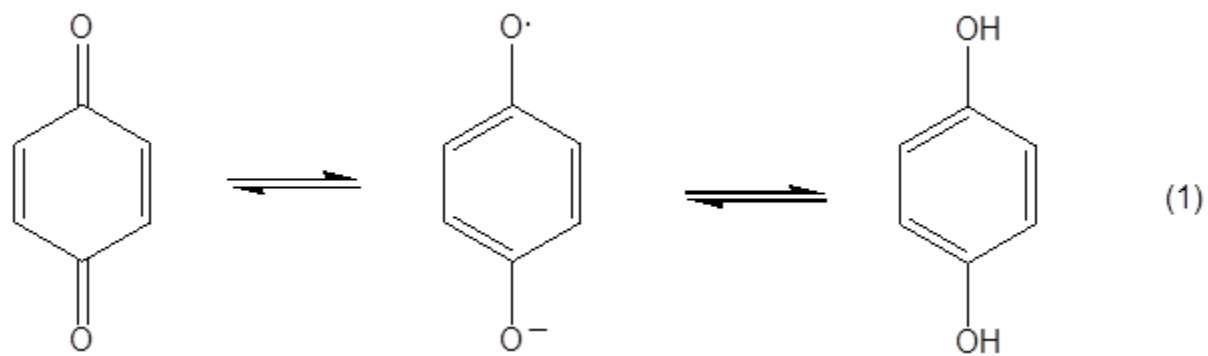
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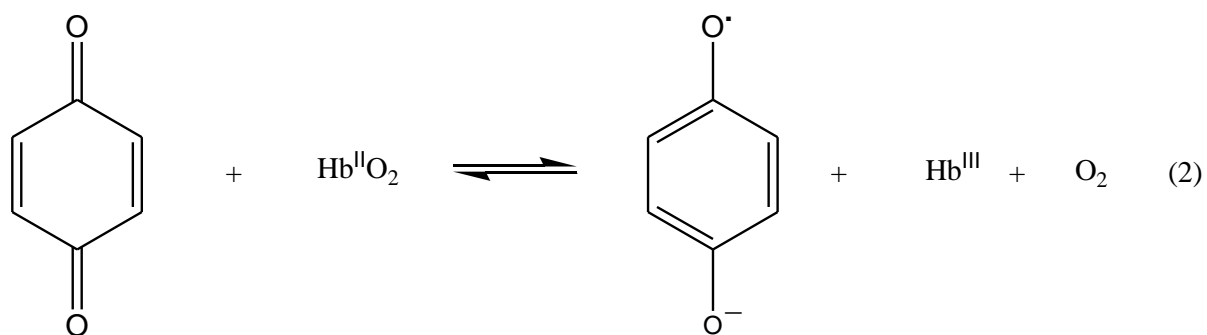
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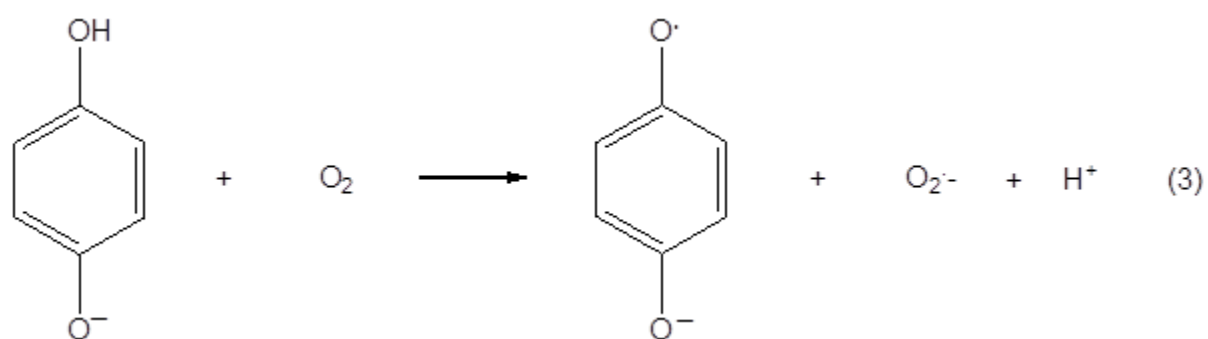
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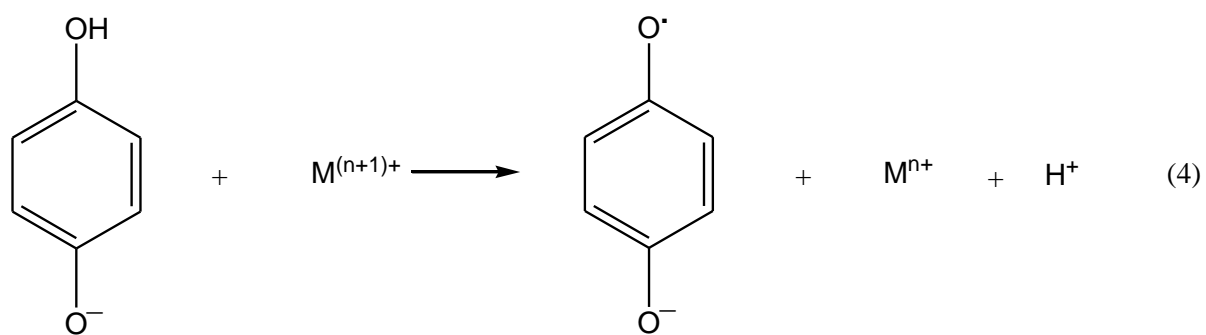
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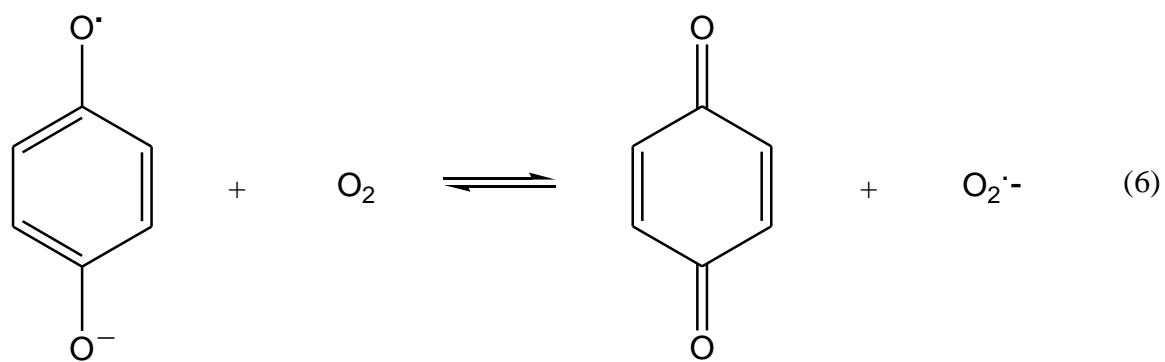
Reaction 1.

Reaction 2.

Reaction 3.

Reactions 4 and 5.



Reaction 6.

Reactions 7 and 8.