Formation and biological targets of botanical $\sigma$-quinones

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Abstract

The formation of $\sigma$-quinones from direct 2-electron oxidation of catechols and/or two successive one electron oxidations could explain the cytotoxic/genotoxic and/or chemopreventive effects of several phenolic botanical extracts. For example, poison ivy contains urushiol, an oily mixture, which is oxidized to various $\sigma$-quinones likely resulting in skin toxicity through oxidative stress and alkylation mechanisms resulting in immune responses. Green tea contains catechins which are directly oxidized to $\sigma$-quinones by various oxidative enzymes. Alternatively, phenolic botanicals could be $\sigma$-hydroxylated by P450 to form catechols in vivo which are oxidized to $\sigma$-quinones. Examples include, resveratrol which is oxidized to piceatannol and further oxidized to the $\sigma$-quinone. Finally, botanical $\sigma$-quinones can be formed by $O$-dealkylation of $O$-alkoxy groups or methylenedioxy rings resulting in catechols which are further oxidized to $\sigma$-quinones. Examples include safrole, eugenol, podophyllotoxin and etoposide, as well as methysticin. Once formed these $\sigma$-quinones have a variety of biological targets in vivo resulting in various biological effects ranging from chemoprevention - > no effect - > toxicity. This U-shaped biological effect curve has been described for a number of reactive intermediates including $\sigma$-quinones. The current review summarizes the latest data on the formation and biological targets of botanical $\sigma$-quinones.

Keywords

Quinones; P450; Bioactivation; Botanicals; Chemoprevention; Carcinogen

1. Introduction

$\sigma$-Quinones are reactive metabolites of a variety of catechol natural products that could be responsible for the cytotoxic/genotoxic and chemopreventive effects of the parent catechols (Bolton, 2002; Dietz et al., 2016). They are electrophilic species that are often not detected, since they rapidly react with a variety of nucleophiles via non-enzymatic Michael addition (Fig. 1). $\sigma$-Quinone formation can be inferred by trapping them with reactive thiol nucleophiles, such as GSH.

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Conflicts of interest

The authors report no conflict of interest.
There are three major pathways by which these intermediates are formed in vivo: direct two electron enzymatic oxidation or two successive one electron chemical oxidations of the parent catechol (Fig. 1), aromatic hydroxylation followed by catechol oxidation (Fig. 2), and O-dealkylation and oxidation of the resulting catechol (Fig. 3). The successive removal of two electrons (or alternatively, an electron and a hydrogen atom) from catechols is usually catalyzed by cytochromes P450 (P450) or other oxidative enzymes, such as peroxidases (Bolton and Dunlap, 2017). Chemical autoxidation can occur generating semiquinone radical and ultimately the quinone. Reactive oxygen species (ROS) are formed during this reaction. Alternatively, phenols can be first hydroxylated at the o-position forming catechols catalyzed by P450 followed by oxidation to o-quinones as described above (Fig. 2). Finally, o-methoxyphenols and methylenedioxy compounds can undergo O-dealkylation reactions catalyzed by P450 resulting in a catechol that is subsequently oxidized to the o-quinone (Fig. 3).

Once formed o-quinones have a variety of biological targets (Fig. 4) (Aggarwal and Shishodia, 2006; Bolton and Dunlap, 2017; Pierce et al., 2016). Initial reaction with GSH the major non-protein thiol leads to GSH depletion either through direct alkylation and/or through oxidation generating GSSG (Fig. 4) (Ishii et al., 2009). Once GSH is depleted reaction with cysteine residues in proteins such as heat shock protein (HSP), protein disulfide isomerase (PDI), and binding immunoglobin protein (BiP) occurs (Liu and Sok, 2003). Alkylation/oxidation of cysteine residues on key proteins can lead to o-quinone signaling. For example, a major protein target of o-quinones is Keap1 leading to induction of detoxification enzymes including NAD(P)H-quinone oxidoreductase 1 (NQO1), glutathione-S-transferase (GST), and heme oxygenase-1 (HO-1) (Pierce et al., 2016). Alkylation/oxidation of IĸB kinase (IKK) results in modulation of NF-κB and inhibition of inflammatory pathways (Bolton and Dunlap, 2017). Finally, some o-quinones form DNA adducts and oxidized DNA bases which could lead to genotoxic effects (Bolton and Dunlap, 2017).

The focus of this mini-review is on botanicals and their bioactive compounds which generate reactive o-quinones either directly or after enzyme catalyzed bioactivation mechanisms. Several examples of natural products whose biological effects could be attributed to o-quinone formation are given. The resulting biological targets of o-quinones are predicted (Fig. 4) (Aggarwal and Shishodia, 2006).

2. Two electron oxidation of catechols

Catechols are very readily oxidized to o-quinones catalyzed by virtually any oxidative enzyme, metal ion, or in some cases molecular oxygen. A semi-quinone radical is initially formed which is readily converted to the o-quinone. This process is characterized by random oxidative damage generating ROS and causing oxidative stress within cells. However, depending on the prooxidant/antioxidant balance within cells, the catechols can quench ROS protecting cells from oxidative stress.
2.1. Urushiol (poison ivy, Toxicodendron radicans)

Urushiol, an oily mixture of catechols with an alkyl side chain, are present in poison ivy and poison oak (Fig. 1a). Brushing up against these plants results in skin toxicity leading to an itchy rash (Hershko et al., 2005). It is likely that oxidation of urushiols to \( \sigma \)-quinones followed by depletion of cellular GSH in skin cells and reaction with cysteine residues on proteins leads to skin toxicity (Dunn et al., 1982; Liberato et al., 1981). The allergic contact dermatitis induced by urushiols is known to be mediated by T lymphocytes that recognize urushiol bound to proteins (Dunn et al., 1982). Urushiol \( \sigma \)-quinones are likely also responsible for the DNA fragmentation observed in ovarian cancer cells treated with urushiol leading to induction of apoptosis (Choi et al., 2001).

2.2. Quercetin (ubiquitous)

Quercetin occurs in a variety of brightly colored plants including capers, onions, cranberries, and blueberries (Fig. 1b) (Rietjens et al., 2005). It has been demonstrated in several bacterial and mammalian mutagenicity experiments that quercetin has mutagenic properties that could be related to quinoid formation (Brown, 1980; MacGregor and Jurd, 1978). Quercetin is initially oxidized to an \( \sigma \)-quinone that rapidly isomerizes to di-quinone methides which could also be called extended quinones (Boersma et al., 2000; Rietjens et al., 2005). These di-quinone methides can be trapped with GSH, although the GSH conjugates are unstable and equilibrate over time producing an isomeric mixture of both quinone and quinone methide GSH conjugates. Protein and DNA adducts have also been observed in Caco-2 and HepG2 cells exposed to \(^{14}\)C-labelled quercetin although these adducts were also unstable (Walle et al., 2003). The transient nature of the quercetin quinoid adducts may partially explain that extrapolating quercetin genotoxicity in vitro to carcinogenicity in vivo is problematic (van der Woude et al., 2005). It has also been shown that quercetin has anti-inflammatory, anti-proliferative, and anti-atherosclerotic effects in human in vivo and in vitro models (Kleemann et al., 2011). For example, quercetin and/or its quinoids inhibit the IKK/NF-\( \kappa \)B signaling pathway leading to decreased inflammation and enhanced apoptosis in colon cancer cells (Peng et al., 2017; Zhang et al., 2015). Quercetin quinoids likely are responsible for the reduced levels of Keap1 protein, which increases Nrf2 and Nrf2 dependent antioxidant response element (ARE) activity leading to induction of several detoxification enzymes (Tanigawa et al., 2007). Finally, it has been shown that the prooxidant effect of flavonoids such as quercetin leads to ARE induction, which was inversely dependent on GSH concentration (Lee-Hilz et al., 2006).

2.3. Catechin (green tea, Camellia sinensis)

Extracts of green tea are reported to have anti-cancer, anti-atherosclerotic, anti-diabetic, anti-bacterial, anti-viral, and anti-obesity effects (Cabrera et al., 2006; Poddar et al., 2011; Singh et al., 2011; Suzuki et al., 2012). Most if not all of the beneficial health effects of green tea are probably due to catechins such as catechol (—)epigallocatechin gallate (EGCG) (Singh et al., 2011) (Fig. 1c). They are likely responsible for the antioxidant, anti-inflammatory, and chemopreventive properties of green tea. Catechins can be oxidized by tyrosinase, peroxidase, and P450 to an \( \sigma \)-quinone which forms a variety of conjugates with GSH (Moridani et al., 2001). It has been shown that EGCG covalently modifies proteins...
through initial autoxidation to the o-quinone and reaction with cysteine residues (Ishii et al., 2008). These thiol protein adducts especially on Keap1 could influence Keap1-Nrf2 signaling and stimulate detoxification pathways through induction of HO-1, NQO1, and GST (Aggarwal and Shishodia, 2006; Sriram et al., 2009; Wang et al., 2015). Due to its ability to scavenge ROS, antioxidative activities have also been described for ellagic acid (Fig. 1c) (Rios et al., 2018). During this process ellagic acid is oxidized to the o-quinone. Similar to EGCG, other cytoprotective activities including anti-inflammatory properties have been depicted for ellagic acid.

2.4. **Procyanidin (cranberry, Vaccinium macrocarpon)**

Procyanidins are bioactive compounds present in cranberry (Fig. 1d). They are likely responsible for the potent antioxidant, anti-inflammatory, and chemopreventive properties of cranberry (Aggarwal and Shishodia, 2006; Neto, 2007a,b). It has been shown that phenolic fractions of cranberry prevent oxidative stress, inflammation, and mitochondrial dysfunction in the intestine (Denis et al., 2015). The targets of procyanidins are likely NF-κB deactivation and Nrf2 up-regulation.

2.5. **Rosmarinic acid and carnosol (rosemary, Rosmarinus officinalis)**

Rosmarinic acid, carnosic acid, and carnosol are major bioactive compounds found in rosemary (Fig. 1e). They have a variety of biological effects including antioxidant, anti-inflammatory, and chemopreventive properties (Gao et al., 2005; Munoz-Munoz et al., 2013). Rosmarinic acid is oxidized by two electrons to give the rosmarinic acid o-quinone which reacts with a variety of cellular proteins mainly at cysteine residues (Tang et al., 2016). For example, tumor necrosis factor α (TNFα)-induced NF-κB activation was suppressed by rosmarinic acid through inhibition of IKK activity (Lee et al., 2006). Carnosol suppressed inducible nitric oxide synthase by down-regulating NF-κB in macrophages (Lo et al., 2002). The mechanism likely involves carnosol o-quinone mediated covalent modification of IKK leading to down regulation of IKK activity preventing NF-κB activation (Fig. 4). Carnosol was also reported to be a potent inducer of cytoprotective enzymes likely through carnosol o-quinone mediated modulation of the Keap1-Nrf2 pathway (Ostreicher et al., 2017; Wu et al., 2014). Similar cytoprotective properties have been reported for carnosic acid, which include inhibition of inflammatory responses and induction of detoxification pathways (Yanagitai et al., 2012). These activities were confirmed in an in vivo model (Kocak et al., 2016).

2.6. **γ-Mangostin (mangosteen, Garcinia mangostana)**

γ-Mangostin is a bioactive compound present in mangosteen that could contribute to the numerous reported beneficial biological effects of mangosteen including antioxidant, anti-inflammatory, anticancer, and chemopreventive properties (Fig. 1f) (Chang and Yang, 2012; Chin and Kinghorn, 2008; Obolskiy et al., 2009). As a catechol it readily undergoes two electron oxidation catalyzed by numerous oxidative enzymes as well as by ROS. γ-Mangostin has been shown to inhibit IKK activity and decrease cyclooxygenase-2 (COX-2) gene expression likely through γ-mangostin o-quinone modification of IKK (Nakatani et al., 2004). Several other catechols are present in mangosteen which likely have similar biological effects (Obolskiy et al., 2009). In addition, mangosteen contains a variety of
3. **O-Hydroxylation of phenols followed by two electron oxidation**

This pathway tends to be more specific since catechol formation must occur catalyzed by P450s in the endoplasmic reticulum (Fig. 2). The resulting catechols will act as pro- and/or antioxidants depending on the redox state of the cell. Given they are in the endoplasmic reticulum they will likely be readily oxidized to o-quinones directly catalyzed by P450 without generating ROS. More stable quinones can leave the endoplasmic reticulum and react with a variety of biological targets (Fig. 4).

### 3.1. Genistein (red clover, Trifolium pratense; soy, Glycine max)

Genistein which is present in red clover and soy is a potent bioactive isoflavone which is known for its preferential estrogen receptor β estrogenic effects (Hajirahimkhani et al., 2013). Genistein can also be oxidized by cytochrome P450 1A2 producing the catechol orobol which is further oxidized to an o-quinone (Fig. 2a) (Bolton and Dunlap, 2017; Breinholt et al., 2003; Lee et al., 2016; Roberts-Kirchhoff et al., 1999; Zhang et al., 2009). Studies show that orobol induced oxidative damage to DNA through metal catalyzed Fenton chemistry, whereas genistein had no effect (Murata et al., 2004). These data suggest that genistein could be carcinogenic via oxidative stress and formation of ROS generated upon autoxiation of orobol to orobol o-quinone. However, such a mode of action would have a threshold and not present a cancer risk at low intake when antioxidant protection is not overwhelmed.

### 3.2. Resveratrol (grapes, red wine, Vitis vinifera)

Resveratrol is present in the skin of red grapes and in red wine (Bhat et al., 2001). It is a potent antioxidant, anti-inflammatory, and inducer of detoxification enzymes including NQO1 (Brisdelli et al., 2009; de la Lastra and Villegas, 2005; Singh et al., 2014). Resveratrol can be hydroxylated by P450 resulting in the catechol piceatannol which is further oxidized to an o-quinone (Fig. 2b) (Piotrowska et al., 2012; Piver et al., 2004; Potter et al., 2002). It has been shown that phorbol ester-induced NF-κB activation and COX-2 expression can be inhibited by piceatannol both *in vitro* and *in vivo* (Liu et al., 2014; Son et al., 2010). It appears that alkylation of cysteine 179 of IKKβ is responsible for the inhibitory activity. Similarly, piceatannol prevents lipopolysaccharide induced nitric oxide production and NF-κB activation by alkylation of IKK (Fig. 4) (Islam et al., 2004). Piceatannol also targets the Keap1-Nrf2 pathway (Fig. 4). For example, it has been shown that piceatannol induces HO-1 expression in human mammary epithelial cells through the activation of the Keap1-Nrf2-ARE-driven signaling pathway (Lee et al., 2010). Piceatannol also blocks c-Jun N-terminal kinase (JNK) activation and protects cells against hydrogen peroxide and peroxynitrite-induced apoptosis (Kim et al., 2008). Taken together these data suggest that a number of biological targets are available to piceatannol o-quinone which may explain some of the numerous biological effects of resveratrol.
4. **O-Dealkylation followed by two electron oxidation**

Because the catechol is masked as an alkyl ether, catechol formation is targeted to the endoplasmic reticulum where P450 catalyzes O-dealkylation. The catechol can act as a pro- and/or antioxidant depending on the redox state of the cell. As described in 3, it is likely that the quinone is formed by direct 2-electron oxidation catalyzed by P450. Once it escapes the endoplasmic reticulum a variety of biological targets are available (Fig. 4).

4.1. **Safrole (sassafras, Sassafras albidum)**

Safrole is a major constituent of the oil of sassafras. It contains a methylenedioxy ring which can be oxidized by P450 forming the catechol hydroxychavicol (Fig. 3a) (Benedetti et al., 1977). Hydroxychavicol is a major component of the Indian betel leaf which is consumed by millions of people every year. Chewing betel quid has been implicated as a major risk factor for the development of oral squamous-cell carcinoma (IARC Working Group, 1985). Hydroxychavicol is readily oxidized by a variety of oxidative enzymes including cytochrome P450 and peroxidases, forming a relatively stable α-quinone \( t_{1/2} = 9 \text{ min, pH 7.4} \) that is readily trapped by thiol nucleophiles including GSH (Bolton et al., 1994). It has been shown that hydroxychavicol significantly inhibits growth and proliferation through ROS formation in human prostate cancer cells. ROS-induced DNA damage was also observed likely through redox cycling of the α-quinone (Gundala et al., 2014).

4.2. **Eugenol (cloves, Syzygium aromaticum)**

Cloves are commonly used as a spice. Eugenol is the major bioactive phenol in cloves (Fig. 3a). Eugenol undergoes direct two electron oxidation to an electrophilic quinone methide which is likely responsible for GSH depletion and protein alkylation (Bolton, 2014). Eugenol also contains an α-methoxy substituent which can be oxidized by P450 producing hydroxychavicol which is further oxidized to an α-quinone (Bertrand et al., 1997). Like safrole, the hydroxychavicol α-quinone formed from eugenol is probably responsible for oxidative damage to cells (Atsumi et al., 2005; Bezerra et al., 2017). As far as signaling is concerned, it has been reported that eugenol inhibits cell proliferation by suppressing NF-κB through IKK modification (Manikandan et al., 2011). It is not clear if the quinone methide and/or the α-quinone are responsible for eugenol signaling.

4.3. **Methysticin (kava, Piper methysticum)**

Kava is consumed as a tea in Polynesia for anxiety and insomnia (Cote et al., 2004). In North America kava is marketed as a dietary supplement and there have been multiple case reports of kava toxicity including liver toxicity requiring liver transplantation (Sarris et al., 2011). It appears that the administration of a traditional kava extract (aqueous) versus kava dietary supplements that are often kava ethanol extracts may explain the different biological effects between the kava preparations (Cote et al., 2004). Kava contains lactones such as methysticin which contains a methylenedioxy ring that can be oxidized to a catechol and quinone similar to safrole (Fig. 3b) (Chen et al., 2011; Johnson et al., 2001, 2003). Formation of the kava quinones leads to GSH depletion and toxicity to hepatocytes (Whitton et al., 2003). Methysticin has also been shown to be a mechanism based inhibitor of numerous P450s likely through quinone formation (Mathews et al., 2002, 2004).
2005). Other potential biological targets of kava quinones include inhibition of NF-κB through IKK modification (Folmer et al., 2006). Interestingly, a comparison of a traditional kava preparation with commercial kava extracts using ethanol, acetone, or methanol as a solvent demonstrated a much higher concentration of kavalactones including methysticin in the commercial preparations (Cote et al., 2004). The commercial extracts also lead to higher inhibition of P450 enzymes indicating an enhanced potential of protein alkylation.

4.4. Curcumin (turmeric, Curcuma longa)

Curcumin is the major bioactive compound in the spice turmeric which has been used as an anti-inflammatory remedy in Ayurvedic medicine for centuries. O-Demethylation of the methoxy substituent gives a catechol which is readily oxidized to an o-quinone (Fig. 3c). These oxidized metabolites of curcumin covalently modify IKK leading to inhibition of NF-κB and anti-inflammatory activity (Edwards et al., 2017). Curcumin also modifies Keap1 which leads to activation of the Keap1-Nrf2-ARE pathway causing the increased synthesis of detoxification enzymes such as GST, NQO1, and HO-1 (Balogun et al., 2003; Satoh et al., 2013).

4.5. Capsaicin (chili peppers, Capsicum annuum)

Capsaicin is the spicy component of chili peppers. It undergoes a variety of oxidative reactions including direct two electron oxidation giving a quinone methide. O-Dealkylation of the O-methoxy substituent gives the catechol which is readily oxidized to an o-quinone (Fig. 3d) (Reilly et al., 2013). The catechol and the o-quinone could contribute to a variety of biological effects of chili peppers including antioxidant, chemopreventive, anti-inflammatory properties, as well as DNA damaging effects (Reyes-Escogido Mde et al., 2011). For example, it has been shown that capsaicin induces HO-1 in HepG2 cells through activation of the Keap1-Nrf2 pathway (Joung et al., 2007). Capsaicin has been shown to induce oxidative damage to DNA likely through redox cycling of the o-quinone (Oikawa et al., 2006). It is possible that capsaicin-mediated DNA damage contributes to potential carcinogenic properties. Epidemiological studies have shown a correlation between red chili pepper consumption and gastric, gallbladder, liver, and pancreatic cancers (Lee et al., 1995; Lopez-Carrillo et al., 2003; Pandey and Shukla, 2002; Serra et al., 2002).

4.6. Podophyllotoxin and etoposide (mayapple, Podophyllum peltatum)

Podophyllotoxin (4’-demethylepipodophyllotoxin) is a potent toxin isolated from the mayapple tree (Montecucco et al., 2015; Sinkule, 1984) (Fig. 3e). As podophyllotoxin is too toxic for internal clinical applications, etoposide, a semisynthetic derivative of podophyllotoxin has been developed. Etoposide has been successfully used as a chemotherapeutic agent against various malignancies (Sinkule, 1984). A major metabolite of etoposide involves O-demethylation catalyzed by P450 giving the catechol which is readily oxidized to an o-quinone (Fig. 3e) (Gibson et al., 2016; Jacob et al., 2013; Mans et al., 1992; Smith et al., 2014; van Maanen et al., 1988). The o-quinone of etoposide causes depletion of GSH and oxidative stress within cancer cells inducing apoptosis (Mans et al., 1992; Usami et al., 1998). Similar reactions occur in normal cells which contributes to side effects. The specific target of the etoposide o-quinone is topoisomerase and the etoposide o-quinone is considered a classical topoisomerase II poison (Jacob et al., 2013; Smith et al., 2014). Other
biological targets of etoposide o-quinone include stress proteins such as BiP (Wang et al., 2016), GST P1-1 and the JNK signaling pathway (Bernardini et al., 2002), and IKK and the NF-κB signaling pathway (Choi et al., 2006) (Fig. 4).

5. Conclusions and future prospects

These are several examples of both structurally-simple and complex catechols for which data strongly implicate o-quinone intermediates as mediators of toxicity, carcinogenesis, and/or chemoprevention. These electrophiles/redox active compounds could be considerably more important to the metabolism and biological properties of the parent naturally occurring catechols or catechol metabolites than is currently recognized. o-Quinones are formed both enzymatically and non-enzymatically, but the details of these processes and relationships to the structures of phenolic compounds are just beginning to emerge. It is clear that binding to both proteins and DNA competes with detoxification, and that o-quinones are capable of inducing cytotoxic and possibly genotoxic responses (Fig. 4), although it is not clear if genotoxic data from in vitro studies translates to in vivo effects. Alternatively, quinone formation could represent a chemopreventive mechanism for example through induction of detoxification enzymes. The various biological activities of these reactive o-quinones can be seen as a function of their reactivity, concentration, and time of exposure (table of content graphic). Based on these functions different biological targets are anticipated. o-Quinones are reactive intermediates with modest reaction rates that can induce detoxification and chemopreventive responses, for example Nrf2 activation and NF-κB reduction, at low concentrations (Dietz and Bolton, 2011) (Fig. 4). However, higher concentrations can also lead to toxic responses, as in the case of kavalactones. In rare cases, when the quinones can reach the DNA, genotoxic or mutagenic effects might occur. Future studies will seek to clarify relationships between reactivities and biological actions of these electrophiles/redox active compounds and to gain insight into the mechanisms involved in cell damage. The data obtained will assist in clarifying the complex biological properties of phenolic compounds and provide new information on intracellular targets as a function of electrophile/redox reactivity which may be applicable to other types of reactive intermediates. Future in vivo studies will also clarify which of the observed in vitro data can translate to meaningful in vivo and clinical results.

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Abbreviations:

| Abbreviation | Description                                |
|--------------|--------------------------------------------|
| ARE          | antioxidant response element                |
| BiP          | binding immunoglobin protein                |
| COX-2        | cyclooxygenase-2                            |
| JNK          | c-Jun N-terminal kinase                     |
| EGCG         | (—)-epigallocatechin gallate                |

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GST glutathione-S-transferase
GSH glutathione
HSP heat shock protein
HO-1 heme oxygenase-1
IKK IκB kinase
NQO1 NAD(P)H-quinone oxidoreductase 1
NF-κB nuclear factor kappa-light-chain-enhancer of activated B cells
PDI protein disulfide isomerase
ROS reactive oxygen species
TNFα tumor necrosis factor α

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Fig. 1.
Formation of o-quinones through two and one electron oxidation mechanisms. Reaction with GSH and generation of ROS.
Fig. 2.

O-Hydroxylation of phenols and oxidation to o-quinone.
Fig. 3.
O-Dealkylation of $\alpha$-alkoxyphenols and methylenedioxy rings followed by $\alpha$-quinone formation.
Biological targets of o-quinones.

The various targets of o-quinones lead to biological activities, including detoxification, chemoprevention, and toxicity. o-Quinones can deplete GSH causing oxidative stress or directly alkylate proteins (PSH) to elicit chemopreventive activity (e.g. Keap1 and IKK) or stress response (e.g. HSP, PDI, BiP, GST-P1). The toxic effects from o-quinones arise from DNA adducts/oxidation which leads to mutagenesis and P450 oxidative enzyme inhibition or from alkylation of key proteins that can lead to toxicity, such as liver toxicity in the case of kava lactones.