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Review

Food components and environmental chemicals of inhibiting human placental aromatase

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ABSTRACT

Human placental CYP19A1 catalyzes the estrogen synthesis from androgens. The enzyme is encoded by *CYP19A1* gene located in chromosome 15q21. This enzyme is a monooxygenase in the smooth endoplasmic reticulum. The various promoters of the *CYP19A1* gene determine its expression in different tissues and the distal promoter I.1 controls its expression in the placenta and retinoids can regulate the expression. Many food components and environmental chemicals inhibit CYP19A1 activity via different modes of action. These chemicals include gossypol, flavones, flavanones, chalconoids, resveratrol, and tobacco alkaloids derived from foods as well as phthalates, insecticides, fungicides, and biocides in the contaminated foods. The inhibition of placental CYP19A1 could impair pregnancy.

1. Introduction

Aromatase (officially called CYP19A1) is a member of the cytochrome P450 superfamily. It is a monooxygenase that catalyzes androgens into estrogens, thus it is also called as estrogen synthase. This enzyme is present in many tissues, including ovary, testis, placenta, brain, adipose tissue, blood vessels, skin, and bone and makes estrogens for many functions in various tissues (Sun et al., 1998). Placental syncytiotrophoblasts express CYP19A1. CYP19A1 requires an external fetal adrenal source of androgen, dehydroepiandrosterone (DHEA), which is converted into androstenedione under the catalysis of 3β-hydroxysteroid dehydrogenase 1 in the placenta and the latter is converted into estrogen by CYP19A1 (Fernandez Freire et al., 2005). Placental estrogen (mainly estradiol, E_2) stimulates placental growth and enhances the blood flow to provide the exchange of gases and nutrients required for the developing fetus (Xu et al., 2016b). Disrupting the E_2 synthesis in the placenta could cause adverse outcome of pregnancy. Many food components (polyphenols, flavones, flavanones, chalconoids, and tobacco alkaloids) as well as environmental chemicals in contaminated foods including phthalates and insecticides/fungicides/biocides can directly inhibit CYP19A1 activity. Here, we review the biochemistry, gene, regulation, structure, and inhibitors of human placental CYP19A1.

2. CYP19A1 biochemistry, regulation, and structure

2.1. CYP19A1 reaction

CYP19A1 catalyzes estrogen synthesis from androgens. In particular, CYP19A1 converts androstenedione into estrone or testosterone into E_2 (Fig. 1). The catalytic reaction contains three successive hydroxylations of the 19-methyl group of androgens, followed by elimination of the methyl group as formate and aromatization of the A-ring (Fig. 1).

To start the catalysis, substrate first binds CYP19A1 heme group, inducing a conformational change of CYP19A1 active site, thus displacing a water molecule from the heme iron (Meunier et al., 2004). The change of the heme iron state has been proven in another P450 enzyme, the bacterial P450cam (Poulos et al., 1987). Substrate binding also causes electron transfer from NADPH via cytochrome P450 reductase. Oxygen binds to the ferrous heme center to result in a dioxygen adduct. A second electron is transferred from cytochrome P450 reductase. The peroxo group formed is rapidly protonated twice, releasing one molecule of water and forming the highly reactive species (Rittle and Green, 2010). P450 hydroxylation has been studied in bacterial P450cam (Nagano and Poulos, 2005). The P450cam dioxygen complex contains the residue pair Thr252–Gly248 carbonyl and two catalytic water molecules, which are involved in the activation of ferrous dioxygen to the hydroxylating Fe(IV) = O species by providing two

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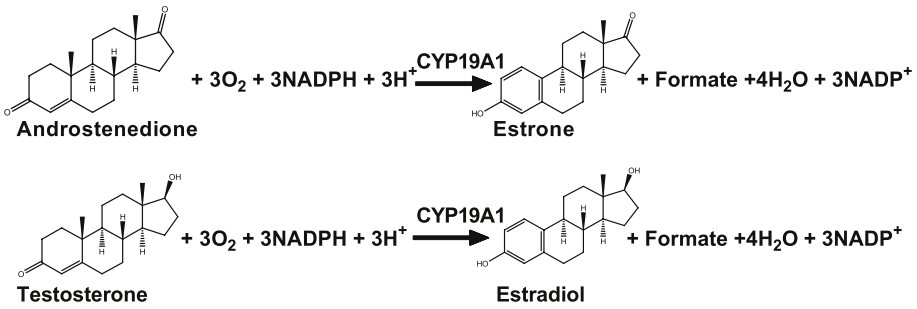

Fig. 1. CYP19A1 catalysis. Androgens (androstenedione or testosterone) are converted by CYP19A1 into estrogens (estrone or estradiol).

protons (Nagano and Poulos, 2005). The CYP19A1 has a similar mechanism (Ghosh et al., 2009).

2.2. CYP19A1 gene

Chen et al. (1986) and Evans et al. (1986) cloned partial human *CYP19A1* cDNA fragments. This cloned *CYP19A1* fragment is used as the probe and it is found that CYP19A1 is present in placentas and fat tissues (Evans et al., 1986). Harada et al. (Harada, 1988) cloned a full-length *CYP19A1* and found that it encodes a 503-amino-acid peptide (Chen et al., 1988). Corbin et al. then cloned the full-length human *CYP19A1* and expressed it in COS1 cells, which can catalyze androstenedione, testosterone, and 16α-hydroxyandrostenedione into their respective estrogens (Corbin et al., 1988). *CYP19A1* gene has 10 exons, and the exon 2 to exon 10 region translates the full-function protein (Toda et al., 1990). *CYP19A1* gene spans more than 123 kb of genomic DNA (Sebastian and Bulun, 2001). The 30-kb 3-prime region encodes *CYP19A1* and the 93-kb 5-prime flanking region is the regulatory unit (Sebastian and Bulun, 2001). *CYP19A1* gene has ten alternative untranslated first exons (Sebastian et al., 2002). The ovarian-specific promoter II, the adipose tissue-specific proximal promoter I.3, and bone-specific promoter I.6 are located within 1 kb of the translation start site (Sebastian and Bulun, 2001). Chen et al. mapped the CYP19A1 gene to chromosome 15q21.1 (Chen et al., 1988). Shozu et al. mapped *CGNL1*, *TMOD3*, and *CYP19A1* in an order from telomere to centromere in chromosome 15q21.1-q21.3 and *CYP19A1* is transcribed in the direction opposite to that of *TMOD3* and *CGNL1* genes (Shozu et al., 2003).

2.3. Regulation of CYP19A1

The tissue-specific expression of *CYP19A1* relies on the *CYP19A1* tissue-specific promoter activities (Simpson et al., 1997). The distal promoter I.1 determines its expression in placenta, which is regulated by retinoids (Sun et al., 1998). Promoter I.4 predominantly and promoter I.3 partially determine *CYP19A1* expression in breast adipose tissue. Promoter I.4 contains a glucocorticoid response element (GRE) that binds to glucocorticoids and an interferon-gamma activation site element via class I cytokines (Agarwal et al., 1997). *CYP19A1* is also expressed in the cells or tissues such as Leydig cells in males, which is regulated by DAX1 (Wang et al., 2001). Promoter I.7 determines its expression in some subcutaneous adipose tissues and breast cancer tissue and this region contains two GATA sites and GATA2 not GATA1 regulates its expression (Sebastian and Bulun, 2001). Promoter II determines its expression in human endometriotic stromal cells and prostaglandin E2 regulates its expression via a cAMP signaling pathway. C/EBP isoforms also regulate *CYP19A1* expression in endometriotic versus eutopic endometrial stromal cells. When −211/-197-bp cAMP-response element (CRE) and −317/-304-bp C/EBP binding sites are mutated, the both baseline and cAMP-induced promoter II activity disappears. C/EBPα up-regulates whereas C/EBPβ and C/EBPΔ inhibit *CYP19A1* promoter activity via binding to the −211/-197-bp CRE site (Yang et al., 2002). Prostaglandin E2 and cAMP signaling regulate coordinately the proximal promoters I.3/II (Imir et al., 2007). The cAMP-induced binding of CEBPβ to multiple motifs in the *CYP19A1* promoters I.3/II determines its expression in leiomyoma smooth muscle cells (Ishikawa et al., 2008). N-terminal 90-amino acid-deleted β-catenin causes its degradation significantly, thus enhancing follicle-stimulating hormone-induced *CYP19A1* expression via NR5A1, which functionally interacts with β-catenin and this action depends on cAMP signaling (Parakh et al., 2006).

2.4. CYP19A1 protein structure

Human CYP19A1 resides in the endoplasmic reticulum. Shimozawa et al. found that the N terminus of CYP19A1 is translocated across the endoplasmic reticulum membrane and it was glycosylated at the luminal side (Shimozawa et al., 1993). The hydrophobicity analysis of CYP19A1 sequence indicates lipid integration for amino acid residues 21–42 and 49–71 with glycosylation at Asn 12 residue in the N terminus at the luminal side (Shimozawa et al., 1993). Lala et al. purified human placental CYP19A1 protein (Lala et al., 2004) and Ghosh et al. crystalized the protein and analyzed 2.90-p resolution crystal structure of the CYP19A1-androstenedione complex (Ghosh et al., 2009). This structure exhibits the characteristic cytochrome P450 fold. Androstenedione binds with its β-face oriented towards the heme group and C19 4.0 Å from the Fe atom. Androstenedione 17-keto oxygen makes a hydrogen bond (2.8 Å) with Met 374 backbone amide and a weak contact (3.4 Å) with Arg 115 NH1. Androstenedione 3-keto oxygen is 2.6 eristic cytochrome P450 fold. Androstenedione binds with its β-face oriented towards the heme group and C19 4.0 Å from the Fe atom. Androstenedione 17-keto oxygen makes a hydrogen bo Ile 133 and Phe 134 from the B–C loop, Val370, Leu372 and Val373 from the K-helix–β loop, Val370, Leu372 and Val373 from the K-helixhrome P4–β loop, Val370, Leu372 and Val373 from the K-helixhrome P450 fold. Androstenedione binds with its β-face o.

3. Placental CYP19A1 and its function

3.1. Placental CYP19A1

Placental trophoblast and cytotrophoblast cells do not express CYP19A1. The syncytiotrophoblasts highly express CYP19A1 after the fusion of cytotrophoblast. CYP19A1 expression is controlled via promoter I.1 of *CYP19A1* gene. Adrenal gland of the fetus provides the source of androgen, DHEA, which is converted to estrone and further into E_2 in the placenta (Baldini et al., 1993).

3.2. Placental CYP19A1 function

The expression of CYP19A1 is essential for the functional differentiation of the syncytiotrophoblast cells. E_2 ensures high production of progesterone in the placenta to maintain pregnancy. Placental estrogens from CYP19A1 catalysis increase the expression of glucocorticoid-

metabolizing enzyme 11 led via promoter I.1 of drogen bo Ile1β-hydroxysteroid dehydrogenase 1 ratio in syncytiotrophoblast membranes, resulting in the subcellular architectural change for estrogen-dependent switch in transplacental glucocorticoid metabolism, which is essential for the maturation of the fetal hypothalamic-pituitary-adrenocortical axis (Pepe et al., 2001). Placental estrogens also stimulate uteroplacental blood flow and placental neovascularisation to ensure the exchange of gases and nutrients for the developing fetus (Albrecht and Pepe, 2010). Indeed, the animal study in baboons with CYP19A1 inhibitors causes the fetal loss (Albrecht et al., 2000). However, CYP19A1 does not interrupt pregnancy as evidence of consequences in the CYP19A1 deficiency (Belgorosky et al., 2009).

Placental CYP19A1 is also critical for the differentiation of the female external genitalia, because the enzyme prevents the female fetus from the androgenic effect of fetal androgens. Placental CYP19A1 eliminates androgen buildup in the maternal circulation. Mothers with fetuses in congenital CYP19A1 deficiency develop maternal androgenisation and hirsutism due to excessive androgens. When female fetus exposes to excessive androgens, permanent defects in external genitalia with external genital ambiguity and pseudohermaphroditism are produced (Belgorosky et al., 2009). However, excessive androgens do not affect ovarian development during the earlier stage. Ovarian function appears influences after birth and during adulthood as shown by the appearance of ovarian cysts in girls during puberty (Mullis et al., 1997).

4. CYP19A1-inhibitory endocrine disruptors

Food components and environmental chemicals (Fig. 2) in contaminated foods act as anti-estrogens via the inhibiting CYP19A1 activity. After blocking CYP19A1 activity, the level of E_2 is lowered and estrogen deficiency occurs. Food components include polyphenols, flavones/flavanones, chalconoids, and tobacco ingredients. Contaminated foods also have phthalates, pesticides/biocides/fungicides. These chemicals target CYP19A1 with different modes of action.

4.1. Food components

4.1.1. Gossypol

Gossypol (Fig. 2) is a natural polyphenol, which can be found in the contaminated cottonseed oil (Zhu et al., 2018). Gossypol was once used to block spermatogenesis in men as a male contraceptive in China (Waites et al., 1998). The medication as a male contraceptive was discontinued because it has severe adverse effects, such as irreversible spermatogenesis and hypokalemia (Waites et al., 1998). Gossypol exists as a mixture of enantiomers, (-)-gossypol and (+)-gossypol. Recently, it has been demonstrated that the (-)-gossypol enantiomer potently blocks BCL-2, thus being able to treat many cancers (Jiang et al., 2004; Mohammad et al., 2005; Volate et al., 2010). There is a distinct structure-activity relationship (SAR) for gossypol enantiomers to inhibit placental CYP19A1. (-)-Gossypol inhibits human CYP19A1 with half maximum inhibitory concentration (IC_{50}) value of 21 istinct structure-activity relationship (SAR) for gossypol enantiomers to inhibit placental +)-gossypol does not inhibit human CYP19A1 at 100 μM. (-)-Gossypol also inhibits E_2 formation in JEG-3 cells while (+)-gossypol does not have the effect at 100 μM (Dong et al., 2016). (-)Gossypol can have a dose-dependent increase in plasma concentration with peak levels up to 300–700 ng/ml (0.58–1.35 μM) after intake of 10 and 20 mg (Zerp et al., 2015), and this concentration is less than its IC_{50} value of inhibiting CYP19A1.

4.1.2. Flavones and flavanones

Flavones and flavanones are polyphenols that are commonly derived from plants, including vegetables, fruits, nuts, berries, tea, and soybeans (Fig. 2) (Reinli and Block, 1996). There are many types of flavones and flavanones isolated from plants. Chrysin is a flavone found in honey, propolis, honeycomb, and passion flowers. 8-Prenylnaringenin is a flavonoid isolated from hop. Among the flavanones, naringenin is a bitter flavanone in grapefruit (Ge et al., 2018a). Eriodictyol is a bitter flavanone extracted from yerba santa (Ley et al., 2005). Hesperidin is a 7-O-glycoside of hesperetin, which is a flavanone, and it is isolated from in lemons (Wang et al., 2018c). Among flavones (Table 1), the potencies of inhibiting human placental CYP19A1 are 8-prenylnaringenin (IC_{50}, 0.065 μM) (Monteiro et al., 2006) > 7-OH-flavone (IC_{50}, 0.2 μM) (Le Bail et al., 2000) > chrysin (IC_{50}, 0.4 μM) (Kellis et al., 1986) > luteolin (IC_{50}, 1.2 μM) (Le Bail et al., 2001) > apigenin (IC_{50}, 2.9 μM) (Le Bail et al., 2000) > flavone (IC_{50}, 48 μM) (Le Bail et al., 2000). 8-Prenylnaringenin is the most potent CYP19A1 inhibitor among flavones and its serum concentration can reach up to 0.43–7.06 nM after intake of hop-derived product containing 0.1 mg 8-prenylnaringenin (Bolca et al., 2010) and this concentration is less than its IC_{50} value of inhibiting CYP19A1.

Among flavanones (Table 1), the potencies of inhibiting human CYP19A1 are eriodictyol (IC_{50}, 0.24 μM)) (Le Bail et al., 2001) > 7-OH-flavanone (IC_{50}, 2.4 μM)) (Le Bail et al., 2001) > hesperetin (IC_{50}, 3.3 μM)) (Le Bail et al., 2001) > naringenin (IC_{50}, 9.2 μM) (Le Bail et al., 2000) > flavanone (IC_{50}, 13.8 μM)) (Le Bail et al., 2001).

4.1.3. Chalconoids

Chalconoids (Fig. 2) have an aromatic ketone and an enone that constitutes the central core for a variety of important biological compounds in plants (Wang et al., 2018b). Xanthohumol and isoxanthohumol are chalconoids isolated from hop. Naringenin chalcone, eriodictyol chalcone, pinostrobin chalcone are common chalconoids synthesized by many plants (Wang et al., 2018b). Of chalconoids (Table 1), the potencies of inhibiting human placental CYP19A1 are naringenin chalcone (IC_{50}, 2.6 μM)) (Le Bail et al., 2001) > eriodictyol chalcone (IC_{50}, 2.8 μM)) (Le Bail et al., 2001) > pinostrobin chalcone (IC_{50}, 14.3 μM) (Le Bail et al., 2001) > xanthohumol (IC_{50}, 20.3 μM) (Monteiro et al., 2006) > hesperetin chalcone (IC_{50}, 24.2 μM)) (Le Bail et al., 2001) > 4′-OH-chalcone (IC_{50}, 30.6 μM) (Le Bail et al., 2001) > 4′-OH-chalcone (IC_{50}, 30.6 μM) (Le Bail et al., 2001) > isoliquiritigenine (IC_{50}, 34.6 μM) (Le Bail et al., 2001) > isoxanthohumol (IC_{50}, 80.1 μM) (Monteiro et al., 2006).

4.1.4. Resveratrol

Resveratrol (Fig. 2) is a natural polyphenol and is produced by grapes and peanuts. Resveratrol has gained much attention due to the facts that it can extend the lifespan of yeast (Howitz et al., 2003), C. elegans (Gruber et al., 2007), and D. melanogaster (Gruber et al., 2007). Resveratrol is also reported to inhibit human CYP19A1. Resveratrol inhibits CYP19A1 with an IC_{50} value of 25 μM (Table 1) (Wang et al., 2006). It exerts both competitive and noncompetitive inhibitory mode (Wang et al., 2006). Healthy human subjects taking 2000 mg resveratrol twice daily with food as the supplement can have a maximum serum concentration of 1274 ng/ml (5.6 μM) (la Porte et al., 2010), a concentration within which resveratrol can inhibit CYP19A1.

4.1.5. Tobacco alkaloids

There is a wide spread use of tobacco products. Nicotine is an alkaloid extracted from tobacco and is present in the cigarette (Fig. 2) (Vanscheeuwijck et al., 2002). Myosmine is a minor tobacco alkaloid occurring in food products of plant. Nicotine disrupts placental function (Gocze and Freeman, 2000). Both nicotine and myosmine inhibit human CYP19A1 with IC_{50} values of 223 and 33 μM (Table 1) (Doering and Richter, 2009). A clinical pharmacokinetic study shows that the level of nicotine in human plasma with 1 cigarette/hour for 9 h can reach 50 ng/ml (about 0.3 μM) (Russell et al., 1976). Therefore, this concentration might not be enough to inhibit CYP19A1.

4.2. Phthalates

Phthalates (Fig. 2) are a class of esters, which contain phthalic acid

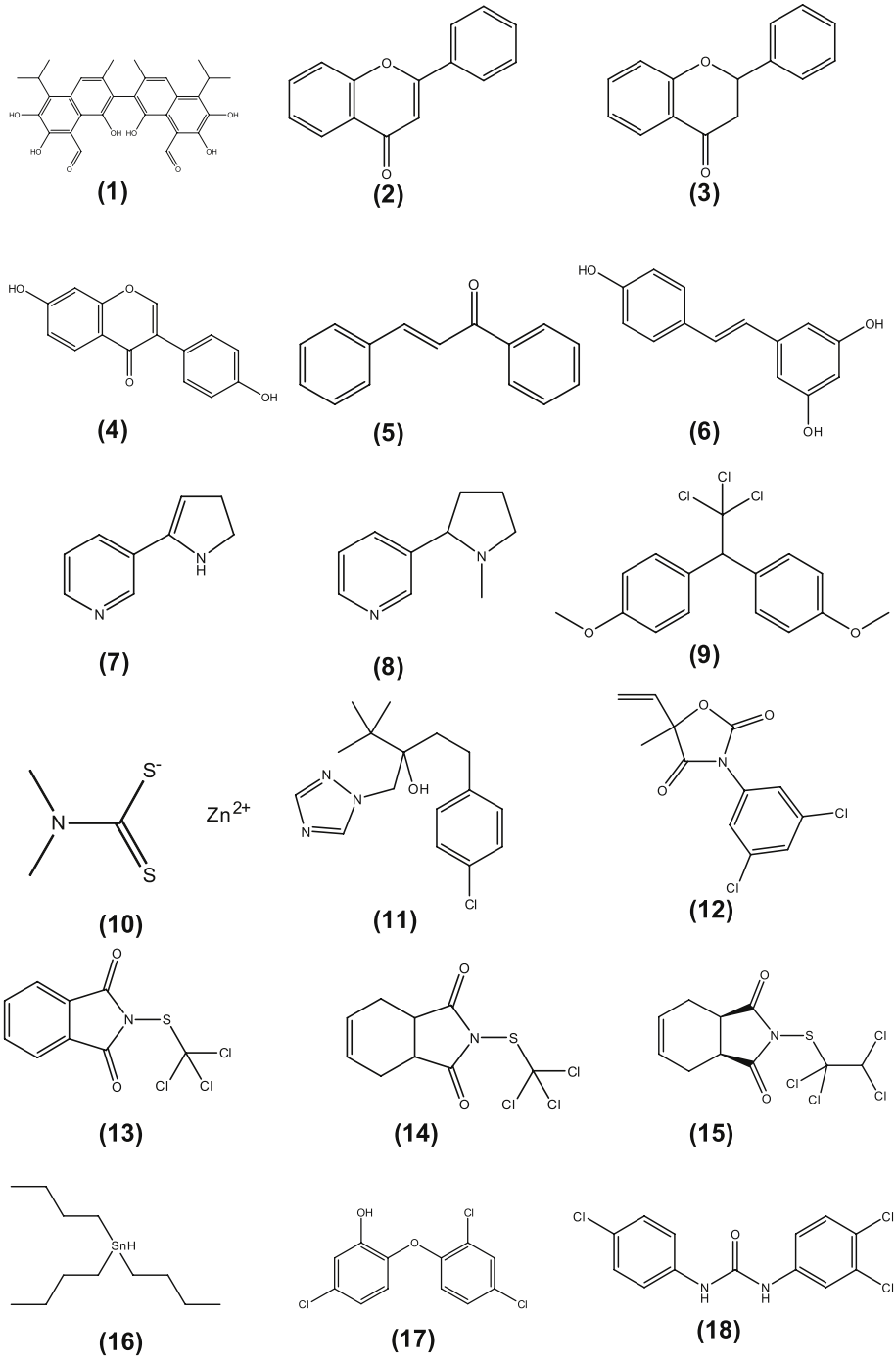

Fig. 2. Chemical structures. Chemical structures: (1) Gossypol; (2) flavone; (3) flavanone; (4) isoflavone; (5) chalcone; (6) resveratrol; (7) myosmine; (8) nicotine; (9) methoxychlor; (10) ziram; (11) tebuconazole; (12) vinclozolin; (13) folpet, (14) captan; (15) captafol; (16) tributyltin; (17) triclosan; (18) triclocarban.

moiety and alcohol moiety. These compounds are synthesized for many applications, including plasticizers that are mixed with polyvinyl chloride (PVC) polymers to soften plastics and as solvents in the liquid preparations. PVC plastics are widely applied in our daily products, including water bottle, food package, film, medical tubing and catheters, and car interior materials (Kohn et al., 2000). As solvents, they are added into soaps, shampoos, cosmetics and even sometimes illegally into soft drinks. In PVC plastics, phthalates do not form chemical bonds with polymers. Therefore, they are easily leaked out into the environment. There are many phthalate compounds, mostly made as di-ethers, due to the change of the carbon chain length and functional residues with alkyl or aryl groups. Carbon chains are made as either the straight chain or the branched chain. When these chemicals enter our body system, the di-ester of a phthalate is rapidly metabolized into a mono-phthalate with one ether group breaking apart to become as an acid. Some phthalates can directly inhibit CYP19A1 activity. Xue et al. conducted a SAR analysis of phthalate ethers in the inhibition of human CYP19A1 (Xu et al., 2016a). A di-phthalate containing C1-5 or C7-9 carbons in the alcohol chain has no inhibitory effect on CYP19A1 at 100 μM. A mono-phthalate with C1 (mono-methyl phthalate) or C4 (mono-butyl phthalate) or C8 (mono-2-ethylhexyl phthalate) in the alcohol chain does not inhibit CYP19A1 at 100 μM. Dicyclohexyl phthalate and bis (2-butoxyethyl) are moderate competitive inhibitors of CYP19A1 and they have IC_{50} values of 56 and 65 itive inhibitors of

Table 1
Potencies of food components in the inhibition of human placental CYP19A1.

Chemicals	Class	IC_{50} (μM)	Mode	Reference
(-)-gossypol	Polyphenol	21	Mixed	Dong et al. (2016)
(+)-gossypol		NI[a]	ND	Dong et al. (2016)
8-prenylnaringenin	Flavone	0.065	ND	Monteiro et al. (2006)
7-OH-flavone		0.2	Competitive	Le Bail et al. (2000)
chrysin		0.4	Competitive	Kellis et al. (1986)
luteolin		1.2	Competitive	Wang et al. (1994)
apigenin		2.9	Competitive	Kellis and Vickery (1984)
flavone		48	Competitive	(Ibrahim and Abul-Hajj, 1990)
hesperetin	Flavanone	3.3	ND	Le Bail et al. (2001)
naringenin		9.2	Competitive	Le Bail et al. (2000)
flavanone		13.8	ND	Le Bail et al. (2001)
7-OH-flavanone		2.4	ND	Le Bail et al. (2001)
xanthohumol	Chalconoid	20.3	Competitive	Monteiro et al. (2006)
isoxanthohumol		80.1	Competitive	Monteiro et al. (2006)
naringenin chalcone		2.6	ND	Le Bail et al. (2001)
eriodictyol chalcone		2.8	ND	Le Bail et al. (2001)
pinostrobin chalcone		14.3	ND	Le Bail et al. (2001)
hesperetin chalcone		24.2	ND	Le Bail et al. (2001)
4′-OH-chalcone		30.6	ND	Le Bail et al. (2001)
isoliquiritigenine		34.6	ND	Le Bail et al. (2001)
Resveratrol	Polyphenol	25	Noncompetitive	Wang et al. (2006)
Myosmine	Alkaloid	33	ND	Gocze and Freeman (2000).
Nicotine		233	ND	Gocze and Freeman (2000).

[a] NI = no inhibition at 100 μM; ND = not detected; IC_{50} = half maximum inhibitory concentration.

CYP19A1(Xu et al., 2016a). Both dicyclohexyl and (2-butoxyethyl) phthalates inhibit E_2 formation in JEG-3 cells (Xu et al., 2016a). A human epidemiological study showed that phthalate exposure is associated with shorter gestational age at birth (Latini et al., 2003). However, the phthalates studied in this study is DEHP and its metabolite MEHP, which do not inhibit human CYP19A1. No data are available for dicyclohexyl phthalate and bis (2-butoxyethyl) phthalate regarding their effects on gestational outcomes in humans. Furthermore, the serum concentrations of the most abundant phthalate, dibutyl phthalate, in maternal blood and cord blood samples from a Chinese cohort showed that the concentration of this phthalate is around 1.4–3.4 mg/L (about 5–12 μM) (Zhang et al., 2009).

4.3. Pesticides, biocides, and fungicides

4.3.1. Metabolite of methoxychlor (MXC)

Methoxychlor (Fig. 2) is a pesticide with structurally containing chlorine group. It is regarded as a weak estrogen (Hall et al., 1997). Of the chemical structure, methoxychlor is very similar to insecticide, DTT, which is a persistent organic pollutant banned in many countries. Methoxychlor has a rapid elimination half-life and is not accumulative in mammal bodies (Gupta et al., 2006). When it enters the body, methoxychlor is metabolized in the liver into de-methane chlorine metabolite hydroxychlor (HPTE) (Akingbemi et al., 2000), and both methoxychlor and HPTE are weak estrogen receptor agonists (Kapoor et al., 1970), with HPTE having higher EC_{50} value (0.75 μM) of binding to a recombinant human estrogen receptor-pt(Bolger et al., 1998). Methoxychlor does not inhibit human placental CYP19A1. However, HPTE inhibits human CYP19A1 with IC_{50} value of 97.16 μM (Table 2). HPTE also concentration-dependently inhibits E_2 synthesis in JEG-3 cells (Liu et al., 2016). The mode of action for HPTE is competitive against testosterone (Liu et al., 2016).

4.3.2. Ziram fungicide

Ziram (Fig. 2) is a zinc-containing fungicide, which has wide applications as an antifungal agent in crops such as nuts, some fruits, potatoes, and grain (Caldas et al., 2001) or as the accelerating agent in latex rubber production. Humans expose to ziram via foods and ziram has been detected in human blood samples (EPA, 2002). Ziram is a potent inhibitor of human placental CYP19A1 with IC_{50} value of 0.33 μM and it inhibits E_2 synthesis in JEG-3 cells (Chen et al., 2017). The mode of action for ziram is competitive (Chen et al., 2017). Apparently, ziram is a potent CYP19A1 inhibitor. Although there is no epidemiological data for ziram-caused placental dysfunction, the other case–control study of Californian population shows the negative relationship between Parkinsons' disease and ziram (Wang et al., 2011).

4.3.3. Azole fungicides

Azole fungicides (Fig. 2) include tebuconazole, triaclimefon, and vinclozolin. Azole fungicides broadly kill various fungi, thus being used to prevent fungal infections in plants. Azole fungicides act via blocking the synthesis of the ergosterol of the membrane of fungi (Li et al., 2016) after inhibiting fungal CYP51 (Li et al., 2016). Tebuconazole, triaclimefon, and vinclozolin moderately inhibit human CYP19A1 with IC_{50} values of 56.84, 58.73, and 57.42 t human CYP19A1 with ICungi, thus being used to prevent fungal infecungicides are non-competitive (Cao et al., 2017).

4.3.4. Phthalimide fungicides

Folpet, captan, and captafol are the phthalimide class of fungicides (Fig. 2). They are widely used in agriculture as the fungicides for protecting fruits, vegetables, and ornamentals on plant seeds. They are also used in industrial products such as pharmaceuticals, lacquers, oil-based paints, plasticizers, rubber stabilizers, polyethylene, vinyl, and textiles. They inhibit human CYP19A1 with captafol (IC_{50}, 1.1 μM) > folpet (IC_{50}, 3.5 μM) > captan (IC_{50} > 10.68 μM) (Table 2). Docking study with CYP19A1 indicates that the binding affinity of these chemicals to CYP19A1 is captafol > folpet > captan. SAR analysis shows that aromatic ring (phthalimide) in the case of folpet seems to increase the potency of inhibiting CYP19A1 when compared to tetrahydrophthalimide in the case of captan (Ge et al., 2018b). The modes of inhibition for three chemicals are competitive (Ge et al., 2018b). Folpet and captan metabolite phthalimide in maternal blood and cord blood samples collected from African-American and Dominican newborns in

Table 2
Potencies of environmental chemicals in the inhibition of human placental CYP19A1.

Chemicals	Class	IC_{50} (μM)	Mode	Reference
dicyclohexyl phthalate	Phthalate	56	Competitive	Xu et al. (2016a).
bis (2-butoxyethyl) phthalate		65	Competitive	Xu et al. (2016a)
C1-C5 phthalates		NI[a]	ND	Xu et al. (2016a)
C7-C9 phthalates		NI[a]	ND	Xu et al. (2016a)
mono-methyl phthalate		NI[a]	ND	Xu et al. (2016a)
mono-butyl phthalate		NI[a]	ND	Xu et al. (2016a)
mono-2-ethylhexyl phthalate		NI[a]	ND	Xu et al. (2016a)
methoxychlor	Organochlorine	Ni[a]	ND	Liu et al. (2016)
hydroxychlor		97	Competitive	Liu et al. (2016)
ziram	Dimethyldithiocarbamate	0.33	Competitive	Chen et al. (2017)
tebuconazole	Azole	56.8	Noncompetitive	Cao et al. (2017)
triaclimefon		58.7	Noncompetitive	Cao et al. (2017)
vinclozolin		57.4	Noncompetitive	Cao et al. (2017)
captafol	Phthalimide	1.1	Competitive	Ge et al. (2018b)
folpet		3.5	Competitive	Ge et al. (2018b)
captan		10.7	Competitive	Ge et al. (2018b)
tributyltin	Organotin	4.6	Competitive	Cao et al. (2017)
tetrabutyltin		NI[a]	ND	Cao et al. (2017)
triclosan	Organoclorine	6.3	Competitive	Li et al. (2017)
triclocarban		15.8	Competitive	Li et al. (2017)

[a] NI = no inhibition at 100 μM; ND = not detected; IC_{50} = half maximum inhibitory concentration.

northern Manhattan and the South Bronx have been found to be 29.0 ± 24.7 (about 100 pM) and 25.3 ± 14.3 pg/g, respectively (Whyatt et al., 2003). Such concentrations of folpet or captafol have the potential to affect CYP19A1 activity but are less than their IC_{50} values.

4.3.5. Organotin biocides

Organotins are compounds in which a metal tin is linked with hydrocarbon groups. They are widely used in variety of industrial processes (Bhosle et al., 2004). They can be commercially applied as stabilizers in polyvinyl chloride. Tributyltin and tetrabutyltin (Fig. 2) are applied as antifouling agents for ships and fishing nets. Tributyltin is a potent inhibitor of human placental CYP19A1 with IC_{50} value of 4.6 μM (Table 2) while tetrabutyltin has IC_{50} value of over 100 μM (Cao et al., 2017). Tributyltin also inhibits rat CYP19A1 with similar inhibitory potency (Satoh et al., 2008). The inhibition on human CYP19A1 is competitive (Cao et al., 2017). Docking study shows that two butyl groups bound to the positively charged tin are required for the interaction of butyltin with the CYP19A1 (Doering et al., 2002). Although there are no epidemiological data for human subjects related to organotin-caused placental dysfunction, there are increased data from animal studies. Tributyltin and triphenyltin can induce irreversible sex-organ alterations in female marine species, in which male sex organs are developed in female animals due to the elevated androgen after inhibition of aromatase, a phenomenon known as “imposex” (Horiguchi et al., 1997; Morcillo and Porte, 1999). In mammals, in utero exposure to tributyltin also causes the reduction of maternal weight gain and fetal weight and induces post-implantation losses (Ema et al., 1997; Harazono et al., 1998).

4.3.6. Triclosan and triclocarban antimicrobials

Triclosan and triclocarban (Fig. 2) are antimicrobial chemicals widely used in many personal care, household, and industrial products. In their chemical structures, they are similar to E_2. Urine sample analysis from U.S. general population in a recent survey found that triclosan and its metabolite levels are detectable in 75% population (Calafat et al., 2008). Triclocarban and its metabolites are detectable in 36.9% of urine samples of U.S. adults (Ye et al., 2016). Both triclosan and triclocarban inhibit human CYP19A1 with IC_{50} values 6.3 and 15.8 μM (Table 2), respectively (Li et al., 2017). This indicates that triclosan is more potent to inhibit CYP19A1 than triclocarban. Triclocarban is a noncompetitive inhibitor while triclosan is a competitive inhibitor of CYP19A1. Docking study using human CYP19A1 (PDB id 4kq8 (Lo et al., 2013)) shows that triclosan has higher binding affinity than triclocarban to bind to human CYP19A1 (Li et al., 2017). A prospective cohort with 537 healthy pregnant women in China showed that increased triclosan exposure was associated with elevated testosterone and decreased E_2 concentrations in cord blood among male infants (Wang et al., 2018a), suggesting that the inhibition of CYP19A1 in the placenta. The concentrations of maternal blood of triclosan and triclocarban were 0–8.54 ng/ml (about 0–30 nM) and 0–2 ng/ml (0–7 nM), respectively (Wang et al., 2018a). A cohort with 185 mothers and 34 paired singleton new-born babies in New York also showed that increased odds of decreased gestational age at birth after exposure to triclocarban (Geer et al., 2017), suggesting that placental function is impaired.

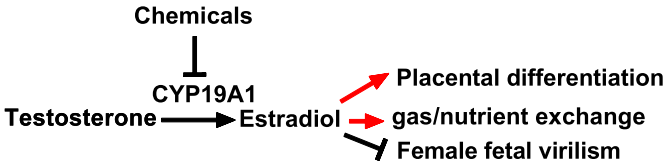

Fig. 3. Illustration of the chemicals that block CYP19A1 and the consequences.

4.4. Summary and conclusion

Many food components and chemicals in the contaminated foods inhibit placental CYP19A1. These chemicals inhibit CYP19A1 by different modes of action. Some chemicals have clear SAR to inhibit CYP19A1. These chemicals inhibit placental CYP19A1, thus decreasing E2 levels, leading to disrupted pregnancy (Fig. 3).

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