Chemical Research in Toxicology

Perspective

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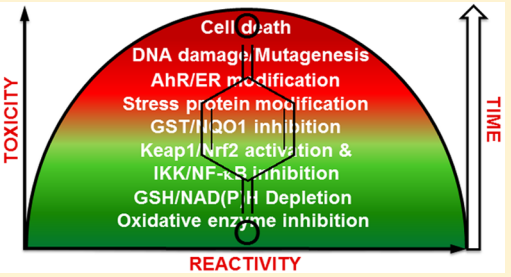
# Formation and Biological Targets of Quinones: Cytotoxic versus Cytoprotective Effects

Judy L. Bolton* and Tareisha Dunlap

Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, Illinois 60612-7231, United States

**ABSTRACT:** Quinones represent a class of toxicological intermediates, which can create a variety of hazardous effects *in vivo* including, acute cytotoxicity, immunotoxicity, and carcinogenesis. In contrast, quinones can induce cytoprotection through the induction of detoxification enzymes, anti-inflammatory activities, and modification of redox status. The mechanisms by which quinones cause these effects can be quite complex. The various biological targets of quinones depend on their rate and site of formation and their reactivity. Quinones are formed through a variety of mechanisms from simple oxidation of catechols/hydroquinones catalyzed by a variety of oxidative enzymes and metal ions to more complex mechanisms involving initial P450-catalyzed hydroxylation reactions followed by two-electron oxidation. Quinones are Michael acceptors, and modification of cellular processes could occur through alkylation of crucial cellular proteins and/or DNA. Alternatively, quinones are highly redox active molecules which can redox cycle with their semiquinone radical anions leading to the formation of reactive oxygen species (ROS) including superoxide, hydrogen peroxide, and ultimately the hydroxyl radical. Production of ROS can alter redox balance within cells through the formation of oxidized cellular macromolecules including lipids, proteins, and DNA. This perspective explores the varied biological targets of quinones including GSH, NADPH, protein sulfhydryls [heat shock proteins, P450s, cyclooxygenase-2 (COX-2), glutathione *S*-transferase (GST), NAD(P)H:quinone oxidoreductase 1, (NQO1), kelch-like ECH-associated protein 1 (Keap1), IκB kinase (IKK), and arylhydrocarbon receptor (AhR)], and DNA. The evidence strongly suggests that the numerous mechanisms of quinone modulations (i.e., alkylation versus oxidative stress) can be correlated with the known pathology/cytoprotection of the parent compound(s) that is best described by an inverse U-shaped dose−response curve.




## CONTENTS



## 1. INTRODUCTION

Quinones are a subset of the quinoid family which also contains the quinone imines and the quinone methides (Figure 1).[1−3]

**Special Issue:** CRT30

**Received:** July 25, 2016
**Published:** September 12, 2016

DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

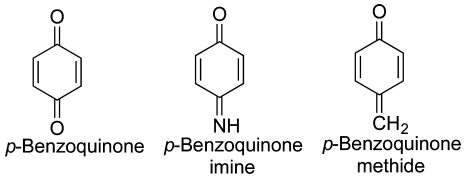



**Figure 1.** Examples of simple quinoids.

Quinones, which contain the cyclohexadienedione structure, are the most numerous of the quinoids and are commonly found in several natural products, endogenous biochemicals, drugs, and environmental chemicals and/or are generated through the metabolism of aromatic compounds (Figure 2). In

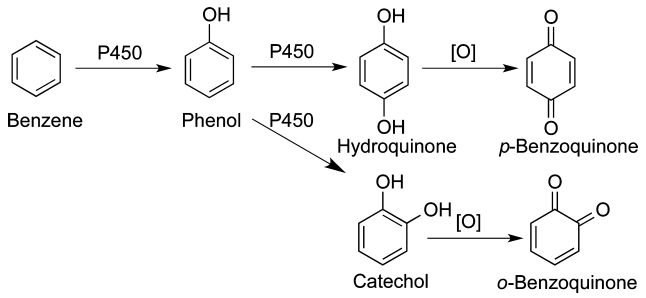



**Figure 2.** Quinone formation from aromatic compounds represents a common bioactivation scheme.

general, the biological properties of quinone precursors (good, bad, or equivocal) are often mediated by their oxidative metabolism to quinones. However, the importance of quinone formation to the off-target effects of drugs, natural products, environmental chemicals, and xenobiotic/endogenous compounds in general is often underestimated. For example, two recent reviews on biological reactive intermediates give varying estimates on the importance of quinone formation. For carcinogenic processes, quinone formation was estimated at 7% of all mutagenic reactive intermediates,[4] whereas for all toxic reactions (7% of total metabolism), quinone formation represents closer to 41%.[5] Both numbers are likely low since quinones are reactive intermediates and usually cannot be observed directly. In biological systems, as quickly as quinones are formed they react with cellular nucleophiles (GSH, protein sulfhydryls) and/or they redox cycle forming ROS (Figure 3). This perspective will focus on our limited knowledge of the varied biological targets of quinones, resulting in numerous biological effects, which could be beneficial, toxic, equivocal, and/or unknown. Quinone methides and quinone imines have been reviewed recently and are beyond the scope of this perspective.[1,2,6−9]

## 2. MECHANISM OF QUINONE FORMATION

**2.1. Stable Quinones (Table 1).** For the purpose of this perspective, quinones that exist in nature as the quinone form were defined as stable. In general, *p*-quinones are considerably more stable compared to *o*-quinones due to the strained 1,2-diketone functionality of the latter. Some *p*-quinones can be crystallized (*t*-butylquinone, menadione), and there are examples of natural products with stable *p*-quinone structures (e.g., juglone, ansamycin antibiotics) as well as endogenous compounds (vitamin K, ubiquinone) (Table 1).[10−14] Ubiquinone is an antioxidant in the mitochondria, and its analogues could be useful for the treatment of both Alzheimer's and Parkinson's disease since mitochondrial failure, often due to ROS, is involved in the progression of both neurodegenerative diseases.[15−17] Mitoquinone is a ubiquinone analogue in clinical trials for the treatment of Parkinson's disease.[15−17] This novel quinone drug is designed to target the mitochondria through its triphenylphosphine cationic moiety that facilitates drug accumulation because of the negative mitochondrial membrane potential. Idebenone is another ubiquinone analogue which may have promise in the treatment of Alzheimer's disease (Table 1).[18] Several potent chemotherapeutic agents [daunorubicin, diaziquone, doxorubicin (adriamycin), emodin, mitomycin C, mitoxantrone, and streptonigrin; Table 1] have highly substituted stable *p*-quinone functionalities, which likely contribute to their ability to kill cancer cells through redox mechanisms (discussed below) as well as cause reactive oxygen species (ROS)-induced toxicity to normal cells.[19−22] The naphthalene *o*-quinones miltirone isolated from danshen and *β*-lapachone from the pink trumpet tree are examples of stable *o*-quinones (Table 1).[23,24]

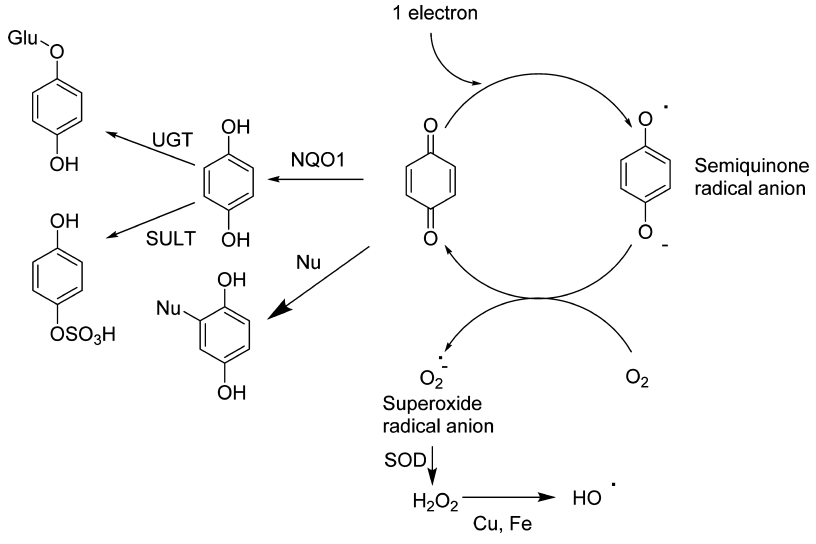
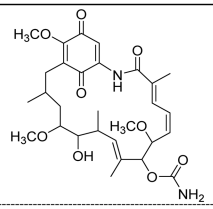
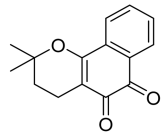
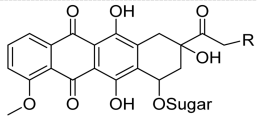
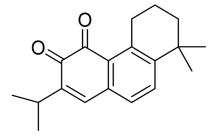
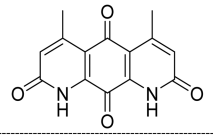
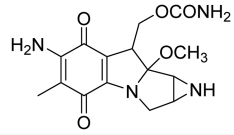
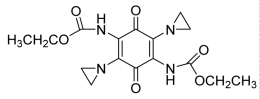
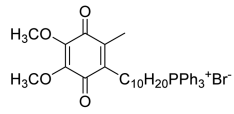
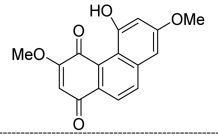
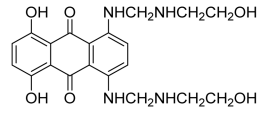
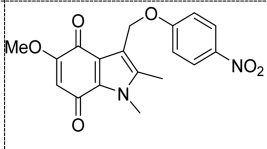
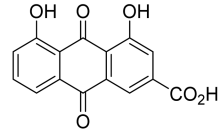
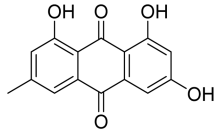
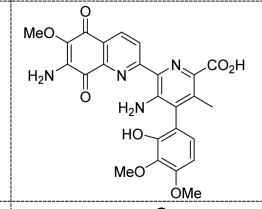
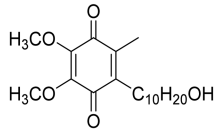
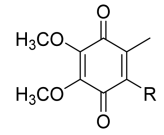
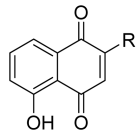
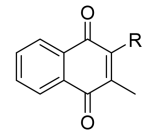



**Figure 3.** Mechanisms of quinone toxicity.



DOI: 10.1021/acs.chemrestox.6b00256
Chem. Res. Toxicol. 2017, 30, 13−37

Table 1. Examples of Stable Quinones[a]

| Quinone | Chemical Structure | Biological Effect[b] | Quinone | Chemical Structure | Biological Effect |
|---|---|---|---|---|---|
| Ansamycins (geldanamycin) |  | Antibiotic, antitumor[11] | β-Lapachone (pink trumpet tree) |  | Antitumor agent[24] |
| Daunorubicin/ Doxorubicin |  Daunorubicin, R=H Doxorubicin, R=OH | Antitumor agent[19] | Miltirone (danshen) |  | TCM[23] |
| Deoxynyboquinone |  | Antitumor agent[191] | Mitomycin C |  | Antitumor agent[19] |
| Diaziquinone |  | Antitumor agent[19] | Mitoquinone |  | Parkinson's disease[17] |
| Denbinobin (Shi-Hu, TCM) |  | Antitumor agent[227] | Mitoxantrone |  | Antitumor agent[20] |
| ES936 |  | NQO1 inhibitor[190] | Rhein (cassic acid, rhubarb) |  | Osteoarthritis[171] |
| Emodin (rhubarb, buckthorn) |  | Antitumor agent[22] | Streptonigrin |  | Antitumor agent[21] |
| Idebenone |  | Alzheimer's disease[18] | Ubiquinone (Coenzyme $Q_{10}$) |  R=alkyl side chain | Co-factor[12] |
| Juglone (Black walnuts) |  Juglone, R=H Plumbagin, R=$CH_3$ | Herbicide[10] | Vitamin K |  R=alkyl side chain R=H, menadione | Vitamin[13] |

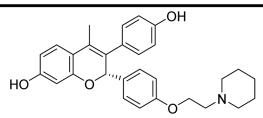
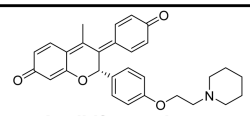
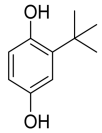
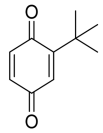
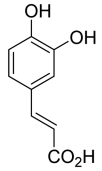
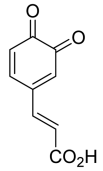
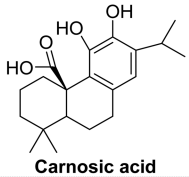
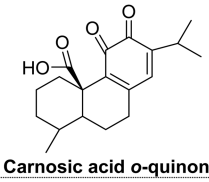
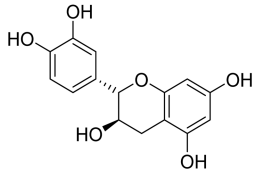
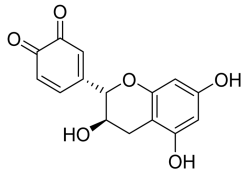
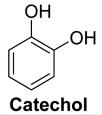
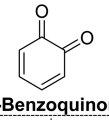
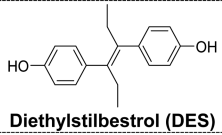
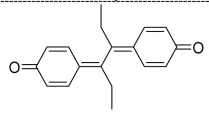
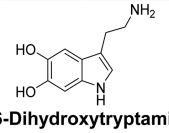
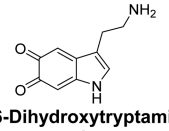
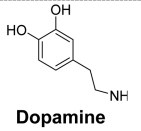
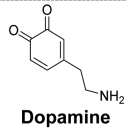
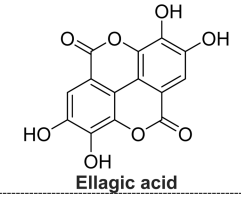
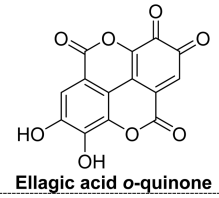
[a]Alphabetical list (16 total, partial list). [b]Only one representative reference is listed for each example.

**2.2. Two-Electron Oxidation of Hydroquinones/Catechols (Table 2).** Hydroquinones and catechols are very easily converted to quinones by oxidation catalyzed by virtually any oxidative enzyme including P450s, COX-2, peroxidase, tyrosinase, xanthine oxidase and monoamine oxidase, and metal ions and in some cases molecular oxygen (Table 2).[3,25−28] *p*-Quinones are formed from oxidation of *t*-butylhydroquinone, hydroquinone, naphthohydroquinone, and thymohydroquinone.[25,29−32] Oxidation of catechols in natural products [caffeic acid, carnosic acid, catechin, ellagic acid, epigallocatechin (ECGC), hydroxychavicol, luteolin, procyanidin, quercetin, taxifolin, and urushiols] gives *o*-



DOI: 10.1021/acs.chemrestox.6b00256
Chem. Res. Toxicol. 2017, 30, 13−37

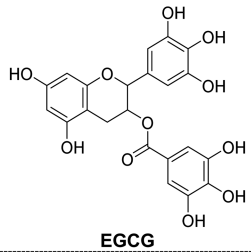
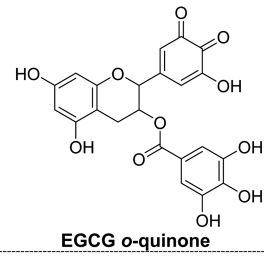
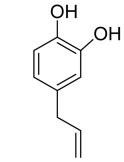
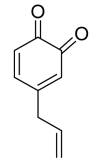
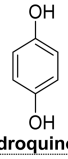
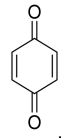
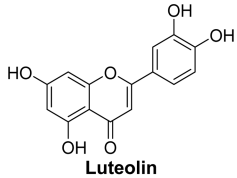
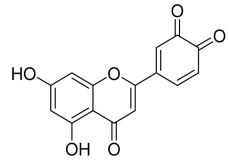
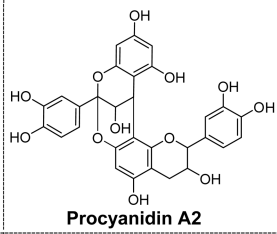
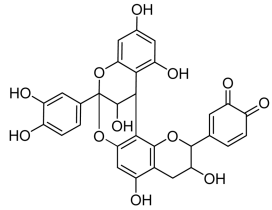
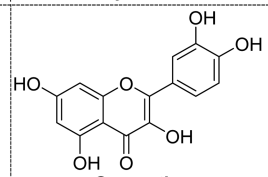
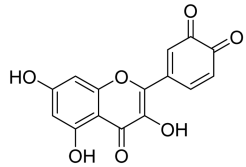
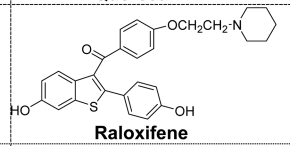
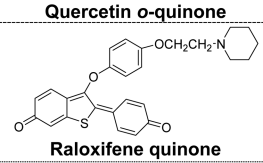
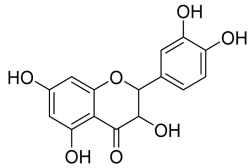
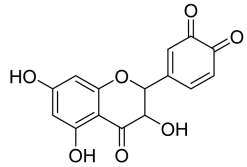
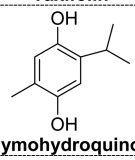
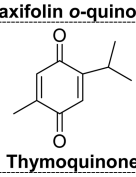
Table 2. Two-Electron Oxidation of Hydroquinones/Catechols to Quinones[a]

| Parent Compound | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|
| Acolbifene (SERM) |  Acolbifene |  Acolbifene quinone | ?[52] |
| *t*-Butyl-hydroquinone (metabolite of food preservative BHA) |  *t*-Butylhydroquinone | [O] →  *t*-Butylquinone | ?[31] |
| Caffeic acid (all plants) |  Caffeic acid | [O] →  Caffeic acid quinone | Chemoprevention[34] |
| Carnosic acid (rosemary) |  Carnosic acid | [O] →  Carnosic acid *o*-quinone | Chemoprevention[39] |
| Catechin (cacao, tea) |  Catechin | [O] →  Catechin *o*-quinone | Chemoprevention[33] |
| Catechol (Fig. 1, benzene metabolite) |  Catechol | [O] →  *o*-Benzoquinone | Leukemia[28] |
| Diethylstilbestrol (estrogen) |  Diethylstilbestrol (DES) | [O] →  DES quinone | Teratogen[60] |
| 5,6-Dihydroxy-tryptamine (serotonin analog) |  5,6-Dihydroxytryptamine | [O] →  5,6-Dihydroxytryptamine *o*-quinone | Neurotoxin[49] |
| Dopamine (neurotransmitter) |  Dopamine | [O] →  Dopamine *o*-quinone →  Aminochrome | Parkinson's disease[50] |
| Ellagic acid (blackberries) |  Ellagic acid | [O] →  Ellagic acid *o*-quinone | Chemoprevention[42] |



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

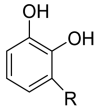
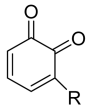
Table 2. continued

| Parent Compound | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|
| Epigallocatechin gallate (EGCG, green tea) |  EGCG |  EGCG *o*-quinone | Chemoprevention[149] |
| Hydroxychavicol (piper betel leaf, see safrole) |  Hydroxychavicol |  Hydroxychavicol *o*-quinone | ?[38] |
| Hydroquinone (Fig. 1, benzene metabolite) |  Hydroquinone |  *p*-Benzoquinone | Leukemia[63] |
| Luteolin (celery, thyme) |  Luteolin |  Luteolin *o*-quinone | Chemoprevention[145] |
| Procyanidin (cranberry) |  Procyanidin A2 |  Procyanidin A2 *o*-quinone | Antibacterial[37] |
| Quercetin (apples) |  Quercetin |  Quercetin *o*-quinone | Chemoprevention[43] |
| Raloxifene (SERM) |  Raloxifene |  Raloxifene quinone | ?[166] |
| Taxifolin (milk thistle) |  Taxifolin |  Taxifolin *o*-quinone | Chemoprevention[41] |
| Thymohydroquinone (*Nigella sativa*) |  Thymohydroquinone |  Thymoquinone | Chemoprevention[147] |



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

Table 2. continued

| Parent Compound | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|
| Urushiol Mixture (poison ivy/oak) |  Urushiols R = alkyl group |  Urushiol *o*-quinones | Skin toxicity[36] |

[a]Alphabetical list (20 total, partial list). [O] refers to any oxidative enzyme or metal ions and in some cases molecular oxygen. [b]Only one representative reference is listed for each example.

quinones with a variety of biological effects (Table 2).[33−43] Most of these *o*-quinones are short-lived, and their contribution to the overall biological profiles of the parent compounds is not clear.[44,45] The endogenous catechol amines (5,6-dihydroxytryptamine and dopamine) are also oxidized to *o*-quinones which may play a role in the etiology of Parkinson's disease.[3,46−50] Dopamine oxidation to dopamine *o*-quinone as well as other quinones is believed to contribute to neurodegeneration through induction of mitochondria and protein dysfunction and oxidative stress (Table 2).[51] The selective estrogen receptor modulators (SERMs) acolbifene and raloxifene form extended quinones in *in vitro* experiments, although both have very short lifetimes and may not have any beneficial/toxic effects (Table 2).[52−57] Extended quinone formation from the estrogen diethylstilbestrol (DES) may contribute to the teratogenic effects of DES in women exposed to this drug to prevent miscarriages and premature births in utero up until its withdrawal in 1971 (Table 2).[58−60]

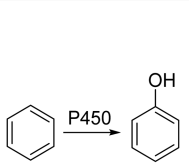
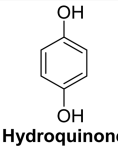
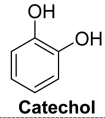
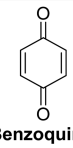
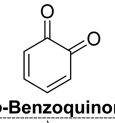
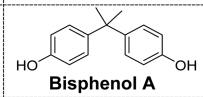
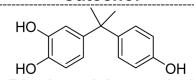
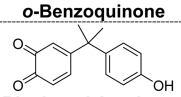
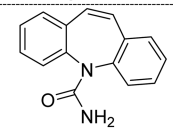
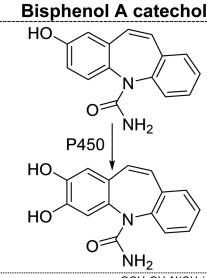
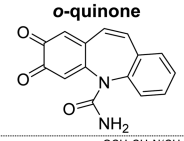
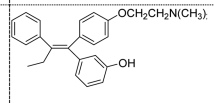
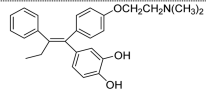
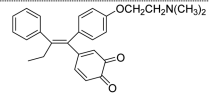
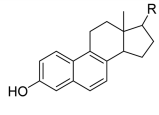
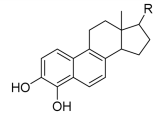
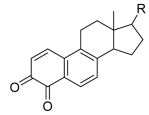
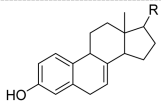
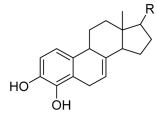
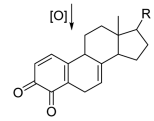
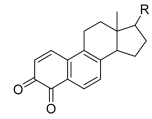
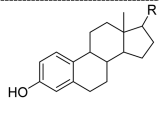
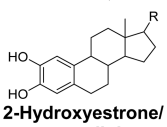
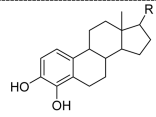
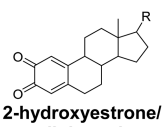
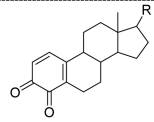
**2.3. Aromatic Hydroxylation(s)/Two-Electron Oxidation (Table 3).** Aromatic rings represent the most common functional group in drugs which suggests that the general bioactivation scheme generating quinones should readily occur as shown for benzene in Figure 2.[3,9,61−64] For example, the anticonvulsant phenytoin causes skin toxicity in 5−10% of patients, and P450-catalyzed *o*-quinone formation has been implicated as the culprit (Table 3).[65] The hepatotoxic effects of the epilepsy drug, carbamazepine, has been shown to proceed through a similar mechanism (Table 3).[66,67] The teratogen thalidomide is metabolized to a phenol, catechol, and *o*-quinone catalyzed by P450 which could contribute to the teratogenic mechanism through *o*-quinone-induced oxidative stress and/or protein binding (Table 3).[68] The environmental contaminants naphthalene, bisphenol A, and some polychlorinated biphenyls (PCBs) readily form *o*- and *p*-quinones through this mechanism (Table 3).[32,69−72] The SERMs (droloxifene, lasofoxifene, LY2066948, raloxifene, tamoxifen, and toremifene) all undergo one or two P-450 catalyzed aromatic hydroxylation reactions followed by two-electron oxidation to *o*-quinones (Table 3).[53,57,73−77] Generally, *o*-quinone formation from SERMs is a minor bioactivation pathway, and the contribution of quinone metabolites to the overall chemopreventive/toxic properties of the parent SERMs are not known. The synthetic estrogen hexestrol, which is the saturated derivative of DES, is converted to the catechol by P450 followed by two-electron oxidation to the *o*-quinone (Table 3).[59,78] Two *o*-quinones are formed from the endogenous estrogens (estrone and estradiol, Table 3); the 2-hydroxyestrogen *o*-quinone pathway is likely a detoxification pathway since the *o*-quinone formed is very unstable and readily isomerizes to a quinone methide.[3,79−81] In contrast, the 4-hydroxyestrogen *o*-quinone is sufficiently long-lived to produce a variety of mutagenic/carcinogenic effects including DNA oxidation and adduct formation as described below.[82,83] Estrogens in hormone therapy (equilin, equilenin, and 8,9-dehydroequilin), all form *o*-quinones through initial P450-catalyzed aromatic hydroxylation followed by two-electron oxidation (Table 3).[79,84−86] Quinone formation from these estrogens could contribute to the increased incidence of hormone-dependent cancer associated with hormone therapy for menopausal symptoms.[87−89] 17$\alpha$-Ethinyl estradiol, which is the most common estrogen in birth control pills, is also converted to *o*-quinones which may contribute to liver toxicity observed at high doses in animal models.[90] However, the doses of ethinyl estradiol are significantly lower than HT drugs, and quinone formation is unlikely to contribute to clinical toxicity for birth control pills.[90] Finally, the natural products resveratrol and genistein both form catechols and *o*-quinones by this mechanism which may contribute to their chemopreventive properties *in vivo*.[91,92]

**2.4. P450-Catalyzed O-Dealkylation/Two-Electron Oxidation (Table 4).** Another mechanism of quinone formation involves P-450-catalyzed unmasking of phenols/catechols through O-dealkylation reactions followed by two-electron oxidation.[9] For example, the methoxy substituent in etoposide is O-dealkylated generating a catechol which is readily oxidized to an *o*-quinone (Table 4).[93] *o*-Quinone formation from etoposide likely contributes to redox toxicity in cells through the generation of ROS contributing to side effects associated with this chemotherapeutic drug.[94,95] A similar mechanism is involved in the generation of the extended quinone from arzoxifene; initial O-dealkylation of arzoxifene generates desmethylarzoxifene followed by two-electron oxidation to the extended quinone (Table 4).[96] Like the raloxifene extended quinone described above, the arzoxifene quinone has a very short half-life and may not make a significant contribution to the overall biological effects of arzoxifene.[57] Eugenol (cloves) can also be metabolized by this pathway initially generating hydroxychavicol followed by two-electron oxidation to the *o*-quinone (Table 4).[9,97,98] *o*-Quinone formation from eugenol represents a minor bioactivation pathway since direct two electron oxidation to the *p*-quinone methide is a more facile metabolic process.[1,99] In an analogous mechanism, curcumin can be O-demethylated giving the catechol, which is further oxidized to an *o*-quinone which was implicated in curcumin induced oxidative DNA damage (Table 4).[100] The synthetic phenolic antioxidant *t*-butylhydroxyanisole (BHA) also is O-demethylated by P450 to *t*-butylhydroquinone and further oxidized to the *t*-butyl-*p*-benzoquinone (Table 4).[101] P450-catalyzed cleavage of the methylenedioxy groups in isosafrole, 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenediox-



DOI: 10.1021/acs.chemrestox.6b00256
Chem. Res. Toxicol. 2017, 30, 13−37

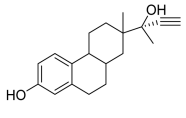
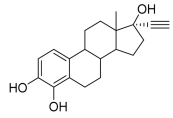
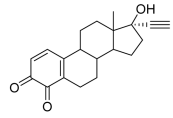
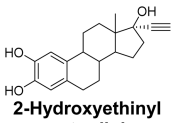
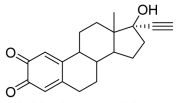
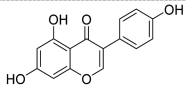
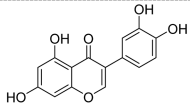
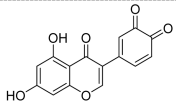
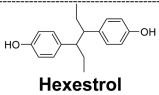
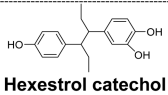
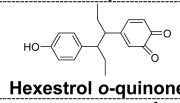
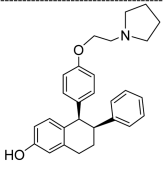
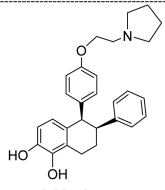
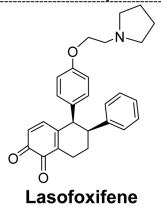
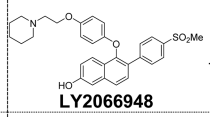
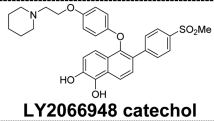
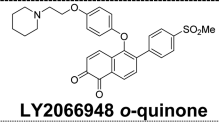
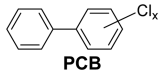
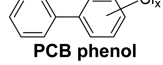
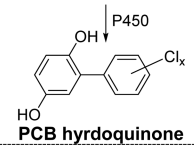
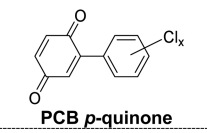
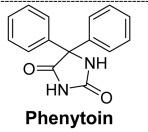
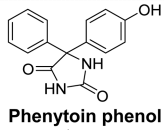
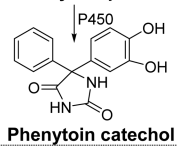
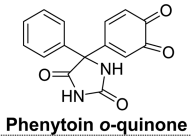
Table 3. Aromatic Hydroxylation(s)/Two-Electron Oxidation to Quinones[a]

| Parent Compound | Hydroxylation | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|---|
| Benzene (environmental contaminant) |  Benzene → Phenol (P450) |  Hydroquinone (P450);  Catechol (P450) |  *p*-Benzoquinone ([O]);  *o*-Benzoquinone ([O]) | Nephrotoxin/ leukemia[64] |
| Bisphenol A (environmental contaminant) |  Bisphenol A |  Bisphenol A catechol (P450) |  Bisphenol A quinone ([O]) | Neurotoxicity[241] |
| Carbamazepine (anti-seizure) |  Carbamazepine (P450) |  Carbamazepine catechol (P450) |  Carbamazepine *o*-quinone ([O]) | Hepatotoxin[67] |
| Droloxifene (SERM) |  Droloxifene (P450) |  Droloxifene catechol ([O]) |  Droloxifene *o*-quinone | ?[75] |
| Equilenin (HT) |  Equilenin,R,=O 17-OH-Equilenin R,=OH (P450) |  4-Hydroxyequilenin ([O]) |  4-Hydroxy equilenin *o*-quinone | Mutagen[86] |
| Equilin (HT) |  Equilin, R,=O 17-OH-Equilin, R,OH (P450) |  4-Hydroxyequilin; [O]  4-Hydroxyequilin *o*-quinone (isomerize)  4-Hydroxyequilenin *o*-quinone | | Mutagen[84] |
| Estradiol/ Estrone (HT) |  Estrone, R, =O Estradiol, R, OH (P450)  2-Hydroxyestrone/ estradiol ([O]) |  4-Hydroxyestrone/ estradiol ([O])  2-hydroxyestrone/ estradiol *o*-quinone |  4-Hydroxyestrone/ Estradiol *o*-quinone | Mutagen/ carcinogen[81] |



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

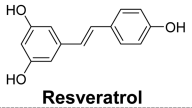
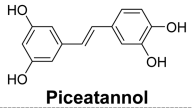
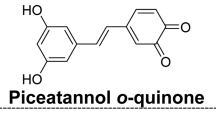
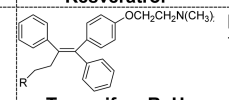
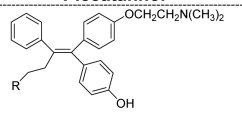
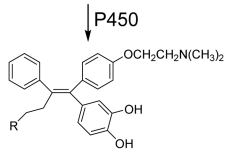
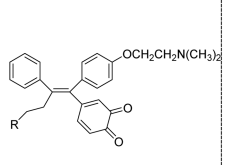
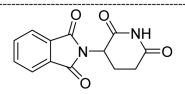
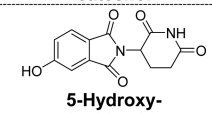
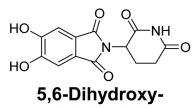
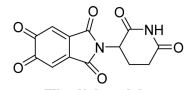
Table 3. continued

| Parent Compound | Hydroxylation | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|---|
| 17α-Ethinylestradiol (birth control pills) |  Ethinylestradiol | P450 →  4-Hydroxyethinyl estradiol | [O] →  4-Hydroxyethinyl estradiol *o*-quinone | Hepatotoxin[90] |
| | P450 ↓  2-Hydroxyethinyl estradiol | [O] →  2-Hydroxyethinyl estradiol *o*-quinone | | |
| Genistein (soy, red clover) |  Genistein | P450 →  Genistein catechol | [O] →  Genistein *o*-quinone | ?[92] |
| Hexestrol (DES derivative) |  Hexestrol | P450 →  Hexestrol catechol | [O] →  Hexestrol *o*-quinone | Antitumor[78] |
| Lasofoxifene (SERM) |  Lasofoxifene | P450 →  4-Hydroxy-lasofoxifene (also 2-Hydroxy) | [O] →  Lasofoxifene *o*-Quinone | ?[74] |
| LY2066948 (SERM) |  LY2066948 | P450 →  LY2066948 catechol | [O] →  LY2066948 *o*-quinone | ?[73] |
| Napthalene | (See benzene, two aromatic rings) | | | Environmental pollutant[32] |
| PCBs |  PCB | P450 →  PCB phenol | [O] →  PCB *p*-quinone | Environmental pollutant[71] |
| | | P450 ↓  PCB hyrdoquinone | [O] →  PCB *o*-quinone | |
| Phenytoin (anti-seizure) |  Phenytoin | P450 →  Phenytoin phenol | | Skin toxicity[65] |
| | | P450 ↓  Phenytoin catechol | [O] →  Phenytoin *o*-quinone | |



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

Table 3. continued

| Parent Compound | Hydroxylation | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|---|
| Resveratrol (grapes) |  Resveratrol | P450  Piceatannol | [O]  Piceatannol *o*-quinone | Chemoprevention[91] |
| Tamoxifen (SERM, tamoxifen catechol and quinone are the same as formed from droloxifene) |  Tamoxifen, R=H Toremifine, R=Cl | P450  P450  Tamoxifen catechol | [O]  Tamoxifen *o*-quinone | ?[77] |
| Thalidomide (morning sickness) |  Thalidomide | P450  5-Hydroxy-thalidomide P450  5,6-Dihydroxy-thalidomide | [O]  Thalidomide *o*-quinone | Teratogen[68] |

[a]Alphabetical list (20 total, partial list). [O] refers to any oxidative enzyme or metal ions and in some cases molecular oxygen. [b]Only one representative reference is listed for each example.

ymethamphetamine (MDMA, ecstasy), methysticin, myristicin, paroxetine, safrole, and sitaxentan generate catechols which are readily oxidized to *o*-quinones by virtually any oxidative enzyme or metal ions (Table 4).[102−108] These data suggest that quinone formation from compounds containing a methylenedioxy substituent might be a general mechanism for *o*-quinone formation.[9]

**2.5. Complex Quinone Formation (Table 5).** Polycyclic aromatic hydrocarbons (PAHs) are metabolized to *o*-quinones through a complex mechanism involving initial P450-catalyzed arene oxide formation, ring opening catalyzed by epoxide hydrolase, aldo-keto reductase (AKR) mediated formation of the catechol, and two-electron oxidation to *o*-quinone (Table 5).[109] Many AKRs can also catalyze redox cycling (see below) by reducing the PAH *o*-quinones to the catechol which autoxidize in air back to the *o*-quinones consuming NADPH.[109] This pathway was found to be equally important with the more commonly known diol-epoxide pathway to the activation of benzo[*a*]pyrene to a human lung carcinogen.[109] *o*-Quinone from PAHs present in industrial pollutants and tobacco smoke could make a major contribution to a variety of human cancers.[109]

A more complex mechanism is also involved in quinone formation from diabetic/anti-inflammatory drug troglitazone and the tocopherols (vitamin E) (Table 5).[110−112] The troglitazone quinone likely contributes to the idiosyncratic liver toxicity which led to the withdrawal of troglitazone from the U.S. market in 2000.[113] The highly substituted tocopherol *p*-quinone likely contributes to the antioxidant effects and signaling mechanisms attributed to the parent vitamin (Table 5).[114,115] The quinone formed from γ-tocopherol has one less methyl group compared to that from α-tocopherol which could influence its biological effects *in vivo*. Even though humans consume considerably more γ-tocopherol in the diet compared to α-tocopherol, α-tocopherol is selectively retained likely due to the enhanced reactivity/toxicity of the less substituted γ-tocopherol quinone.[114,116]

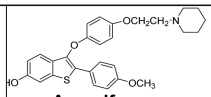
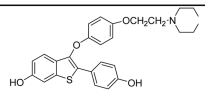
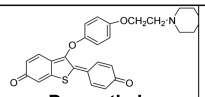
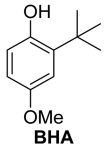
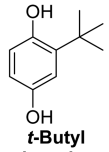
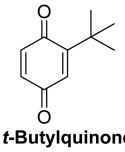
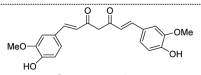
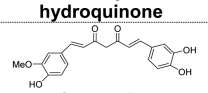
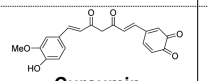
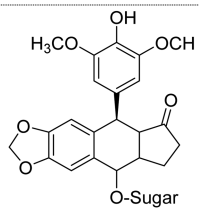
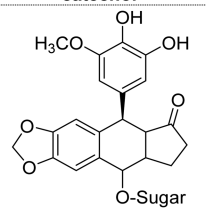
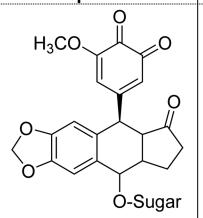
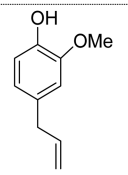
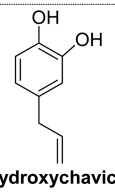
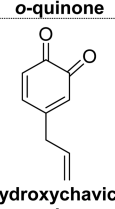
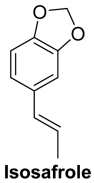
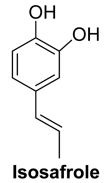
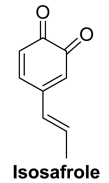
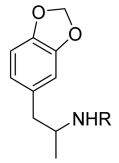
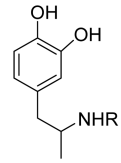
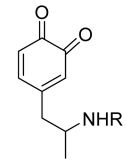
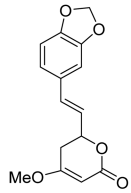
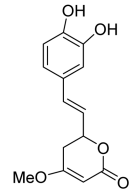
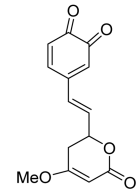
## 3. CHEMISTRY OF QUINONES

**3.1. Covalent Modification.** Quinones are Michael acceptors and readily react with soft nucleophiles like sulfhydryl residues on cysteine in GSH and proteins (Figure 4). *p*-Quinones react via 1,4-reductive addition reactions regenerating the hydroquinone with covalent attachment to the cysteine residue. Unsubstituted *o*-quinones generally undergo 1,6-reductive addition reactions with thiol nucleophiles due to extended conjugation, although 1,4-reductive addition is often observed as a minor product (Figure 4).[38,117] There is some evidence to suggest that the conjugation reaction with cysteine residues is reversible, which could regenerate the quinone and free cysteine and could play a role in quinone signaling mechanisms.[118−121] The hydroquinone/catechol thioethers are more readily oxidized compared to unsubstituted parent compounds, and quinone thioethers with multiple cysteine substituents are often reported.[122,123] Reaction with nitrogen nucleophiles such as lysine, histidine, N-terminal amino acids, and purine and pyrimidine bases on DNA are much slower compared to that of sulfur nucleophilic additions, although they do occur.[71,124] Generally, reductive 1,4-Michael additions predominate over Schiff base formation.[36] Very unstable *o*-



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

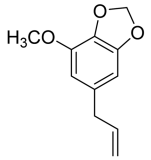
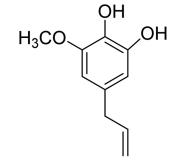
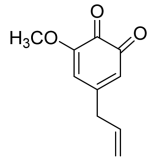
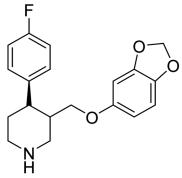
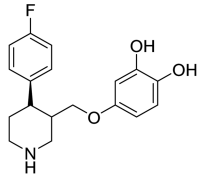
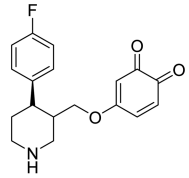
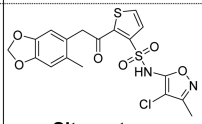
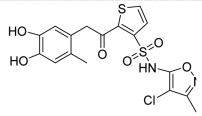
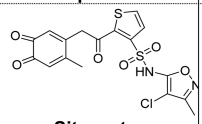
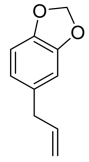
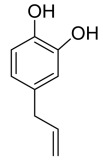
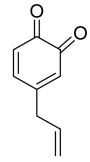
Table 4. P450-Catalyzed O-Dealkylation/Two-Electron Oxidation[a]

| Parent Compound | O-dealkylation | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|---|
| Arzoxifene (SERM) |  Arzoxifene | P450 →  Desmethyl-arzoxifene | [O] →  Desmethyl-arzoxifene Quinone | ?[96] |
| *t*-Butylhydroxy anisole (BHA, food preservative) |  BHA | P450 →  *t*-Butyl hydroquinone | [O] →  *t*-Butylquinone | Antioxidant[101] |
| Curcumin (turmeric) |  Curcumin | P450 →  Curcumin catechol | [O] →  Curcumin *o*-quinone | Chemoprevention[100] |
| Etoposide (May apple) |  Etoposide | P450 →  Etoposide catechol | [O] →  Etoposide *o*-quinone | Antitumor agent[93] |
| Eugenol (cloves) |  Eugenol | P450 →  Hydroxychavicol | [O] →  Hydroxychavicol *o*-quinone | Anesthetic/ antioxidant[98] |
| Isosafrole |  Isosafrole | P450 →  Isosafrole catechol | [O] →  Isosafrole *o*-quinone | ?[107] |
| 3,4-Methylenedioxy-amphetamine (MDA) MAO 3,4-Methylenedioxy-methamphetamine (MDMA, Ecstasy) |  MDA, R=H MDMA, R=$CH_3$ | P450 →  MDA/MDMA catechol | [O] →  MDA/MDMA *o*-quinone | Neurotoxin[102] |
| Methysticin (Kava) |  Methysticin | P450 →  Methysticin catechol | [O] →  Methysticin *o*-quinone | Hepatotoxin[104] |



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

Table 4. continued

| Parent Compound | O-dealkylation | Two-electron oxidation | Quinone | Biological Effect |
|---|---|---|---|---|
| Myristicin (parsley, carrots) |  Myristicin | P450 →  Myristicin catechol | [O] →  Myristicin *o*-quinone | ?[103] |
| Paroxetine (SSRI) |  Paroxetine | P450 →  Paroxetine catechol | [O] →  Paroxetine *o*-quinone | Non-toxic[105] |
| Sitaxentan (Thelin) |  Sitaxentan | P450 →  Sitaxentan catechol | [O] →  Sitaxentan *o*-quinone | Idiosyncratic toxicity[106] |
| Safrole (sassafras) |  Safrole | P450 →  Hydroxychavicol | [O] →  Hydroxychavicol *o*-quinone | Hepatotoxin[38] |

[a]Alphabetical list (11 total, partial list). [O] refers to any oxidative enzyme or metal ions and in some cases molecular oxygen. [b]Only one representative reference is listed for each example.

quinones ($t_{1/2}$ < 1 s) like those formed from genistein (Table 3), luteolin, and quercetin *o*-quinones (Table 2) which have a $C_2-C_3$ double bond in the C ring are rapidly hydrated and unlikely to damage important biological molecules.[45,92,125] Instead, quinone formation from these natural products might be a chemopreventive mechanism through the Keap1/Nrf2 pathway as discussed below.[125]

**3.2. Redox Chemistry.** Quinones are also potent redox active compounds.[3,126] They are readily reduced by one electron catalyzed by P450/NADPH oxidoreductase generating semiquinone radical anions (Figure 3). These intermediates are very unstable and are easily oxidized back up to quinones by molecular oxygen. The reduction of molecular oxygen generates the first of the ROS, the superoxide anion radical. The superoxide anion radical is dismutated by superoxide dismutase generating hydrogen peroxide. Hydrogen peroxide can be reduced by Fenton chemistry through oxidation of iron and/or copper generating the highly reactive hydroxyl radical. This futile redox cycling is responsible for oxidative stress within cells and is a major contributor to overall quinone toxicity.[3] Most quinones can also be reduced by two electrons back to the hydroquinone or catechol catalyzed by NADPH/quinone oxidoreductase (NQO1), which represents a major detoxification mechanism.[127,128] In some cases as with the PAH *o*-quinones, AKRs can catalyze the two-electron reduction reaction.[109] The relative ability of quinones to redox cycle is highly dependent on the ring substituents. Electron rich substituents, extended ring systems, and extensive substitution promote redox cycling since they stabilize the semiquinone radical anion.[126] This often leads to a paradox where GSH conjugation does not result in detoxification since the quinone-thioether quinone is more redox active than the unsubstituted quinone due to the electron donating sulfur substituent.[2]

In normal cells, a strict balance is maintained between oxidation and reduction, and anything that changes this delicate redox balance is thought to contribute to a number of diseases.[129] Quinones cause oxidative stress through the consumption of reducing equivalents including GSH (alkylation and oxidation) and NAD(P)H (oxidation).[130] Production of ROS can alter redox balance within cells through the formation of oxidized cellular macromolecules including lipids, proteins, and DNA. Formation of oxidatively damaged bases such as 8-oxodeoxyguanosine (8-oxo-dG) has been associated with aging and carcinogenesis.[131,132] Furthermore, ROS can activate a number of signaling pathways including protein kinase C and RAS.[133] The redox potential between the quinone and hydroquinone/catechol pair has a major effect on their prooxidant and/or antioxidant effects and ultimately their cytotoxic versus cytoprotective biological properties.[134] For example, it has recently been shown that the more easily *p*-hydroquinones are oxidized, the more potent their antiproliferative effects are in MC38 cells.[135] It is likely that the equine catechol estrogens (4-hydroxyequilin, 4-hydroxyequilenin) and PAH quinones, which only require oxygen to autoxidize to their respective highly redox active *o*-quinones, cause considerably more oxidative stress as compared to those formed from the endogenous catechol estrogens from estradiol and estrone.[79,109,136] These differences in redox activities may explain


DOI: 10.1021/acs.chemrestox.6b00256
Chem. Res. Toxicol. 2017, 30, 13−37

**Table 5. Complex Quinone Formation**[a]

| Parent compound | Complex quinone formation | Quinone | Biological Effect |
|---|---|---|---|
| PAHs (i.e., benzo[a]pyrene) | B[a]P → (1.P450, 2.Epoxide hydrolase) B[a]P-7,8 dihydrodiol → (AKR) B[a]P-7,8-catechol → ([O]) | B[a]P-7,8-quinone | Mutagen/ carcinogen[109] |
| Tocopherols (vitamin E) | α-Tocopherol, R=$CH_3$ γ -Tocopherol, R=H → ([O]) | α-Tocopherol quinone, R=$CH_3$ γ-Tocopherol quinone, R=H | γ-T (toxic)[112] |
| Troglitazone (antidiabetic) | Troglitazone → (P450) | Troglitazone *p*-quinone | Idiosyncratic liver toxicity[110] |

[a]Alphabetical list (3 total, partial list). [O] refers to any oxidative enzyme or metal ions and in some cases molecular oxygen. [b]Only one representative reference is listed for each example.

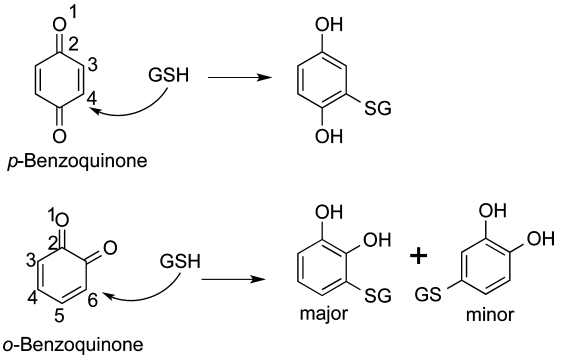



**Figure 4.** Michael addition of GSH to quinones.

variations in epidemiology studies on the link between different types of hormone therapies and risk of breast cancer.[137,138]

## 4. QUINONE TARGETS (FIGURES 5 AND 6)

**4.1. GSH (Figure 5).** The most important nonprotein sulfhydryl in cells is glutathione (GSH) whose major purpose is to protect cells from reactive electrophiles and free radicals.[139] As soft electrophiles, quinones are particularly susceptible to GSH conjugation reactions, and usually, the reaction is so facile that enzymatic catalysis by glutathione *S*-transferase (GSTs) is not required. Model oxidation reactions with microsomes, peroxidase/hydrogen peroxide, and tyrosinase, in the presence of GSH, are all effective methods for generating and trapping quinones.[9,108,122,123,140] Under circumstances where quinone

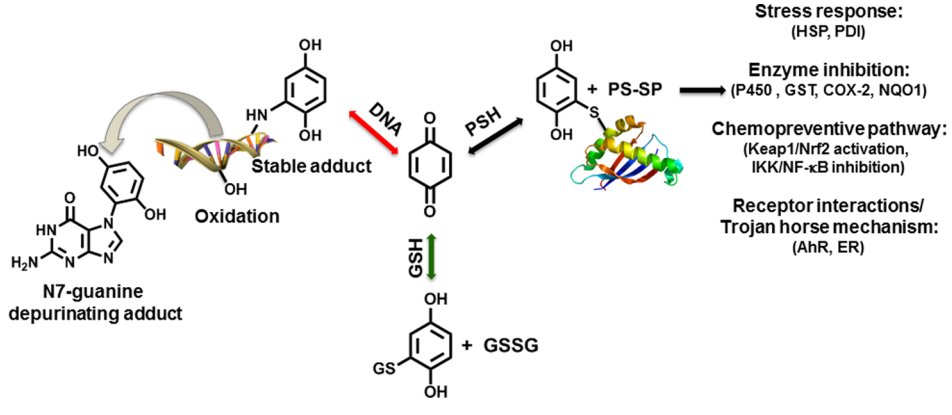



**Figure 5.** Quinone toxicity targets.



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

formation is low and GSH levels are high (i.e., healthy liver cells, 5−10 mM GSH), nonenzymatic reaction with GSH generates reduced GSH hydroquinone/catechol conjugates, which are readily excreted through the mercapturic acid pathway (Figures 3 and 4). Along with two-electron reduction catalyzed by NQO1 and or AKR, GSH conjugation represents a common detoxification pathway for most quinones. GSH can also be oxidized to GSSG by hydroxyl radicals generated during redox cycling of quinones.[130] Several drugs, environmental chemicals, natural products, and endogenous compounds form quinone GSH conjugates and/or cause GSH depletion.[3,10,70,79,92,103,105,106,109,121,141−149]

**4.2. Protein Modification.** *4.2.1. General Protein Modification (Figure 5).* As GSH concentrations are depleted, other sulfhydryl nucleophiles such as cysteine residues on proteins become quinone biological targets. For highly reactive quinones, the major proteins alkylated are those present in the highest concentration containing the largest number of cysteine residues. For example, heat shock proteins [Hsp60, Hsp70, Hsp90, and protein disulfide isomerases (PDIs)] are produced in cells in response to stressful conditions including the generation of electrophilic/redox active quinones.[114,150] These stress proteins are cysteine-rich and thus ideal protein targets of quinones both for alkylation and oxidation (Figure 5).[151−156] For example, using covert oxidatively activated tag (COATag) methodology the extended quinone formed from two-electron oxidation of raloxifene was shown to mainly modify the stress protein GrP78/BiP, three PDIs, and a microsomal GST in rat liver microsomes.[152] PCB *p*-quinones also modify GrP78/BiP and induce the unfolded protein response.[157] The arylating quinone from γ-tocopherol but not the more substituted α-tocopherol quinone induced endoplasmic reticulum stress.[114] The ansamycin quinones have potent antitumor activity through mechanisms involving inactivation, destabilization, and degrading Hsp90 proteins.[11,158] Some dopamine *o*-quinones cause mitochondrial protein damage which has been implicated in Parkinson's disease.[159] The dopamine quinones were found to inhibit the 20/26S proteasome, which is a cytosol protein with numerous cysteines.[156] There are a variety of protein targets of quinones, and identifying reversible unstable protein adducts is challenging for proteomic research, as well as determining the relative importance of the identified biological targets to the overall cytotoxic/cytoprotective effects.[160] Some specific quinone protein targets are enzymes that catalyze their formation and detoxification as well as proteins involved in cell signaling (GST/MAPK, Keap1/Nrf2, IKK/NF-κB) and nuclear receptor proteins [arylhydrocarbon receptor (AhR), estrogen receptor (ER)] as outlined below.

*4.2.2. P450 Inhibition (Figure 5).* Since P450 is the most likely enzyme catalyzing quinone formation, it is to be expected that particularly reactive quinone metabolites have been reported to be inhibitors of P450s.[103,161−163] For example, 4-hydroxytamoxifen and raloxifene were found to be potent mechanism-based inactivators of P450 as a result of quinone-mediated alkylation of the apoprotein.[164−166] With raloxifene, analysis of the P450 3A4 peptide showed that Cys239 was the site of the raloxifene extended quinone reaction.[167] Sitaxentan contains a methylenedioxy ring, which is metabolized by P450 to the catechol and oxidized to the *o*-quinone, which could be responsible for the reported inhibition of P450 3A4 (Table 4).[106] *o*-Quinone formation by sitaxentan could be responsible for the reports of idiosyncratic drug toxicity, which led to its worldwide withdrawal in December, 2010. Similarly, the methyenedioxy group in myristicin is oxidized to an *o*-quinone leading to mechanism-based inhibition of P4501A2.[103] GSH was shown to block the inhibition which suggests that the *o*-quinone was the inhibitor and not the carbene formed from the methylenedioxy moiety.[103] The SSRI paroxetine was shown to be an inhibitor of P450 2D6, and the *o*-quinone metabolite was implicated as the reactive intermediate responsible for the inhibitory effect which ultimately leads to clinical drug−drug interactions with other P450 2D6 substrates.[168,169] Finally, the methoxyestrogens are feedback inhibitors of P450 1A1 and P450 1B1 likely through the formation of the catechol estrogen *o*-quinones.[170]

*4.2.3. COX-2 Inhibition (Figure 5).* Several synthetic and natural stable quinones have been reported to have anti-inflammatory activity through a COX-2 inhibitory mechanism with a potency similar to indomethacin.[171] For example, nanomolar $IC_{50}$s have been reported for jugalone and thymoquinone against human recombinant COX-2 activity (Table 1).[171,172] The catechol metabolite of resveratrol, piceatannol (Table 3), was found to be a selective COX-2 inhibitor with potency similar to that of celecoxib which may contribute to the chemopreventive properties of both compounds.[91,173,174] The diethylester prodrug, diacerein (rhubarb), which is hydrolyzed to the stable *p*-quinone rhein (Table 1), has been shown to be effective for treatment of osteoarthritis.[175,176] Like P450, the peroxidase activity of COX-2 catalyzes the oxidation of catechols and hydroquinones during prostaglandin biosynthesis, and these quinones can inhibit the enzyme.[27] For example, the peroxidase activity of COX-2 catalyzes the formation of the dopamine quinone, which is implicated in the pathogenesis of Parkinson's disease (Table 2).[177] It has been suggested that COX-2 inhibitors may be valuable therapies aimed at slowing the progression of this neurodegenerative disease.[178] Similarly, COX-2 catalyzed formation of the methamphetamine *o*-quinone as well as endogenous neurotransmitter *o*-quinones causing oxidative stress and mitochondrial protein damage has been implicated in neurotoxicity and aging.[179,180] Finally, COX-2 has been shown to oxidize diethylstilbestrol and catechol estrogens to the extended quinone and *o*-quinones, respectively (Table 3).[181−183]

*4.2.4. COMT Inhibition (Figure 5).* In addition to inhibiting enzymes which catalyze their formation, quinones can also inhibit enzymes which detoxify them or their hydroquinone/catechol precursors. For example, catechol *O*-methyl transferase (COMT) catalyzes the conversion of catechols to methoxyethers which cannot be further oxidized to quinones and therefore represents a catechol detoxification mechanism. The equine estrogen metabolites 4-hydroxyequilenin and 4-hydroxyequilin have been shown to be potent inhibitors of COMT likely because they can autoxidize to *o*-quinones (Table 3).[184,185] Inhibition of COMT-mediated catechol estrogen clearance may play a role in the toxicity of endogenous estrogens and estrogens in HT.[186] The catecholamine quinones are also potent irreversible inhibitors of COMT which could contribute to the neurotoxicity mechanism (Table 3).[187,188]

*4.2.5. NQO1 Inhibition (Figure 5).* Two-electron reduction of quinones to catechols and hydroquinones is a major detoxification mechanism for most quinones.[128] However, some quinones have been shown to be mechanism-based inhibitors of NQO1. For example, the *p*-quinone ES936 (Table 1) is a nanomolar inhibitor of NQO1 in cell-based assays.[189]


DOI: 10.1021/acs.chemrestox.6b00256
Chem. Res. Toxicol. 2017, 30, 13−37

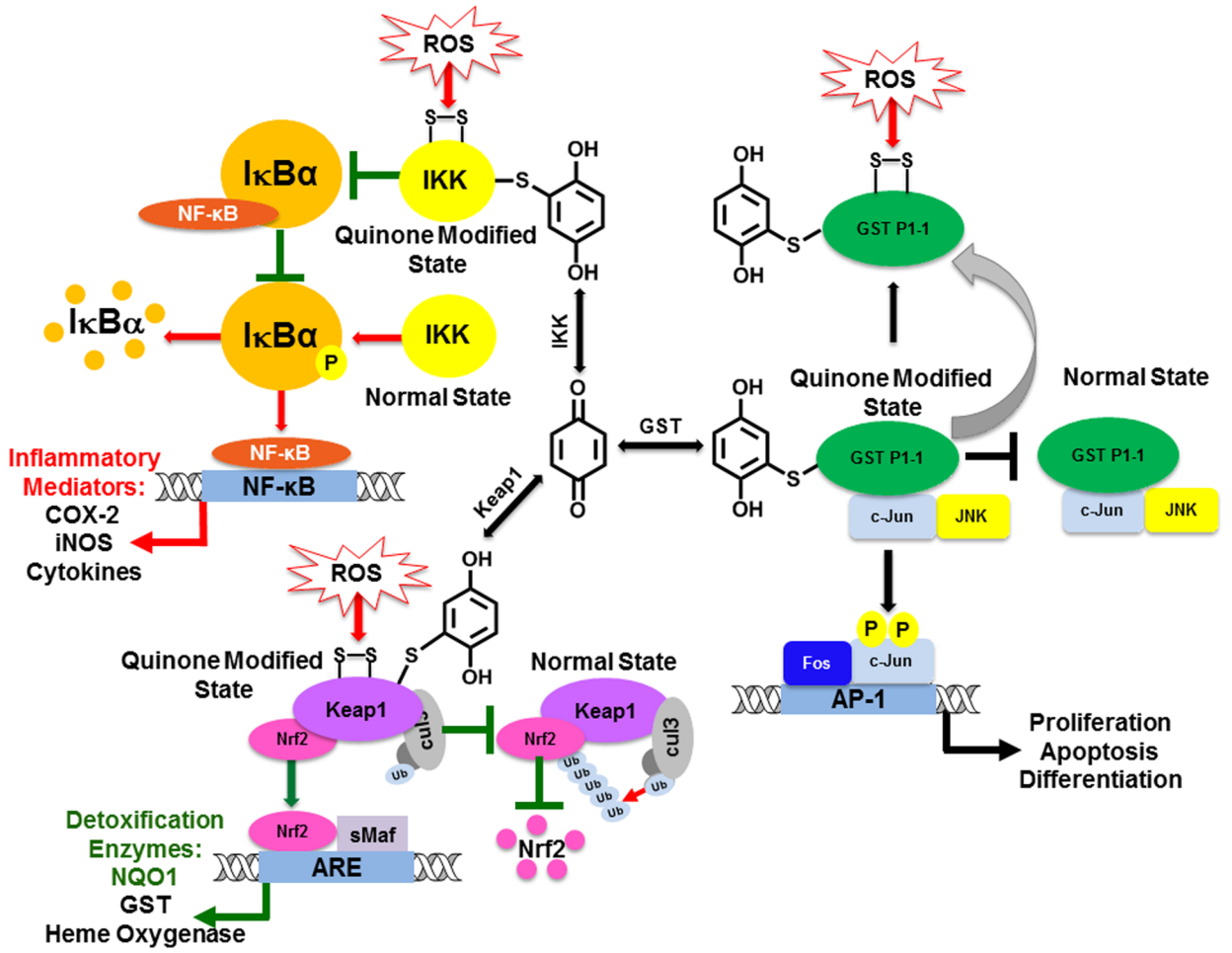



**Figure 6.** Quinone signaling targets.

Similarly, the antitumor agent mitomycin C (Table 1) undergoes bioreductive activation catalyzed by NQO1, but it is also a mechanism-based inhibitor of the enzyme both *in vitro* and *in vivo*.[190] Since NQO1 activity is much higher in cancer cells compared to that in normal cells, quinone-mediated inhibition of NQO1 could be an effective anticancer strategy.[191] For example, the natural product deoxynyboquinone is a potent NQO1 substrate and inhibitor through an NQO1-catalyzed redox cycling mechanism and deoxynyboquinone could have considerable potential as a chemotherapeutic agent (Table 2).[191]

*4.2.6. GST Inhibition (Figure 6).* GSTs are often covalently modified and/or oxidized by quinones likely in an attempt by GSTs to catalyze detoxification of quinones.[192−198] This usually results in the inhibition of GSTs, and the effect on GST P1−1 in particular could play a role in regulating the c-Jun N-terminal kinase (JNK) cell signaling pathway. JNK is a MAPK which effects cell growth, differentiation, stress response, and cellular transformation.[192,199−201] GST P1−1 forms an inhibitory complex with JNK−c-Jun that inhibits the phosphorylation of c-Jun by JNK. Quinone mediated oxidative or covalent modification of GST P1−1 leads to activation of JNK phosphorylation of c-Jun resulting in the induction of stress response, differentiation, and proliferation. Some specific examples include metabolites of the equine estrogens 4-hydroxyequilenin *o*-quinone and 4-hydroxyequilin *o*-quinone, which were found to be potent irreversible inhibitors of GST P1−1 (Table 3).[79,192,198] In contrast, the *o*-quinones of the endogenous catechol estrogen 4-hydroxyestrone *o*-quinone did not significantly inhibit GST P1−1 activity in human breast cancer cells perhaps due to differences in the reactivity of these estrogen quinones.[193] Plant polyphenols including quercetin, ellagic acid, juglone, luteolin, and caffeic acid have been reported as GST inhibitors likely through quinone formation.[196,202,203]

*4.2.7. Keap1/Nrf2/ARE Pathway (Figure 6).* *para* and *o*-quinones were among the first characterized small molecule inducers of the Keap1/Nrf2/ARE pathway.[204] This pathway controls gene expression of an elaborate network of protective proteins including heme oxygenase, NQO1, AKT, and GST that defend cells from electrophiles and free radicals.[205,206] Under normal conditions, the levels of these protective enzymes is low due to the repressor function of Keap1, which sets up Nrf2 for ubiquitination and proteosomal degradation (Figure 6). Modification of Keap1 by either alkylation or oxidation of crucial cysteine residues (CYS23, 151, 273, and 288) leads to the loss of the repressor function of Keap1, increased stability of Nrf2, translocation of Nrf2 to the nucleus, and activation of ARE-mediated target genes.[204,207,208] For example, BHA and its metabolite *t*-butylhydroquinone are classical activators of Nrf2 genes resulting in potent induction of heme oxygenase and NQO1 (Table 4).[209] It has been shown that catechol estrogen *o*-quinones (Table 3) can covalently modify Keap1 leading to Nrf2 activation and induction of heme


DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

oxygenase.[210] Similarly, catechols from green tea including EGCG and its epimer gallocatechin gallate and flavonoids such as quercetin form *o*-quinones can activate the Keap1/Nrf2/ARE pathway leading to cytoprotection (Table 2).[125,211−214] In addition, the quercetin quinone methide formed by isomerization of the quercetin *o*-quinone could also contribute to Keap1/Nrf2/ARE activation.[43] Interestingly, the level of induction could be enhanced by pretreatment with the GSH synthesis inhibitor buthionine sulfoximine and diminished in the presence of the electrophile scavenger *N*-acetylcysteine.[125,214] Other natural product catechols including carnosic acid and caffeic acid had analogous Keap1 modulatory effects through their corresponding *o*-quinone mediated mechanisms (Table 2).[129,215,216]

Activators of the Keap1-Nrf2 pathway are generally considered as chemopreventive agents since they enhance the levels of detoxification enzymes. However, it is important to realize that Nrf2 is very much involved in the initiation, promotion, and metastasis of cancer.[207,208,217−219] In fact, cancer cells hijack Nrf2 to support their malignant growth, and activators of Nrf2 could have unwanted effects including the development of resistance to chemotherapeutic agents. For example, *t*-butylhydroquinone upregulated Nrf2 and enhanced the resistance of cancer cells to cisplatin, doxorubicin, and etoposide in neuroblastoma cells.[217] Similarly, the electrophilic and prooxidant signals produced from PAH *o*-quinones can lead to the induction of ARE-regulated genes which could influence the initiation and promotion stages of PAH carcinogenesis (Table 4).[206,220] Quinone Nrf2 activators could be an effective strategy for cancer chemoprevention; however, the effect of quinone exposure on long-term Nrf2 levels are not known, and they may not be safe for cancer patients. Finally, based on the crucial role of Nrf2 in redox homeostasis in cells, it is likely that the dose−response curve for quinone Nrf2 activators is U-shaped and that cytoprotection/chemoresistance depends on the amount of quinone formed as well as its electrophilic/redox activity (Figure 7).[206]

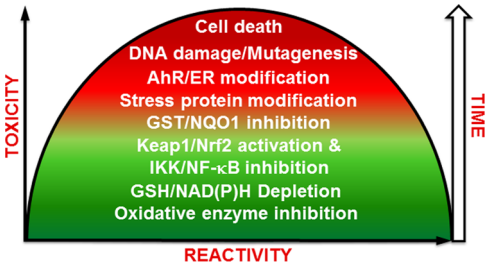



**Figure 7.** Inverse U-shaped modulation of toxicity as a function of dose and reactivity of quinone. Reactivity is defined as $d[P]/dt = k[\text{quinone}]$. The timeline refers to the likely order of events occurring within the cell.

*4.2.8. NF-κB Pathway (Figure 6).* NF-κB proteins are a family of transcription factors that play a major role in inflammation and carcinogenesis.[221,222] NF-κB activity is regulated by the IκB proteins, which are controlled through phosphorylation by upstream IκB kinases (IKK). These kinases are attractive targets for electrophilic quinones, which can covalently modify IKK leading to the inhibition of IKK and NF-κB-mediated gene transcription resulting in anti-inflammatory activities. For example, it has been shown that 1,2-naphthoquinone and *β*-lapachone (Table 1) inhibited phosphorylation of IκB by IKK and disrupted NF-κB signaling.[223,224] Similarly, the catechol metabolite of resveratrol, piceatannol (Table 3), is oxidized to an *o*-quinone, which targets Cys179 of IKK leading to inhibition of phorbol ester induced NF-κB activation.[225,226] The antitumor anthroquinone denbinobin also inhibits NF-κB through the modulation of IKK in human leukemic cells, and the inhibitory effects could be prevented by *N*-acetylcysteine.[227] The ansamycin antibiotic herbimycin A (Table 1) preferentially inhibits IKK likely through interaction with Cys59, resulting in the prevention of expression of NF-κB-dependent genes and anti-inflammatory activity.[228] In contrast, the carcinogenic metabolite of estradiol, 4-hydroxyestradiol (Table 3), is oxidized to an *o*-quinone which generates ROS causing the activation of IKK and NF-κB leading to the transformation of MCF-10A breast cells into a malignant phenotype.[229]

*4.2.9. Nuclear Receptor Modification (Figure 5).* It has been shown that PAH *o*-quinones and 1,2-naphthoquinone can covalently modify AhR leading to the activation of the AhR/XRE pathway and induction of P450 1A1.[230,231] Similar results have been reported for 1,4-benzoquinone, *t*-butyl-1,4-benzoquinone, and PCB quinones suggesting that some quinones could be bifunctional inducers of both phase I and phase II enzymes.[230−232] Interaction of these genotoxic quinones with AhR targets them into the nucleus where they can redox cycle generating ROS and cause oxidative damage to DNA in a manner similar to the Trojan horse estrogen receptor mechanism and 4-hydroxyequilenin (see below).[136] In support of this mechanism, the levels of DNA strand breaks and 8-oxo-dG levels were lower in AhR-deficient Hepa and AhR knockdown H358 cells treated with the PAH *o*-quinone, benzo[*a*]pyrene-7,8-dione.[233]

A similar Trojan horse DNA damage mechanism was observed with the estrogen receptor (ER) and the equine catechol estrogen, 4-OHEN.[136] The rate of 4-OHEN-induced oxidative DNA damage was significantly enhanced in ER*α* positive cells. The mechanism likely involves ER*α* acting as a Trojan horse, which is covalently modified by 4-OHEN *o*-quinone, concentrating the ER-quinone complex in the nucleus, accelerating the rate of ROS formation, and enhancing DNA oxidation.[79] The Trojan horse mechanism of estrogen carcinogenesis could explain why there is a positive association between 8-oxo-dG excretion levels and risk for ER positive breast cancer.[234]

**4.3. DNA.** Several quinones are known to cause a variety of DNA lesions, including depurinating bases resulting from N7-guanine or N3-adenine adduction, stable adducts at the exocyclic amino groups of guanine and adenine, as well as oxidized bases (Figure 5).[3] Depurinating N7-guanine and N3-adenine adducts have been reported from dopamine *o*-quinones as well as from 4-hydroxyestrone/estradiol *o*-quinones.[82,235,236] The estrogen depurinating DNA adducts have been detected in much higher levels in prostate and breast cancer patients compared to that in samples from disease-free individuals.[237−239] There is speculation and some *in vitro* studies suggesting that similar depurinating adducts could be formed by a number of quinones including those from diethylstilbestrol, bisphenol A, PAHs, and benzene.[69,240−242] In contrast to these unstable depurinating adducts which would be repaired by base excision repair enzymes, the equine estrogens 4-hydroxyequilin and 4-hydroxyequilenin *o*-quinones also form stable cyclic adducts similar to those reported for the PAH *o*-quinones.[3,243−251] Highly mutagenic cyclic DNA adducts have


DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

also been reported for *p*-benzoquinone which could contribute to the carcinogenic effects of benzene.[252−254] DNA adducts have been reported from quercetin, although these adducts likely result from covalent modification by the quinone methide tautomer of the quercetin *o*-quinone.[255] In addition, these quercetin DNA adducts were found to be transient and are unlikely to contribute to mutagenicity *in vivo*. Although quercetin has tested positive in the Ames test in the presence of S9 activation,[256] the transient nature of the DNA adducts likely explains why no genotoxic effects have been observed in animal models.[257]

Oxidative damage to DNA is also a common cytotoxic mechanism for quinones. Biomarkers for oxidative damage to DNA include the formation of 8-oxo-dG which is considered to be an important biomarker in carcinogenesis.[258,259] PAH *o*-quinones and PCB quinones have been reported to cause oxidative DNA damage.[109,260,261] PAH *o*-quinones generated oxidized pyrimidines and 8-oxo-dG through redox cycling resulting in G → T transversions which may contribute to lung cancer risk.[109,262,263] 8-oxo-dG formation has been correlated with p53 mutations observed in human lung cancer which strongly implicates the PAH *o*-quinones as ultimate carcinogens.[264,265]

The excessive production of ROS in breast cancer tissue has been linked to metastasis of tumors in women with breast cancer.[266] The source of ROS has been suggested to be the result of redox cycling between the estrogen *o*-quinones and their semiquinone radicals generating superoxide, hydrogen peroxide, and ultimately reactive hydroxyl radicals (Figure 3) which cause oxidative cleavage of the phosphate-sugar backbone as well as oxidation of the purine/pyrimidine residues of DNA.[267] In support of this mechanism, a variety of ROS mediated damage has been reported in hamsters treated with 17$\beta$-estradiol including DNA single-strand breaks, 8-oxo-dG formation, and chromosomal abnormalities.[267−271] The equine catechol estrogens, 4-hydroxyequilin, and 4-hydroxyequilenin are much more redox active since they autoxidize to *o*-quinones generating extensive oxidative DNA damage.[79,272,273] For example, 4-OHEN induced DNA single-strand breaks as well as the formation of 8-oxo-dA and 8-oxo-dG.[274−276] These and other data are evidence for a mechanism of estrogen-induced tumor initiation by redox cycling of estrogen quinones generating ROS which damage DNA. Finally, a variety of redox active halogenated quinones have been shown to induce epigenetic modulation of DNA demethylation affecting the expression of thousands of genes involved in a broad range of cellular processes.[277]

## 5. TOXICITY VERSUS CYTOPROTECTION. IMPORTANCE OF DOSE, TIME, AND REACTIVITY

It is now becoming generally accepted that quinones and compounds that form them likely have inverse U-shaped dose−response curves (Figure 7).[129,206,208,278,279] This is because they have opposing effects in biological systems which depending on the dose, cellular targets, and time of exposure could result in toxicity or cytoprotection. At low doses and for relatively stable/selective quinones, cytoprotection comes from the electrophilic counterattack resulting in the induction of detoxification enzymes through the Keap1/Nrf2 pathway. At higher doses and for less selective/more reactive quinones, GSH depletion, NAD(P)H oxidation, and protein degradation led to the endoplasmic reticulum stress response and altered signal transduction. DNA adducts especially from estrogen and PAH quinones which are not repaired efficiently over long-term exposure can initiate and promote the carcinogenic process. Very reactive quinones likely only target the enzymes that sythesize them (P450, COX-2, etc.) or react with water and have little toxic/cytoprotective effects.

In general, the higher the potency of the drug, the lower is the dose and the decreased risk of toxicity.[9] For example, paroxetine does form an *o*-quinone which can decrease GSH and inhibit P450 2D6; however, the dose of the drug is low, and *o*-quinone formation is unlikely to contribute to significant clinical problems.[168] Similarly, *o*-quinones are the major metabolites of endogenous estrogens and estrogens in estrogen replacement formulations. As with paroxetine, the dose is very low for these drugs especially for oral contraceptives, and *o*-quinone formation may not be an issue. However, in addition to the generally accepted hormonal carcinogenesis mechanism, long-term exposure to low doses of estrogen *o*-quinones in estrogen replacement formulations could contribute to enhanced risk of breast cancer especially in older women.

## 6. CONCLUSIONS AND FUTURE DIRECTIONS

The above are several examples of both structurally simple and complex aromatic compounds for which data strongly implicate quinone intermediates as mediators of toxicity and/or cytoprotection for a variety of drugs, natural products, environmental contaminants, and endogenous chemicals. These reactive metabolites could be considerably more important to the metabolism and biological properties of synthetic and naturally occurring aromatic compounds than is currently recognized. Quinones are formed both enzymatically and nonenzymatically, but the details of these processes and relationships to the structures of aromatic compounds are just beginning to emerge. Variations in the contributions of electrophilicity/redox activity modulate quinone reactivity over a wide range, suggesting substantial differences in the biological targets and intracellular effects of quinones. It is clear that covalent modification of both proteins and DNA competes with detoxification mechanisms such as reaction with GSH and that quinones are capable of inducing cytotoxic and cytoprotective responses. Future studies will seek to clarify relationships between reactivities and biological actions of these electrophiles and to gain insight into the mechanisms involved in cellular damage/cytoprotection. These data obtained will assist in clarifying the complex biological properties of a number of aromatic drugs and natural products and provide new information on intracellular targets as a function of electrophile/redox reactivity, which may be applicable to other types of electrophilic intermediates. Developing a better understanding of factors affecting phase II conjugation and rapid elimination of the parent aromatic compounds versus formation of quinones, their reactivities, and biological targets will allow advances in the drug discovery process to either enhance or prevent this pathway *in vivo*. Given the high cost of drug withdrawal especially for idiosyncratic drug toxicity, it is important to screen for potential quinone formation early in the drug discovery process.

## AUTHOR INFORMATION

### Corresponding Author

*Phone: 312-996-5280. Fax: 312-996-7107. E-mail: Judy.Bolton@UIC.edu.



DOI: 10.1021/acs.chemrestox.6b00256
*Chem. Res. Toxicol.* 2017, 30, 13−37

### Funding

This work was supported in part by the Office of Dietary Supplements (ODS) and National Center for Complementary and Integrated Health (NCCIH) through the NIH grant P50 AT000155 and T32 AT007533.

### Notes

The authors declare no competing financial interest.

### Biographies

**Judy L. Bolton, Ph.D.** I am currently a full professor and Head of the Department of Medicinal Chemistry and Pharmacognosy at the University of Illinois at Chicago. I am an associate editor for *Chemical Research in Toxicology*, and I have served as chair of the Cancer Etiology Study Section, NIH. My research is focused on bioactivation of estrogens and antiestrogens and mechanisms of botanical dietary supplements. I currently have over 150 publications and have already mentored 22 Ph.D. students, 8 masters students, and 27 postdoctoral fellows. Finally, I was recognized with Fellow of the American Chemical Society, 2011.

**Tareisha L. Dunlap, Ph.D.** I am currently a senior research specialist in the Department of Medicinal Chemistry and Pharmacognosy at the University of Illinois at Chicago. I am a former American Chemical Society scholar, and I more recently received a NIH National Center for Complementary and Alternative Medicine Research Training Fellowship (2013−2015). My research is focused on studying the effects of botanical dietary supplements on cross-talk between biomolecules in the inflammatory and estrogen chemical carcinogenesis pathways. I have several manuscripts (9 total) on cancer prevention, both published and in preparation.

## ■ ACKNOWLEDGMENTS

We thank Birgit Dietz and Atieh Hajirahimkhan for helpful discussions.

## ■ ABBREVIATIONS

AKR, aldo-keto reductase; ARE, antioxidant response element; BHA, *t*-butylhydroxyanisole; COX-2, cyclooxygenase-2; dA, 2′-deoxyadenosine; dG, 2′-deoxyguanosine; DT, diaphorase; ER, estrogen receptor; GST, glutathione *S*-transferase; γ-GT, γ-glutamyl transpeptidase; 5-HT, 5-hydroxy-tryptamine; HT, hormone therapy; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; KEAP1, kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; MDA, 3,4-(+)-methylenedioxyamphetamine; MDMA, 3,4-(+)-methylenedioxymethamphetamine; α-MeDA, α-methyldopamine; NF-κB, nuclear factor kappa B; Nrf2, NF-E2-related factor 2; NQO1, NAD(P)H:quinone oxidoreductase; 2-OHE, 2-hydroxyestrone; 4-OHE, 4-hydroxyestrone; 4-OHEN, 4-hydroxyequilenin; 8-oxo-dA, 8-oxodeoxyadenosine; 8-oxo-dG, 8-oxodeoxyguanosine; P450, cytochrome P450; PAHs, polycyclic aromatic hydrocarbons; PDIs, protein disulfide isomerases; ROS, reactive oxygen species; XRE, xenobiotic response element

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DOI: 10.1021/acs.chemrestox.6b00256
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DOI: 10.1021/acs.chemrestox.6b00256
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