

Effect of Natural Compounds on Catechol Estrogen-Induced Carcinogenesis

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The hydroxylation of estradiol results in the formation of catechol estrogens such as 2-hydroxyestradiol (2-OHE₂) and 4-hydroxyestradiol (4-OHE₂). These catechol estrogens are further oxidized to quinone metabolites by peroxidases or cytochrome P450 (CYP450) enzymes. Catechol estrogens contribute to hormone-induced carcinogenesis by generating DNA adducts or reactive oxygen species (ROS). Interestingly, many of the natural products found in living organisms have been reported to show protective effects against carcinogenesis induced by catechol estrogens. Although some compounds have been reported to increase the activity of catechol estrogens via oxidation to quinone metabolites, many natural products decreased the activity of catechol estrogens by inhibiting DNA adduct formation, ROS production, or oxidative cell damage. Here we focus specifically on the chemopreventive effects of these natural compounds against carcinogenesis induced by catechol estrogens.

Key Words: Catechol estrogen, 4-Hydroxyestradiol, Carcinogenesis, Natural compounds, Cancer prevention

INTRODUCTION

Excessive exposure to estrogen increases the risk of breast cancer and other types of hormone-related cancers. Catechol estrogens are active estrogen metabolites, formed by aromatic hydroxylation of primary estrogens at either the C-2 (2-hydroxyestradiol; 2-OHE₂) or C-4 position (4-hydroxyestradiol; 4-OHE₂); the 4-OHE₂ has been suggested as a more potent carcinogen than 2-OHE₂ (MacLusky et al., 1981; Zhu and Conney, 1998). The catechol estrogens are further oxidized to quinone metabolites such as catechol estrogen-2,3-quinone (CE-2,3-Q) and catechol estrogen-3,4-quinone (CE-3,4-Q) by peroxidases or cytochrome P450

(CYP450), which may lead to the formation of DNA adducts or the generation of reactive oxygen species (ROS) (Cavalieri et al., 1997; Cavalieri et al., 2006). In addition, the increased level of quinone metabolites has been associated with cancer cell growth as well as DNA mutation or transformation in normal epithelial cells (Lareef et al., 2005; Cavalieri et al., 2006).

Many natural products have been shown to exhibit protective effects against catechol estrogen-induced carcinogenesis by inhibiting the formation of DNA adducts or the production of ROS. Moreover, some of the natural substances have been reported to induce important enzymes involved in the detoxification or conjugation of catechol estrogens and their quinone metabolites. Although certain

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Table 1. Chemopreventive effects of natural compounds on catechol estrogen-induced carcinogenesis

Natural compounds	Experimental model	Effects	Ref
Chrysoeriol	Molecular docking study	↓human recombinant CYP1B1 activity	Takemura et al., 2010a
	MCF-7 cells	↓formation of 4-OHE ₂ from 17β-estradiol	Takemura et al., 2010b
Genistein	MCF-7 cells	↑expression of MnSOD	Borras et al., 2006
Isoflavone	A randomized soy isoflavone intake study (premenopausal women)	↓urinary excretion of 17β-estradiol, 4-OHE ₂ , 2-OHE ₂ and other metabolites	Xu et al., 1998
Lipoic acid/ Melatonin	LC/MS/MS	↓formation of depurinating estrogen-DNA adduct CE-3,4-Q	Zahid et al., 2007
Quercetin	MCF-10F cells	↓production of CYP1B1 and 4-OHE ₂ ↑production of CYP1A1 and 2-OHE ₂	Mense et al., 2008
	MCF-10A cells	↓formation of 2-OHE ₂ and 4-OHE ₂ from 17β-estradiol	Chen et al., 2004
Resveratrol	LC/MS/MS, MCF-10F cells	↓formation of depurinating estrogen-DNA adduct CE-3,4-Q	Zahid et al., 2007; Zahid et al., 2011
	MCF-10F cells	↑expression of NQO1 ↓formation of depurinating estrogen-DNA adducts from 4-OHE ₂ or CE-3,4-Q ↑formation of methoxy-catechol estrogens	Zahid et al., 2008
	MCF-10F cells	↓formation of depurinating estrogen-DNA adduct ↑Nrf2 activity	Lu et al., 2008
	MCF-10A cells	↓intracellular ROS formation ↓oxidative DNA damage	Chen et al., 2004
Sulforaphane	MCF-10A cells	↓4-OHE ₂ -induced ROS production ↓4-OHE ₂ -induced cell transformation	Park et al., 2012
	Female Sprague-Dawley rats	↑expressions of Nrf2 and UGT1A8 ↑elimination of catechol estrogens ↓DNA damage ↓pathological development of breast cancer	Zhou et al., 2018
	MCF-10A cells	↓formation of depurinating estrogen-DNA adducts	Yang et al., 2013
Tocopherol	MCF-10A cells	↑expression of DNA repair proteins, BRCA1 and PARP-1 ↑GSH/GSSG ratio	Lee et al., 2009

Abbreviations: CYP1B1; Cytochrome P450 1B1, 2-OHE₂; 2-hydroxyestradiol, 4-OHE₂; 4-hydroxyestradiol, CE-3,4-Q; estrogen-3,4-quinone, NQO1; NAD(P)H:quinone oxidoreductase 1, Nrf2; nuclear factor erythroid 2-related factor 2, ROS; reactive oxygen species, UGT1A8; UDP-glucuronosyltransferase 1A8, LC/MS/MS; liquid chromatography/tandem mass spectrometry, BRCA1; breast cancer susceptibility gene 1, PARP-1; poly (ADP-ribose) polymerase-1, GSH; glutathione, GSSG; glutathione disulfide

natural compounds have been shown to display carcinogenic effect against cancers by increasing the activity of estrogen, this review focuses specifically on the protective effect of natural products against carcinogenesis induced by catechol estrogens (Fig. 1, Table 1).

Effects of natural compounds on estrogen metabolizing enzymes

The effects of natural compounds on estrogen metabolism

have been reported in several studies. Some studies have described the harmful effects of certain natural compounds in women with breast cancer. Phytochemicals with a catechol structure such as quercetin, catechin, and (–)-epicatechin have been shown to reduce catechol-O-methyltransferase (COMT) activity in the cytosol of healthy mammary tissues, while other compounds without a catechol structure (genistein, chrysin, and flavone) showed no effect (van Duursen et al., 2004). Isoflavones, especially genistein and daizein,

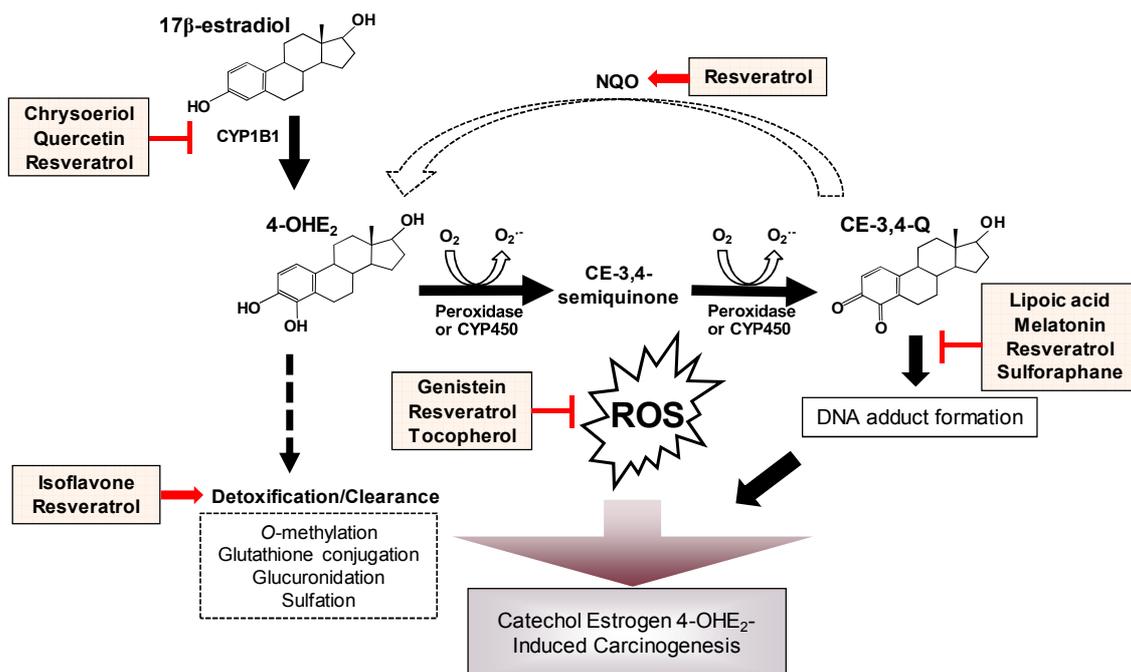


Fig. 1. Protective effects of natural compounds on catechol estrogen 4-OHE₂-induced carcinogenesis. 4-OHE₂ is metabolized by CYP1B1 from 17β-estradiol and it is further oxidized to the genotoxic CE-3,4-Q. During their redox cycling, ROS is overproduced. The natural compounds shown in the figure indicate that each compound inhibits or promotes certain stages of the catechol estrogen-induced carcinogenesis. 4-OHE₂: 4-hydroxyestradiol, CE: catechol estrogen, Q: quinone, CYP450: cytochrome P450, ROS: reactive oxygen species, NQO: NAD(P)H: quinone oxidoreductase.

significantly reduced the levels of both COMT mRNA and enzyme activity as well as the methylation of 4-OHE₂ in human mammary adenocarcinoma MCF-7 cells (Lehmann et al., 2008). In addition, genistein and daizein stimulated the formation of estrogen genotoxic metabolites and inhibited the detoxification of catechol estrogens in MCF-7 cells by suppressing the expression of COMT (Wagner et al., 2008).

On the other hand, studies have reported that natural compounds exert protective effects against estrogen-induced carcinogenesis. In a randomized soy isoflavone intake study, the urinary excretion of 17β-estradiol, 4-OHE₂, 2-OHE₂ and other metabolites was significantly reduced in both low and high isoflavone diets (Xu et al., 1998). Interestingly, certain natural products regulate estrogen metabolism by inhibiting the production of CYP1B1-mediated 4-OHE₂ and increasing the production of CYP1A1-mediated 2-OHE₂. Quercetin, a natural flavonoid found abundantly in fruits and vegetables, decreased the production of CYP1B1 and 4-OHE₂, while increasing the CYP1A1 metabolism and the production of

2-OHE₂ (Mense et al., 2008). Resveratrol (3,4',5-trihydroxy stilbene), a phytoalexin present in grapes, strongly reduced the formation of both 2-OHE₂ and 4-OHE₂ from 17β-estradiol (Chen et al., 2004). In addition, chrysoeriol, a natural methoxyflavonoid, selectively inhibited human recombinant CYP1B1 activity and prevented the formation of carcinogenic 4-OHE₂ from 17β-estradiol (Takemura et al., 2010a; Takemura et al., 2010b).

Effects of natural compounds on the formation of estrogen-DNA adducts

CE-3,4-Q and significantly smaller amounts of CE-2,3-Q form depurinating DNA adducts such as 4-OHE₂-N7-guanine, 4-OHE₂-N3-adenine, and 2-OHE₂-N3-adenine (Cavalieri et al., 2006). These DNA adducts result in apurinic sites, and the error-prone repair of the apurinic sites generates critical mutations triggering cancer (Gaikwad et al., 2007). The formation of catechol estrogen-derived quinones could be prevented with certain natural compounds, such as lipoic acid,

melatonin, and resveratrol. These natural products have been reported to inhibit the formation of depurinating estrogen-DNA adduct CE-3,4-Q (Zahid et al., 2007). Another study also reported that resveratrol effectively inhibited the formation of catechol estrogen-DNA adducts (Zahid et al., 2011). The levels of the depurinated adducts, 4-OHE₂-N7-guanine and 4-OHE₂-N3-adenine, were also reduced by sulforaphane, an isothiocyanate found in cruciferous vegetables (Yang et al., 2013).

Lowering the level of depurinating DNA adducts as well as reduction or detoxification of estrogen quinones may be critical to reduce the risk of cancer initiation (Zahid et al., 2008). The reduction of estrogen quinones is catalyzed by NAD(P)H:quinone oxidoreductase 1 or 2 (NQO1 or NQO2) (Gaikwad et al., 2007). Resveratrol acts as an inducer of NQO1. It induced the expression of NQO1, decreased the formation of depurinating estrogen-DNA adducts from 4-OHE₂ or CE-3,4-Q, and increased the formation of anti-proliferative methoxy-catechol estrogens (Zahid et al., 2008).

Effects of natural compounds on catechol estrogen-induced oxidative damage

The catechol estrogens, and their semiquinones or quinones, undergo further redox cycling resulting in the production of ROS. Excessive ROS production results in oxidative DNA damage or cell transformation, which increases the risk of cancer. Therefore, it is important to inhibit the catechol estrogen-derived ROS production. Genistein up-regulated the expression of antioxidant enzyme manganese-superoxide dismutase (MnSOD) (Borras et al., 2006) and resveratrol activated the nuclear factor erythroid 2-related factor 2 (Nrf2), a representative transcription factor of antioxidant enzymes, by inducing the nuclear translocation of Nrf2 (Lu et al., 2008). Resveratrol attenuated the intracellular ROS formation and oxidative DNA damage induced by catechol estrogens (Chen et al., 2004). It also efficiently inhibited 4-OHE₂-induced cell transformation as well as ROS production (Park et al., 2012). More recently, resveratrol has been reported to increase the expressions of Nrf2 and UDP-glucuronosyltransferase 1A8. This accelerated metabolic elimination of catechol estrogens, inhibited estrogen-induced DNA damage, and suppressed the pathological development of breast cancer *in vivo* (Zhou

et al., 2018).

Reduced glutathione (GSH) has been known to protect cells from oxidative damage. The GSH/oxidative glutathione (GSSH) ratio is tightly regulated under normal conditions; however, the ratio decreases under oxidative conditions (Pastore et al., 2003; Lee et al., 2009; Zitka et al., 2012). It has been reported that α - and γ -tocopherols, which are abundant in tree nuts, regulate the markers of oxidative stress and the expression of DNA repair elements. The human breast epithelial MCF-10A cells treated with 4-OHE₂ showed an increase in intracellular ROS formation and a decrease in the GSH/GSSG ratio. However, α -tocopherol treatment up-regulated the expression of DNA repair proteins and γ -tocopherol treatment increased the GSH/GSSG ratio by reducing the level of GSSG (Lee et al., 2009).

CONCLUSION

Catechol estrogens act as endogenous tumor initiators when their quinone metabolites react with DNA to form specific depurinating adducts (Cavalieri et al., 1997). They may also act as tumor promoters via ROS overproduction leading to changes in gene expression associated with the progression or promotion of tumor growth (Park et al., 2009; Parl et al., 2009; Fussell et al., 2011). Diverse natural products have been shown to exhibit anti-inflammatory, anti-proliferative, or anti-metastatic effects in many types of cells both *in vitro* and *in vivo* (Yuan et al., 2006; Jiang and Liu, 2011). In this review, we focused specifically on the impact of natural products on critical events of hormone-induced carcinogenesis following exposure to catechol estrogen.

Considering the safety issues associated with conventional anti-cancer drugs, natural compounds extracted from diets have been considered as an interesting alternative (Dias et al., 2012). Many studies suggest that certain natural products may act as potential chemopreventive agents against hormonal cancer initiated by catechol estrogens. Selected natural products have been shown to block most of the critical steps in estrogen-derived genotoxic pathways. They have been reported to inactivate catechol estrogens, inhibit the production of DNA adducts, or modify enzymes that inhibit the oxidative cell damage.

Although dietary agents have undergone extensive mechanistic and preclinical studies, no such compounds have been approved for routine cancer treatment. The large variation in COMT activity or CYP profile between breast tissue samples is a hindrance to prediction of the effects of individual exposure to natural compounds (Thompson and Ambrosone, 2000; Moon et al., 2006; Ji et al., 2008). Moreover, the general mechanisms of certain compounds are not established and even the safety of highly concentrated food supplements is unclear. Therefore, in order to prevent catechol estrogen-mediated carcinogenesis, it is necessary to investigate the precise mechanisms, determine the exact dosages, and obtain quantitative insights into the specific composition of natural substances.

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CONFLICT OF INTEREST

The authors have no conflict of interest regarding the publication of this article.

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